Medical Sciences Sector

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582. Age Related Alteration in the Lacrimal Gland of Adult Albino Rat: A Light and Electron Microscopic Study
Amina B. El-Fadaly, El-Badry, A.A. El-Shaarawy, Ayman A. Rizk, Mogeda M. Nasralla and Doaa M.A. Shuaib

Background: Age related changes in the lacrimal gland are associated with alterations in the structural organization and functional response in the gland of diverse mammalian species. Dry eye syndrome is one of the most common ocular problems in the world especially in old age. It results when the lacrimal gland fails to secrete proteins and fluid in sufficient quantity or appropriate composition.

Aim of the work: The present study is designed to demonstrate the influence of aging on the structural lacrimal gland of albino rat and to provide a morphological basis to explain the pathogenesis of the dry eye syndrome with ageing. It also aims to carry out a comparative analysis of age-dependent changes in male and female rats and to address how the lacrimal gland ages in each sex.

Material and Methods: Eighty albino rats were used in this study. The animals were divided into two age groups, young adult and senile. Tear secretion was measured using a modified Schirmer test. Corneal impression cytology of the anesthetized rats was done. The glands were subjected to gross morphologic examination, microscopic examination using H&E, PAS, Masson’s trichrome and Giemsa stains. Electron microscopic examination was done in addition to quantitative histomorphometric estimations included acinar density, ductal count and mast cell count.

Results: Light microscopic examination of the lacrimal glands of the senile rats revealed different pathological changes. These included acinar, ductal as well as stromal changes. Electron microscope examination of the lacrimal gland of the senile group showed a decrease in the electron dense secretory vesicles, mitochondrial swelling and lipofuscin-like inclusions were frequently seen in the cytoplasm of acinar cells in senile rats. Conclusion: The structural changes in the lacrimal glands of senile rats were associated with reduction in tear secretion as well as alterations in corneal epithelium. Gender difference in lacrimal gland structure was recorded.

Keywords: Aging; cytology; Histology; Lacrimal gland; Pathology.

583. Effect of Glucocorticoids on Indomethacin-Induced Gastric Ulcer in the Adult Male Albino Rat – Histological, Morphometric and Electron Microscopy Study
Sherif Mohamed Zaki and Enas Ahmed Mohamed
Archives of Medical Science, 10(2): 381-388 (2014) IF: 1.89

Introduction: Indomethacin is a non steroidal anti-inflammatory drug (NSAID) which is capable of producing injury to gastric mucosa. To prevent NSAID-induced gastropathy, it is important to evaluate the risk factors. One of them is steroid. The aim is to study time dependent effects of glucocorticoids (GC) on indomethacin induced gastric ulcer.

Material and Methods: Forty-nine albino rats were used. They were divided into control and experimental groups. The experimental group was subgroup I (rats were given indomethacin and were sacrificed 1 day after drug intake), subgroup II (rats were given indomethacin + dexamethasone and were sacrificed 1 day after drug intake), subgroup III (rats were given indomethacin + dexamethasone and were sacrificed 3 days after drug intake) and subgroup IV (rats were given indomethacin + dexamethasone and were sacrificed 7 days after drug intake). Histological, scanning electron microscopy and morphometric studies were used.

Results: Indomethacin induced gastric ulceration with shredding of the superficial epithelial cells. The fundic glands were dilated in the subgroups II, III, IV. The surface epithelial cells were shredded and the ulcer sizes were big in subgroup IV. All subgroups exhibited abnormal surface epithelial cells within the gastric ulcer area.

Conclusions: Indomethacin is capable of producing injury to gastrointestinal mucosa. With prolonged use of GC the surface epithelial cells became more affected and the ulcer sizes became bigger. Concomitant use of both medications will delay the healing of the indomethacin induced gastric ulcer and induce more gastric complication.

Keywords: Indomethacin; Glucocorticoids; Gastric ulcer.

584. Lung Damage After Long-Term Exposure of Adult Rats to Sodium Fluoride
Fayza Abdel-Raouf Abdel-Gawad, Maha Hussein Ashmawy, Sherif Mohamed Zaki and Gaber Hassan Abdel-Fatat
Archives of Medical Science, 10(5): 1035-1040 (2014) IF: 1.89

Introduction: Fluorides, when taken in amounts exceeding the standard therapeutic dosage, are regarded as toxic substances. Chronic fluorosis causes marked destruction of lung tissues. The study aimed to determine whether the effect of a chronic toxic dose of sodium fluoride on the lung of an adult male albino rat is reversible or irreversible. This was done through light and electron microscopic studies. Morphometric study was also done.

Material and Methods: Forty adult male rats were used. The animals were divided into 3 groups: control group; group I (chronic fluorosis group) in which sodium fluoride was given daily for 3 months; and group II (recovery group) in which sodium fluoride was given daily for 3 months and after that the rats survived for another month.

Results: The lung of group I was characterized by presence of blood and lymph congestion. Thickening of alveolar septa was also observed with rupture of septa and widening of the air spaces. The area % of collagen (1.13 ±0.5), septal wall thickness (13.47 ±6.1), and number of macrophages (5 ±2.5) increased in comparison to the control group (p ≤ 0.05). With discontinuation of sodium fluoride (group II), no much improvement was observed.

Conclusions: Chronic fluorosis has many pathological effects on the lung which are irreversible.

Keywords: Chronic fluorosis; Lung damage.

585. Morphological and Morphometrical Study of the Nasolacrimal Duct in Man
E. A.A. El-Shaarawy
Folia Morphologica, 73 (3): 321-330 (2014) IF: 0.524

www.gsr.dcu.edu.eg
**Background**: Epiphora constitutes one of the major and very common problems in all age groups. Recent developments in ophthalmology such as balloon dilatation, stent implantation, laser therapy and endoscopy of the lacrimal drainage system raise the need for a detailed anatomical knowledge of this system. It is also important for formulation of principles and techniques in the management of lacrimal problems.

**Aim of the work**: The aim of this study was to demonstrate variations in shape, size and location of the opening of the nasolacrimal duct and of the lacrimal fold.

**Materials and methods**: Twenty sagittal head sections were obtained, the nasal septum was removed and the lateral wall of the nasal cavity was examined and exposed. The opening of the nasolacrimal duct (NLD) was demonstrated and was subjected to anatomical observations for the shape, site, size, opening type and the presence of the lacrimal fold. The different measurements for the distances between the opening of NLD and anterior nasal spine, palate and inferior concha were made.

**Results**: The examined specimens showed that the opening of the NLD was variable in shape taking the form of sulcus in 70% and fissure in 30% of specimens. The sulcus was either vertical or oblique while the fissure was either vertical, oblique or in the form of anteroposterior one. Regarding the location, the opening of the NLD was located at anterior one third below line of attachment of the inferior concha in nearly half of cases (45%). The lacrimal fold was present in most of examined specimens (70%) and absent in 30%. The fold take 5 different forms.

**Conclusions**: The knowledge of the morphology and morphometry of the lacrimal drainage system enables the ophthalmologist to plan intervention on the lacrimal drainage system precisely and avoid unnecessary manipulations and also minimizing the risk of injury during intra-nasal surgery.

**Keywords**: Nasolacrimal duct (NLD) opening; Morphology of NLD; Morphometry of NLD.

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**586. Morphological and Radiometrical Study of the Human Intervertebral Foramina of the Cervical Spine**

S. H. Ahmed, E. A. A. El-Shaarawy, M. F. Ishaq and M. H. Abdel Moniem

*Folia Morphologica, 73 (1): 7-18 (2014) IF: 0.524*

**Background**: Degenerative changes of the cervical spine are an inevitable response to certain occupational status and aging processes. Compression of cervical nerve roots may result from disc degeneration, disc herniation or intervertebral foraminal stenosis. The precise and detailed anatomical knowledge of the intervertebral foramen of the cervical spine is essential for the diagnosis and management of cervical radiculopathy.

**Aim of the work**: The significance of the observations and findings of the present study was to elucidate the correlation between the morphology and disorders of the cervical intervertebral foramina in normal and pathological conditions especially at the level of C3-C4 to C6-C7 on both sides and in both sexes. Moreover, it will help greatly in the planning of both surgical and conservative strategies.

**Materials and Methods**: In the present study, 5 formalin-fixed adult cadavers and radiological specimens of the cervical region of the vertebral column of 28 normal and 209 subjects suffering from cervical disorder from both sexes and different age groups. They subjected for morphological and radiometrical analysis.

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**Results**: All measurements of the present study of the cervical disorders in females were found to be 6% less than in males in all age groups, which is statistically significant (p < 0.01) as compared with the control group (2%). The mean intervertebral foraminal areas in the control group of C5-C6 and C6-C7 are significantly greater than those of C3-C4 and C4-C5.

**Conclusions**: The mean intervertebral foraminal area was greater in the lower cervical region than the upper in normal adult individuals. In pathological condition the affection of C3-C4 and C4-C5 intervertebral foramina was more due to narrower surface area. The pathology of cervical spine affecting the intervertebral foramina of female which complaint earlier than male due to narrower foramina.

**Keywords**: Cervical spine; Cervical radiology; Cervical radiculometry.

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**587. Relationship Between Biochemical Bone Markers and Bone Mineral Density in Patients With Phenylketonuria Under Restricted Diet**

Hala M. Koura, Sherif M. Zaki, Nagwa A. Ismail, Emad E. Salama, Dalia H. El Lebedy and Laila K. Effat


**Objective**: Most of phenylketonuria (PKU) develops bone turnover impairment and low bone mineral density (BMD). Measurements of BMD reflect only bone mineral status but not the dynamics of bone turnover. Bone markers are a noninvasive tool useful for the assessment of bone formation and bone resorption processes. Our study was to assess the levels of bone markers in PKU in order to select a screen marker and detect the most specific marker which can be combined with BMD for appropriate follow up.

**Methods**: Thirty three PKU patients were studied. BMD and bone mineral content (BMC) were measured. Total alkaline phosphatase (ALP), osteocalcin (OC) and carboxy-terminal propeptide of type I collagen (CICP), osteoprotegerin (OPG), receptor activator of nuclear factor κB ligand (RANKL) and Deoxypyridinoline (DPD) were measured.

**Findings**: Nineteen (57.6%) male and fourteen (42.4 %) female PKU patients were involved in the current study. Their mean age was 8.4±4.6 yrs and the age range 3-19 yrs. The control group consisted of twenty two (52.4%) males and twenty (47.6%) females. Their mean age was 8.52±3.3 yrs and th age range 2-17 yrs. Using the Z score values, there was a significant decrease of total BMC (TBMC-Z), BMD of the femoral neck BMD-FN-Z, BMD of lumbar vertebrae (BMD-L-Z), BMD-FN and DPD while RANKL increased. There was a negative correlation between CICP and TBMC and between CICP and BMD-L in these patients. Also, a negative correlation between ALP and TBMC and between ALP and BMD-L was observed. It was concluded that the ALP provides a good impression of the new bone formation in the PKU patients and it has a highly significant negative correlation with the many parameters of the bone mineral status beside the wide availability of inexpensive and simple methods. So a screening test and/or follow up for the PKU patients using ALP would be available. Once the level of ALP decrease is detected, one can combine it with BMD to explore the bone mineral status and with specific bone markers (OC, RANKL and DDP), to verify the dynamics of bone turnover.

**Conclusion**: This schedule will reduce the risk of exposure of these patients to the risk hazards of DXA and limit its use only to a limited number of the highly suspected cases.
Keywords: Phenylketonuria; PKU; Bone mineral density; RANKL; Osteocalcin; Bone mineral content.

Dept. of Andrology & Sexology

588. Seminal BAX and BCL2 Gene and Protein Expressions in Infertile Men With Varicocele

Taymou Mostafa, Laila Rashed, Nashaat Nabil and Rania Amin

Objective: To assess seminal BAX and BCL2 gene and protein expressions in infertile men with varicocele (Vx).

Materials and Methods: A total of 111 men were investigated and divided into the following groups: healthy fertile men (n = 20), fertile men with Vx (n = 16), infertile oligoasthenoteratozoospermic men without Vx (n = 29), and infertile oligoasthenoteratozoospermic men with Vx (n = 46).

They were subjected to history taking, clinical examination, and semen analysis. In their seminal plasma, BAX and BCL2 gene and protein expressions were estimated.

Results: The mean level of seminal BAX gene and protein was significantly decreased, and the mean level of seminal BCL2 gene and protein was significantly increased in fertile men compared with fertile men with Vx and in infertile men without Vx compared with infertile men with Vx. The mean level of seminal BAX gene and protein were significantly increased in men associated with bilateral Vx compared with men associated with unilateral Vx and in cases with Vx grade III compared with Vx grade I and II cases. Seminal BAX demonstrated significant negative correlation with sperm concentration, sperm motility, and sperm normal forms. Seminal BCL2 demonstrated significant positive correlation with sperm concentration, sperm motility, and sperm normal forms and significant negative correlation with seminal BAX.

Conclusion: Seminal BAX is significantly increased and seminal BCL2 is significantly decreased in men associated with Vx. Seminal BAX is significantly increased in men associated with bilateral Vx compared with unilateral Vx and in cases with Vx grade III compared with Vx grade I and II cases. Seminal BAX demonstrates significant negative correlation with sperm concentration, sperm motility, and sperm normal forms, whereas seminal BCL2 demonstrates significant reverse positive correlations.

Keywords: Male infertility; Semen; Varicocele; Apoptosis.

589. Seminal Helicobacter Pylori Treatment Improves Sperm Motility in Infertile Asthenozoospermic Men

Yehia El-Garem, Mohamed El-Sawy and Taymou Mostafa

Objective: To assess the effect of treatment of seminal Helicobacter pylori in infertile asthenozoospermic men.

Methods: In all, 223 infertile asthenozoospermic men were consecutively selected. They were subjected to history taking, clinical examination, semen analysis, and estimation of H pylori IgA antibodies in their seminal fluid. Infertile men with high seminal H pylori IgA were subjected to triple drug treatment, omeprazole, 20 mg; tinidazole, 500 mg; and clarithromycin, 250 mg twice a day for 2 weeks. Semen analysis as well as H pylori IgA antibodies was estimated after 3 months.

Results: In all, 22 of 223 men (9.87%) demonstrated H pylori IgA antibodies in their seminal plasma. After treatment, mean seminal H pylori IgA levels demonstrated significant decrease (1.55 0.4 vs 0.52 0.26; 95% confidence interval, 0.83-1.21; P ¼ .001) concomitant with improved progressive as well as nonprogressive sperm motility, H pylori IgA antibodies demonstrated significant negative correlation with progressive sperm motility, nonprogressive sperm motility, normal sperm morphology, and significant positive correlation with immotile sperm motility.

Conclusion: H pylori treatment significantly improves sperm motility in infertile asthenozoospermic men with elevated seminal H pylori IgA.

Keywords: Male infertility; Semen; Sperm motility; H. Pylori.

590. Female Sexual Dysfunction Across the Three Pregnancy Trimesters: An Egyptian Study

Samy Hanafy, Neveen E. Srour and Taymou Mostafa


Background: Pregnancy is a special period in the life of women characterised by physical, hormonal and psychological changes that, in conjunction with social and cultural influences, could affect women’s sexuality as well as couples’ sexual relationships. This cross-sectional study aimed to evaluate female sexual dysfunction (FSD) among the three pregnancy trimesters.

Methods: A total of 300 healthy heterosexual pregnant Egyptian women with stable marital relationships were included. The Female Sexual Function Index (FSFI) questionnaire was used as a standard method for measuring female sexual function in each pregnancy trimester.

Results: There was no significant relationship between FSD and women’s education, work, gravidity and parity. The incidence of FSD demonstrated significant alterations throughout pregnancy, being 68% in the first trimester, decreasing in the second trimester to 51% and increasing to 72% in the third trimester. Sexual desire decreased in the first trimester, was variable in the second trimester and decreased at the end of the third trimester (3.51.2, 3.71.2 and 3.41.1 respectively). Sexual satisfaction declined significantly in the first trimester compared with the second and the third trimesters (4.21.1, 4.80.8 and 4.61.0 respectively). Scores for the arousal, lubrication and orgasm domains were significantly decreased in the third trimester, whereas pain was increased in the second trimester compared with the first and third trimesters.

Conclusion: Female sexual function is affected during pregnancy, with a significant change in all Female Sexual Function Index domains, especially in the first and third trimesters.

Keywords: Desire; Female sexual function index; Satisfaction.

591. In Vitro Study of Cypermethrin on Human Spermatozoaa and the Possible Protective Role of Vitamins C and E


Andrologia, 46(10): 1141-1147 (2014) IF: 1.172

Cypermethrin, a type II synthetic pyrethroid pesticide, is widely used in pest control programmes in agriculture and public health. This study aimed to assess the potential effect of cypermethrin on human spermatozoa and the possible ameliorative effects of...
vitamins C and E. Semen samples of 20 healthy normozoospermic men were divided into six aliquots at room temperature. The first aliquot served as control not exposed to treatments, and the second was incubated with 20 mM vit. C and 2 mM vit. E where the third one was exposed to 10 μM cyanmethrin for 6 h. The other three aliquots were incubated with vit. C, vit. E and both vitamins for 30 min before cyanpermethrin exposure. Semen aliquots were analysed for sperm motility, sperm viability, hypo-osmotic swelling test and modified alkaline comet assay. The results demonstrated a significant decrease in sperm motion, sperm function and increased sperm DNA damage in the cyanmethrin group. Addition of vitamins C and E alone/combined led to significant improvement in sperm motion, sperm function and DNA damage, being maximal with both vitamins together. It is concluded that in vitro cyanmethrin can alter sperm function and induce DNA damage in spermatozoa, which is improved after using vitamins C and E. 

**Keywords:** Antioxidants; Cypermethrin; Male infertility; Pyrethroid; Spermatozoa.

592. Oestrogen Receptor Alpha Gene Polymorphisms Relationship With Semen Variables in Infertile Men

A. Zalata, H. A. Abdalla, Y. El-Bayoumy and T. Mostafa

*Andrologia, 46(6): 618-624 (2014) IF: 1.172*

This study aimed to assess the association of oestrogen receptor alpha (ER-a) gene polymorphisms and semen variables in infertile oligoasthenoteratozoospermic (OAT) men. In all, 141 men were grouped into fertile men (n = 60) and infertile OAT men (n = 81). They were subjected to assessment of semen analysis, acrosin activity, serum reproductive hormones and genotyping of ER-a gene. Frequencies of p and x alleles in ER-a gene PvuII and XbaI polymorphisms were more prevalent among fertile men compared with infertile OAT men. Presence of P and X alleles was associated with increased incidence of male infertility for genotypes PP, XX compared with genotypes pp and xx (OR = 2.8; 95% CI: 2.36–6.97; P = 0.001 and OR = 4.1; 95% CI: 1.49–11.39; P = 0.001, respectively). The mean of semen variables and sperm acrosin activity were significantly higher in cases associated with pp than PP and in xx than XX genotypes of ER-a gene. Mean levels of all serum reproductive hormones demonstrated nonsignificant differences in different ER-a genotypes except oestrogen that was elevated in PP and XX ER-a gene genotypes. It is concluded that as oestrogen is concerned in male gamete maturation, ER-a gene polymorphisms might play a role in the pathophysiology of male infertility.

**Keywords:** Hormones; Male infertility; Oestrogen; Polymorphism; Semen.

593. Seminal Androgens, Oestradiol and Progesterone in Oligoasthenoteratozoospermic Men With Varicocele

A. Zalata, M. El-Mogy, A. Abdel-Khabir, Y. El-Bayoumy, M. El-Baz and T. Mostafa

*Andrologia, 46 (7): 761-765 (2014) IF: 1.172*

This study aimed to assess seminal androgens, oestradiol, progesterone levels in oligoasthenoteratozoospermic (OAT) men with varicocele (Vx). In all, 154 men with matched age and body mass index were investigated that were divided into healthy fertile controls (n = 35), OAT men with Vx (n = 55), OAT men without Vx (n = 64). They were subjected to assessment of semen parameters, seminal levels of testosterone (T), androstenedione (A), 5α-androstane-3 α,17 β-diol (3 α-diol), oestradiol (E2), 17-hydroxyprogesterone (17-OHP) and progesterone (P). Seminal levels of T and A were significantly decreased where seminal levels of 3 α-diol, E2, 17-OHP, P were significantly higher in OAT men with/without Vx compared with fertile controls. Sperm count, sperm motility and sperm normal forms percentage demonstrated significant positive correlation with seminal T and A and significant negative correlation with seminal 3 α-diol, E2, P. It is concluded that in fertile men, seminal T and A are significantly increased and seminal 3 α-diol, E2, 17-OHP, P are significantly decreased compared with infertile OAT men with/without Vx. Association of Vx demonstrated a nonsignificant influence on these hormonal levels in OAT cases. Sperm count, sperm motility and sperm normal forms demonstrated significant positive correlation with seminal T, A and significant negative correlation with seminal 3 α-diol, E2, P.

**Keywords:** Male infertility; Oestrogen; Progesterone; Semen; Testosterone; Varicocele

594. Smoking Influence on Sperm Vitality, DNA Fragmentation, Reactive Oxygen Species and Zinc in Oligoasthenoteratozoospermic Men With Varicocele


*Andrologia, 46 (6): 687-691 (2014) IF: 1.172*

This study aimed to assess the influence of smoking duration and intensity on sperm vitality, sperm DNA fragmentation, reactive oxygen species (ROS) and zinc (Zn) levels in oligoasthenoteratozoospermic (OAT) men with varicocele (Vx). A total of 246 men were investigated who were divided into OAT nonsmokers, OAT smokers, OAT nonsmokers and OAT smokers with Vx. They were subjected to history taking, clinical examination and semen analysis. In their semen, sperm hypo-osmotic swelling (HOS) test, sperm DNA fragmentation test, seminal ROS and seminal Zn were assessed. The results demonstrated significantly decreased HOS test, seminal Zn level and significantly increased sperm DNA fragmentation, seminal ROS levels in OAT smokers with Vx more than OAT smokers compared with OAT nonsmokers. Smoking intensity, smoking duration and Vx grade demonstrated significant negative correlations with sperm motility, HOS test percentage and significant positive correlations with sperm DNA fragmentation, seminal ROS level. It is concluded that smoking has a negative impact on sperm progressive motility, HOS test, seminal Zn and positive impact on sperm DNA fragmentation, seminal ROS level that are exaggerated if Vx is associated being correlated with smoking intensity, smoking duration and Vx grade.

**Keywords:** DNA fragmentation; HOS test; Male infertility; Semen; Smoking; Varicocele; Zinc.

595. Triorchidism: Two Case Reports

A. Hassan, S. Elhanbly, M. S. El-Mogy and T. Mostafa

*Andrologia, 46 (9): 1073-1077 (2014) IF: 1.172*

In this study, two cases of triorchidism are reported. The first case (29 years) had two right discrete ovoid nontender, firm, mobile lumps with testicular sensation. The second case (32 years) had
two left discrete ovoid nontender, firm, mobile lumps with normal testicular sensation. They were subjected to the estimation of serum follicle-stimulating hormone, luteinising hormone, free and total testosterone, alpha-fetoprotein, prostate-specific antigen, karyotyping and semen analysis. Imaging included ultrasonography, transrectal ultrasound, magnetic resonance imaging and intravenous pyelography. The first case had two testes in the right side. Each one had an epididymis where one vas deferens was palpated. The second case had two left testes with normal testicular sensation. The lower left lump represented normal-sized testis attached to its epididymis and a single palpated vas deferens. Diagnosis of the first case was triorchidism associated with left varicocele (grade I) with oligoasthenoteratozoospermic semen profile. Intracytoplasmic sperm injection was carried out resulting in twin. Diagnosis of the second case was triorchidism with accessory testis on the left side associated with left varicocele (grade I) and asthenozoospermic semen profile that was submitted to medical treatment. It is concluded that triorchidism is an uncommon congenital anomaly that should be not overlooked in diagnosing scrotal masses.

Keywords: Infertility; Polorchidism; Testis; Triorchidism; ultrasonography.

Dept. of Anesthesiology

596. Acute Pain Services; An Egyptian Experience

Amany Ezzat Ayad Ibrahim


Inadequacies in postoperative pain relief have been evident for decades despite the availability of variable drugs and sophisticated techniques for management [1,2]. This is thought of due to lack of an appropriate service that deploys available expertise rather than the need for new medications or pain management modalities. Thus, establishing an acute pain service (APS) based on an evidence-based approach within the available resources sounds like a solution Perineal Cancer-Related Pain Impar-Ganglion Neurlysis Lower End Block (Intrathecal Neurlysis)* Consider always a test dose.

597 Infection Complications and Pattern of Bacterial Resistance in Living-Donor Liver Transplantation: A Multicenter Epidemiologic Study in Egypt


Transplantation Proceedings, 46: 1444-7 (2014) IF: 0.984

Introduction: Data on the prevalence and pattern of infection after living-donor liver transplantation (LDLT) are scarce in Egypt. We therefore conducted this study to quantify the incidence, risk factors, and pattern of bacterial resistance post-LDLT in 3 hospitals in Egypt.

Patients and Methods: We conducted a retrospective, multicenter study of the medical records of 246 patients who underwent LDLT between January 2006 and April 2011 at 3 transplant centers in Egypt.

Results: Of 246 patients enrolled in this study, 127 (52%) developed infectious complications after LDLT, with 416 episodes of infection occurring within 3 months of transplantation. Biliary tract infection was the most common, occurring in 169 (40.6%) patients. The rate of infection with Gram-negative bacteria was higher than that of infection with Gram-positive bacteria (310 [74%] vs 87 [21%]; P < .001). Overall, 75% of Gram-negative isolates were multidrug resistant.

Significant independent risk factors for infection were portal vein thrombosis (odds ratio, 2.4; P = .037) and biliary complications (odds ratio, 5.4; P < .001).

Conclusions: Our data showed a high-resistance pattern of bacterial infection after LDLT in Egypt. Early biliary complications were an independent risk factor for bacterial infection.

Keywords: Liver transplantation; Infection; Egypt.

Dept. of Cardiology

598. TGF-β Signaling Mediates Endothelial-To-Mesenchymal Transition (EndMT) During Vein Graft Remodeling

Brian C. Cooley, Jose Nevado, Jason Mellad, Dan Yang, Cynthia St. Hilaire, Alejandra Negro, Fang Fang, Guibin Chen, Hong San, Avram D. Walts, Robin L. Schwartzbeck, Brandi Taylor, Jan D. Lanzer, Andrew Wragg, Abdalla Elagha, Leilani E. Beltran, Colin Berry, Robert Feil, Renu Virmani, Elena Ladich, Jason C. Kovacic and Manfred Boehm

Science Translational Medicine, 6: 227-234 (2014) IF: 14.414

Veins grafted into an arterial environment undergo a complex vascular remodeling process. Pathologic vascular remodeling often results in stenosed or occluded conduit grafts. Understanding this complex process is important for improving the outcome of patients with coronary and peripheral artery disease undergoing surgical revascularization. Using in vivo murine cell lineage–tracing models, we show that endothelial-derived cells contribute to neointimal formation through endothelial-to-mesenchymal transition (EndMT), which is dependent on early activation of the Smad2/3-Slug signaling pathway. Antagonism of transforming growth factor–β (TGF-β) signaling by TGF-β neutralizing antibody, short hairpin RNA–mediated Smad3 or Smad2 knockdown, Smad3 haploinsufficiency, or endothelial cell–specific Smad2 deletion resulted in decreased EndMT and less neointimal formation compared to controls. Histological examination of postmortem human vein graft tissue corroborated the changes observed in our mouse vein graft model, suggesting that EndMT is operative during human vein graft remodeling. These data establish that EndMT is an important mechanism underlying neointimal formation in interposition vein grafts, and identifies the TGF-β–Smad2/3–Slug signaling pathway as a potential therapeutic target to prevent clinical vein graft stenosis.

Keywords: TGF-β; Endothelial-to-mesenchymal transition; Vein graft remodeling.

599. Idiopathic Left Ventricular Outflow Tract Ectopy: A Single Focus With Extremely Divergent Breakouts

Sherif Gouda, Dan Wichterle, Petr Peichl and Josef Kautzner

Bmc Cardiovascular Disorders, 14; 1-5 (2014) IF: 1.5

Background: Idiopathic ventricular tachycardia (VT) and/or premature ventricular contractions (PVCs) arise most commonly from the right ventricular outflow tract and less frequently from...
the left ventricular outflow tract (LVOT), either below or above the semilunar valves.

**Case presentation:** We report a case of 24-year-old man with idiopathic ventricular tachycardia from a single focus in the supravalvular left ventricular outflow tract with two extremely divergent breakouts observed during the ablation procedure.

**Conclusion:** Focal sources of ventricular arrhythmia in the aortic root may have different preferential exits and meticulous activation sequence mapping is the preferable strategy to delineate the site of origin.

**Keywords:** Ventricular tachycardia; Premature ventricular contractions; Left ventricular outflow tract; Preferential conduction; Non-coronary Aortic cusp; Catheter ablation.

**Dept. of Chemical Pathology**

**600. Durable Diagnosis of Seminal Vesicle and Sexual Gland Diseases Using the Nano Optical Sensor Thin Film Sm-Doxycycline Complex**

Attia M.S., Youssif A.O. and El-Sherif RH


A new method in which a nano optical sensor for diagnosis of different diseases of seminal vesicle and sexual gland was prepared. The working principle of the method depends on the determination of the fructose concentration in semen of different patients by using nano optical sensor thin film Sm-doxycycline doped in sol-gel matrix.

The assay is based on the quenching of the characteristic emission bands of Sm(3+) present in silica doped Sm-doxycycline nanoopptide thin film by different fructose concentrations in acetonitrile at λex = 400 nm.

This method was optimized for parameters, such as, solvent effect, operational stability, shelf life and interference parameters. Good and reproducible linearity (1 × 10(-9) - 5.0 × 10(-5) mol L(-1)) with a detection limit of 9.0 × 10(-10) mol L(-1) and quantification limit of detection (LOQ) 2.7 × 10(-9) mol L(-1) were obtained. Seminal fructose determination in different patient samples after appropriate dilutions confirmed the reliability of this technique.

The method was successfully applied for routine fructose monitoring in human semen samples of different cases such as: obstructive and non-obstructive azoospermia, inflammation of male accessory glands, atrophy of seminal vesicle, congenital vas deferens and retrograde ejaculation.

**Keywords:** Luminescence intensity; Nano optical sensor thin film; Quenching; Seminal fructose; Seminal vesicle; Sm-doxycycline.

**601. Increased DNA Damage in Hepatitis C Virus-Related Hepatocellular Carcinoma**

Shereen M. Shawki, Sufa S. Meshaal, Aliaa S. El Dash, Naglaa A. Zayed and Mariam Onsy F. Hanna

*DNA and Cell Biology, 33: 884-890 (2014) IF: 1.991*

One consequence of hepatitis C virus (HCV) infection is an elevated cancer risk. During chronic viral infection, deoxyribonucleic acid (DNA) damage is being induced by reactive oxygen and nitrogen species, which may play a pathogenic role in HCV-induced carcinogenesis. The study investigated DNA damage in peripheral blood lymphocytes from patients with hepatocellular carcinoma (HCC) and those with HCV infection with and without associated cirrhosis and normal controls. As a measure for genomic damage, the comet assay (single cell gel electrophoresis) was applied, which detects single- and double-strand breaks and alkali-labile sites through electrophoretic mobility of the resulting fragments.

The levels of DNA damage were significantly higher in HCC and HCV-associated cirrhosis compared to HCV without cirrhosis and the control group. Patients presenting with DNA damage more than mean + two standard deviation of the controls had a 3.6-fold risk of having HCC more than those with undamaged DNA. HCV disease progression was the only discriminator predicting the extent of DNA damage. The accumulation of DNA damage is important in HCC evolution. DNA damage indicating intracellular oxidative and nitrative stress may lead to mutagenesis and consequently malignant transformation, which emphasizes the need to optimize the therapy for reducing the degree of genomic damage.

**Keywords:** Comet assay; HCV, HCC, DNA damage.

**Dept. of Clinical & Chemical Pathology**

**602. Repeat Endocarditis: Analysis of Risk Factors Based on the International Collaboration on Endocarditis-Prospective Cohort Study**


*Clinical Microbiology and Infection, 20: 566-575 (2014) IF: 5.197*

Repeat episodes of infective endocarditis (IE) can occur in patients who survive an initial episode. We analysed risk factors and 1-year mortality of patients with repeat IE. We considered 1874 patients enrolled in the International Collaboration on Endocarditis – Prospective Cohort Study between January 2000 and December 2006 (ICE-PCS) who had definite native or prosthetic valve IE and 1-year follow-up.

Multivariable analysis was used to determine risk factors for repeat IE and 1-year mortality. Of 1874 patients, 1783 (95.2%) had single-episode IE and 91 (4.8%) had repeat IE; 74/91 (81%) with new infection and 17/91 (19%) with presumed relapse. On bivariate analysis, repeat IE was associated with haemodialysis (p 0.002), HIV (p 0.009), injection drug use (IDU) (p < 0.001), Staphylococcus aureus IE (p 0.003), healthcare acquisition (p 0.006) and previous IE before ICE enrolment (p 0.001).

On adjusted analysis, independent risk factors were haemodialysis (OR, 2.5; 95% CI, 1.2–5.3), IDU (OR, 2.9; 95% CI, 1.6–5.4), previous IE (OR, 2.8; 95% CI, 1.5–5.1) and living in the North American region (OR, 1.9; 95% CI, 1.1–3.4). Patients with repeat IE had higher 1-year mortality than those with single-episode IE (p 0.003).

Repeat IE is associated with IDU, previous IE and haemodialysis. Clinicians should be aware of these risk factors in order to recognize patients who are at risk of repeat IE.

**Keywords:** Complication of endocarditis; Recurrence of endocarditis; Relapse of endocarditis; Repeat endocarditis; Risk factors for endocarditis.
603. Clinical Utility of Chitotriosidase Enzyme Activity in Nephopathic Cystinosis

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Orphanet Journal of Rare Diseases, 9 (1): 155 (2014) IF: 3.958

Background: Nephopathic cystinosis is an inherited autosomal recessive lysosomal storage disorder characterized by the pathological accumulation and crystalization of cystine inside different cell types. WBC cystine determination forms the basis for the diagnosis and therapeutic monitoring with the cystine depleting drug (cysteamine).

The chitotriosidase enzyme is a human chitinase, produced by activated macrophages. Its elevation is documented in several lysosomal storage disorders. Although, about 6% of Caucasians have enzyme deficiency due to homozygosity of 24-bp duplication mutation in the chitotriosidase gene, it is currently established as a screening marker and therapeutic monitor for Gaucher’s disease.

Methods: Plasma chitotriosidase activity was measured in 45 cystinotic patients, and compared with 87 healthy controls and 54 renal disease patients with different degrees of renal failure (CKD1-5). Chitotriosidase levels were also correlated with WBC cystine in 32 treated patients. Furthermore, we incubated control human macrophages in vitro with different concentrations of cystine crystals and monitored the response of tumor necrosis factor-alpha (TNF-a) and chitotriosidase activity. We also compared plasma chitotriosidase activity in cystinotic knocked-out (n=10) versus wild-type mice (n=10).

Results: Plasma chitotriosidase activity in cystinotic patients (0-3880, median 163 nmol/ml/h) was significantly elevated compared to healthy controls (0-90, median 18 nmol/ml/h) and to CKD patients (0-321, median 52 nmol/ml/h), P <0.001 for both groups. Controls with decreased renal function had mild to moderate chitotriosidase elevations; however, their levels were significantly lower than in cystinotic patients with comparable degree of renal insufficiency.

Chitotriosidase activity positively correlated with WBC cystine content for patients on cysteamine therapy (r=0.8), P<0.001. In culture, human control macrophages engulfed cystine crystals and released TNF-a into culture supernatant in a crystal concentration dependent manner. Chitotriosidase activity was also significantly increased in macrophage supernatant and cell-lysate. Furthermore, chitotriosidase activity was significantly higher in cystinotic knock-out than in the wild-type mice, P=0.003.

Conclusions: This study indicates that cystine crystals are potent activators of human macrophages and that chitotriosidase activity is a useful marker for this activation and a promising clinical biomarker and therapeutic monitor for nephopathic cystinosis.

Keywords: Lysosomal storage disorders; Nephopathic cystinosis; Cystine crystals; Macrophage activation; Chitotriosidase enzyme; Clinical screening; Cysteamine; Therapeutic monitoring.

604. Analysis of Oxidative Stress Status, Catalase And catechol-O-Methyltransferase Polymorphisms In Egyptian Vitiligo Patients

Dina A. Mehaney, Hebatallah A. Darwish, Rehab A. Hegazy, Mohammed M. Nooh, Amira M. Tawdy, Heba I. Gawdat and Maha M. El-Sawalhi


Vitiligo is the most common depigmentation disorder of the skin. Oxidative stress is implicated as one of the probable events involved in vitiligo pathogenesis possibly contributing to melanocyte destruction. Evidence indicates that certain genes including those involved in oxidative stress and melanin synthesis are crucial for development of vitiligo. This study evaluates the oxidative stress status, the role of catalase (CAT) and catechol-O-Methyltransferase (COMT) gene polymorphisms in the etiology of generalized vitiligo in Egyptians. Total antioxidant capacity (TAC) and malondialdehyde (MDA) levels as well as CAT exon 9 T/C and COMT 158 G/A polymorphisms were determined in 89 patients and 90 age and sex-matched controls. Our results showed significantly lower TAC along with higher MDA levels in vitiligo patients compared with controls. Meanwhile, genotype and allele distributions of CAT and COMT polymorphisms in cases were not significantly different from those of controls. Moreover, we found no association between both polymorphisms and vitiligo susceptibility. In conclusion, the enhanced oxidative stress with the lack of association between CAT and COMT polymorphisms and susceptibility to vitiligo in our patients suggest that mutations in other genes related to the oxidative pathway might contribute to the etiology of generalized vitiligo in Egyptian population.

Keywords: Vitiligo; Oxidative; Molecular.

605. Triple Test Screening for Down Syndrome: An Egyptian-Tailored Study

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Plos One, 9 (10): (2014) IF: 3.534

Background: The incidence of Down syndrome (DS) in Egypt varies between 1:555 and 1:770 and its screening by triple test is becoming increasingly popular nowadays. Results, however, seem inaccurate due to the lack of Egyptian-specific information needed for risk calculation and a clear policy for programme implementation. Our study aimed at calculation and validation of the triple marker medians used in screening Egyptian females as well as to recommend programme conventions to unify screening in this country.

Methods: The study was conducted on 668 Egyptian women, in weeks 15–20 of pregnancy as proven by sonar. Chorionic gonadotropin (CG), a-fetoprotein (AFP) and unconjugated oestriol (uE3) were measured on Siemens Immulite analyzer. Medians of the three parameters were calculated, regressed against gestational age (GA) and weighted by the number of participants/week. Equations were derived to adjust each parameter to the maternal weight and were centered on the median Egyptian weight. Prisca software was fed with the above data, multiples-of-median (MoM) and DS risks were calculated and the screening performance was evaluated at a mid-trimester risk cutoff of 1:270.

Results: Log-linear [AFP/uE3 = 10^(A+B*GA)] and exponential equations [CG = A*e^(-B*GA)] were derived and the regressed medians were found to follow similar patterns to other Asian and

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Western medians. Oestriol was always lowest (even halved) while CG and AFP were intermediate. A linear reciprocal model best fitted weight distribution among Egyptians and successfully adjusted each parameter to a weight of 78.2 kg. Epidemiological monitoring of these recommendations revealed satisfactory performance in terms of 6.7% initial positive rate and 1.00 grand MoM.

Conclusions: Adoption of the above recommendations is hoped to pave the way to a successful DS screening programme tailored to Egyptian peculiarities.

Keywords: Down syndrome.

606. the Clinical Relevance and Prognostic Significance of Adenosine Triphosphate-ATP-Binding Cassette (ABCB5) and Multidrug Resistance (MDR1) Genes Expression in Acute Leukemia: An Egyptian Study

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Aim: Multidrug resistance (MDR1) represents a major obstacle in the chemotherapeutic treatment of acute leukemia (AL). Adenosine triphosphate ATP-binding cassette (ABCB5) and MDR1 genes are integral membrane proteins belonging to ATP-binding cassette transporters superfamily.

Purpose: The present work aimed to investigate the impact of ABCB5 and MDR1 genes expression on the response to chemotherapy in a cohort of Egyptian AL patients. The study included 90 patients: 53 AML cases and 37 ALL cases in addition to 20 healthy volunteers as controls.

Methods: Quantitative assessment of MDR1 and ABCB5 genes expression was performed by quantitative real-time polymerase chain reaction. Additional prognostic molecular markers were determined as internal tandem duplications of the FLT3 gene (FLT3-ITD) and nucleophosmin gene mutation (NPM1) for AML cases, and mbcr-abl fusion transcript for B-ALL cases.

Results: In AML patients, ABCB5 and MDR1 expression levels did not differ significantly between de novo and relapsed cases and did not correlate with the overall survival or disease-free survival. AML patients were stratified according to the studied genetic markers, and complete remission rate was found to be more prominent in patients having low expression of MDR1 and ABCB5 genes together with mutated NPM1 gene. In ALL patients, ABCB5 gene expression level was significantly higher in relapsed cases and MDR1 gene expression was significantly higher in patients with resistant disease.

Conclusion: In conclusion, the results obtained by the current study provide additional evidence of the role played by these genes as predictive factors for resistance of leukemic cells to chemotherapy and hence treatment outcome

Keywords: ABCB5; MDR1; AML; ALL; Egypt.

607. Evaluation of Squamous Cell Carcinoma Antigen-Immunoglobulin M Complex (SCCA-IGM) and Alpha-L-Fucosidase (AFU) as Novel Diagnostic Biomarkers for Hepatocellular Carcinoma

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Tumour Biol. 35: 11559-11564 (2014) IF: 2.84

Hepatocellular carcinoma (HCC) surveillance lacks a reliable biomarker. Alpha-fetoprotein (AFP) is the most widely used. However, not all HCCs secrete AFP.

AFP may be elevated with cirrhosis in the absence of HCC. Serum alpha-L-fucosidase (AFU) and squamous cell carcinoma antigen-immunoglobulin M complex (SCCA-IgM) were found to be useful markers in diagnosing HCC. SCCA-IgM and AFU were assessed by ELISA technique; AFP was measured by enzyme chemiluminescence in serum of 40 patients with HCC, 30 patients with liver cirrhosis, and 20 healthy control participants to compare their accuracy in early diagnosis of HCC.

Serum SCCA-IgM and AFU levels were significantly elevated in HCC group compared to cirrhotic group (P value<0.001 and <0.001, respectively). Receiver operating characteristic curve showed the optimal cutoff value for SCCA-IgM was 233 AU/ml with sensitivity 87.5% and specificity 66% and for AFU was 25 U/L with sensitivity 87.5% and specificity 98%. AFP cutoff value was 48 ng/mL with sensitivity of 70% and specificity of 53.3%. The simultaneous determination of AFP and SCCA-IgM activity increased the sensitivity to 92.5% and specificity to 62.1%. There were positive significant correlations between SCCA-IgM and each of AFU (r=0.296, P=0.005) and AFP (r=0.284, P=0.007) and no correlation between AFP and AFU. All markers did not correlate with the tumor size or affected by the Child score. The significant difference between SCCA-IgM and AFU levels among HCC and cirrhotic patients suggests their use as potential diagnostic tools and allows identifying a new group of HCC patients even in the absence of elevated AFP.

Keywords: SCCA; IGM; AFU; AFP; HCC.

608. Comparative Characteristics of Endothelial-like Cells Derived from Human Adipose Mesenchymal Stem Cells and Umbilical Cord Blood-Derived Endothelial Cells

Taghrid M. Gaafar, Hala A. Abdel Rahman, Wael Attica, Hala S. Hamza, Konrad Brockmeier and Rabab E. El Hawary

Clinical and Experimental Medicine, 14: 177-184 (2014) IF: 2.824

Adult peripheral blood contains a limited number of endothelial progenitor cells that can be isolated for treatment of ischemic diseases. The adipose tissue became an interesting source of stem cells for regenerative medicine. This study aimed to investigate the phenotype of cells obtained by culturing adipose-derived mesenchymal stem cells (ad-MSCs) in the presence of endothelial growth supplements compared to endothelial cells obtained from umbilical cord blood (UCB).

Passage 3 ad-MSCs and mononuclear layer from UCB were cultured in presence of endothelial growth media for 3 weeks followed by their characterization by flow cytometry and polymerase chain reaction. After culture in endothelial inductive media, ad-MSCs expressed endothelial genes and some endothelial marker proteins as CD31 and CD34, respectively. Adipose tissue could be a reliable source for easy obtaining, expanding and differentiating MSCs into endothelial-like cells for autologous cell-based therapy.

Keywords: Adipose tissue; Mesenchymal stem cells; Endothelial progenitor cells; Regenerative medicine.
609. Association of Cytotoxic T-Lymphocyte Antigen 4 Genetic Polymorphism, Hepatitis C Viral Infection and B-Cell Non-Hodgkin Lymphoma: An Egyptian Study

Merevat Mamdooh Khorshied, Heba Mahmoud Gouda and Ola M. Reda Khorshid

Genetic and environmental factors are involved in the pathogenesis of non-Hodgkin lymphoma (NHL). The present study aimed to investigate the association between cytotoxic T-lymphocyte antigen 4 (CTLA-4) genetic polymorphism, hepatitis C virus (HCV) infection and B-cell NHL risk in Egypt. Genotyping of CTLA-4 single nucleotide polymorphisms (SNPs) was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay for 181 adult patients with B-NHL and 200 controls. Our study revealed that CTLA-4 + 49 A/G polymorphism conferred increased risk of B-NHL (odds ratio [OR] = 1.7, 95% confidence interval [CI] = 1.36-2.565). The prevalence of HCV infection in individuals harboring the mutant genotype + 49 A/G and - 318 C/T SNPs was higher in patients with B-NHL and was associated with increased risk of B-NHL (OR = 2.79, 95% CI = 1.24-6.93 for + 49 A/G and OR = 3.9, 95% CI = 1.01-15.98 for - 318 C/T). In conclusion, some SNPs of CTLA-4 are genetic risk factors for B-NHL. Moreover, this study identified an association of CTLA-4 + 49 A/G and - 318 C/T polymorphisms with HCV infection.

Keywords: CTLA-4; Genetic polymorphism; HCV; B-NHL; Egypt.

610. Genetic Polymorphisms of Surfactant Protein D Rs2243639, Interleukin (IL)-1β Rs16944 and IL-1RN rs 2234663 in Chronic Obstructive Pulmonary Disease, Healthy Smokers, and Non-Smokers

Issac MS, Ashur W and Mousa H
Molecular Diagnosis and Therapy, 18: 343-354 (2014) IF: 2.589

Background and Objectives: Chronic obstructive pulmonary disease (COPD) is a complex chronic inflammatory disease that involves the activity of various inflammatory cells and mediators. It has been suggested that susceptibility to COPD is, at least in part, genetically determined. The primary aim of this study was to investigate the association between surfactant protein D (SFTPD) rs2243639, interleukin (IL)-1β rs16944 and IL-1 receptor antagonist (IL-1RN) rs2234663 gene polymorphisms and COPD susceptibility, as well as examining the association between various IL-1RN/IL-1β haplotypes and pulmonary function tests (PFT). Secondly, we aimed to examine the influence of SFTPD rs2243639 polymorphism on serum surfactant protein D (SP-D) level.

Methods: A total of 114 subjects were recruited in this study and divided into three groups: 63 COPD patients, 25 asymptomatic smokers, and 26 healthy controls. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was performed for the detection of SFTPD rs2243639 and IL-1β rs16944 polymorphisms. Detection of variable numbers of an 86 bp tandem repeat (VNTR) of IL-1RN was done using PCR. Serum SP-D level was measured using enzyme linked-immunosorbent assay. PFTs were measured by spirometry.

Results: Carriers of the SFTPD AG and AA polymorphic genotypes constituted 71.4% of COPD patients versus 48% in asymptomatic smokers, with a statistically significant difference between the two groups (p = 0.049). Smokers who were carriers of the polymorphic SFTPD rs2243639 A allele (AG and AA genotypes) have a 2.708 times risk of developing COPD when compared with wild-type GG genotype carriers (odds ratio (OR) 2.708 (95% CI 1.041-7.047]). Forced expiratory flow (FEF) 25-75% predicted was higher in IL-1RN *1/1 when compared with *1/2 (p = 0.013), FEF25-75% predicted in carriers of haplotype IL-1RN *1/IL-1β T (49.21 ± 10.26) was statistically significantly higher than in carriers of IL-1RN *2/IL-1β T (39.67 ± 12.64) [p = 0.005]. Forced expiratory volume in 1 s (FEV1) forced vital capacity (FVC) in carriers of haplotype IL-1RN *1/IL-1β T (64.09 ± 6.39) was statistically significantly higher than in carriers of IL-1RN *2/IL-1β T (59.44 ± 7.71) [p = 0.048]. There was no association between SFTPD rs2243639 genotypes and serum SP-D level.

Conclusions: Smokers who are carriers of the SFTPD AG and AA polymorphic genotypes may be at a higher risk of developing COPD when compared with wild-type GG genotype carriers. IL-1RN rs2234663/IL-1β rs16944 haplotypes influence FEF25-75% predicted and FEV1/FVC. SFTPD rs2243639 polymorphism did not influence serum SP-D levels in our group of recruited subjects.

Keywords: Surfactant Protein D, Interleukin -1B, IL-1RN, Copd.

611. Is There A Role for MDR1, EPHX1 and Protein Z Gene Variants in Modulation of Warfarin Dosage? A Study on A Cohort of the Egyptian Population

Issac MS, El-Nahid MS and Wissa MY
Molecular Diagnosis and Therapy, 18: 73-83 (2014) IF: 2.589

Background: There is considerable inter-individual variability in warfarin dosages necessary to achieve target therapeutic anticoagulation. Polymorphisms in genes, which master warfarin pharmacokinetics and pharmacodynamics, might influence warfarin dose variation. Genes encoding drug transporters, such as human multidrug resistance (MDR1), as well as epoxide hydrolase 1 (EPHX1), which is a putative subunit of the vitamin K epoxide reductase, and Protein Z (PZ), which is a vitamin K-dependent plasma glycoprotein, are among those candidate genes.

Objective: The purpose of this study was to investigate the contribution of MDR1 C3435T, EPHX1 H139R and Protein Z A13G gene polymorphisms in warfarin dose variation in a cohort of the Egyptian population.

Methods: Eighty-four patients whose international normalized ratio (INR) was in the range of 2-3, 41 males and 43 females, with a mean (±SD) age of 40.9 (13.3) years were recruited into this study. MDR1 C3435T, EPHX1 H139R and PZ A13G gene polymorphisms were detected by polymerase chain reaction-restriction fragment length polymorphism. Primarily, linear regression analysis, including the variables age, gender, MDR1 C3435T, EPHX1 H139R and combined MDR1 C3435T, EPHX1 H139R and PZ A13G genotypes, was used to assess the effective factors for warfarin maintenance dose. Secondly, the previously examined cytochrome P450 (CYP) 2C9 A1075C and vitamin K epoxide reductase complex subunit 1 (VKORC1) C1173T were added to the regression analysis.

Results: Warfarin dose/week was not influenced by each of the MDR1 C3435T, EPHX1 H139R, and PZ A13G gene polymorphisms when examined separately. However, when these single nucleotide polymorphisms (SNPs) were combined, MDR1 TT/EPHX1 RH,RR/PZ AA subjects showed statistically significant increase in warfarin dose/week when compared with
MDR1 CC/EPHX1 RH.RR/PZ AA subjects [median (25th-75th percentiles): 49.0 (42.0-59.5) vs. 35.0 (24.5-42.0) mg/week, respectively] (p = 0.014). In contrast, in the presence of wild-type EPHX1 HH, there was a decrease in warfarin dose/week in MDR1 TT subjects when compared with CT and CC subjects [median (25th-75th percentiles): 22.0 (17.5-30.6), 42.0 (35.0-49.0) and 42.0 (28.0-54.3) mg/week, respectively] (p = 0.005 and 0.030, respectively). Age had a significant contribution (p = 0.048) to the overall variability in warfarin dose. Calculated weekly dose = 52.928 (0.289 × age) + (9.709 × combined genotype). The multivariate linear regression equation of warfarin maintenance dose accounted for about 8 % of variation in dose (R (2) = 0.079), age accounted for 5 % of variation, while combined genotypes added the extra 3 %. However, the new regression equation accounted for 20.9 % of variation in dose. Age accounted for 5 %, while VKORC1 C1173T accounted for an extra 13 % of variation and MDR1 C3435T accounted for the remaining 3 % of variation. Calculated dose = 64.909 - (0.282 × age) - (13.390 × VKORC1) - (7.164 × MDR1).

Correlation analysis showed a close and significant relationship between the calculated and actual warfarin dose (r = 0.457; p < 0.0005).

**Conclusion:** Warfarin dose/week was significantly influenced by the combined MDR1 C3435T and EPHX1 H139R gene polymorphism since no polymorphism of PZ A-13G SNP was detected in our studied Egyptian population. Future studies with larger sample size will be needed to confirm our findings before definitive conclusions can be made.

**Keywords:** MDR1; EPHX1; Protein Z; Warfarin.

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612. Association Between Matrix Metalloproteinase 2 (MMP2) Promoter Polymorphisms and the Susceptibility To Non-Hodgkin’S Lymphoma in Egyptians

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Matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases capable of extracellular matrix degradation. MMP2 is the key molecule that control invasion, tumor growth, and metastasis, and has been associated with poor prognosis in several tumors. Several epidemiological studies have focused on the associations between MMP2 promoter polymorphisms and cancer susceptibility; however, little is known about their role in hematological malignancies. The present study aimed to investigate the association of MMP2 -735C/T and -1306C/T promoter polymorphisms with B-NHL susceptibility and their clinicopathological characteristics. The study included 100 B-NHL patients and 100 healthy controls. Genotyping of MMP2 -735C/T and MMP2 -1306C/T was done by polymerase chain reaction restricted fragment length polymorphism (PCR-RFLP) technique. MMP2 -735C/T heterozygous genotype (CT) was detected in 23 % of patients, and the homomutant genotype (TT) was detected in 7 % of patients. The polymorphic allele, T allele, was associated with susceptibility to B-NHL (OR = 2.895 %CI = 1.48-5.28). For MMP2 -1306C/T, the frequencies of the polymorphic variants were 5 % for the heterozygous genotype (CT) and 3 % for the homomutant genotype (TT). The polymorphic allele, T allele, conferred almost fourfold increased risk of B-NHL (OR = 3.8, 95 %CI = 1.05-13.9), and the risk elevated to be almost eight folds when confined to diffuse large B-cell lymphoma (DLBCL) (OR = 7.9, 95 %CI = 1.67-32.27). MMP2 -735C/T polymorphic genotypes were correlated with advanced clinical stages of the disease (stages III and IV). In conclusion, the study revealed that the variant alleles of MMP2 -735C/T and MMP2 -1306C/T can be considered as molecular risk factors for B-NHL among Egyptians.

**Keywords:** MMP2-735C/T; MMP2 -1306C/T; B-NHL; Egypt.

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613. Toll-Like Receptor 2 and 9 Genetic Polymorphisms and the Susceptibility to B Cell Non-Hodgkin Lymphoma in Egypt

Hala Aly Abdel Rahman, Mervat Mamdooh Khorsheed, Ola M. Reda Khoshid and Shirihan Mahmoud Mahgoub


Non-Hodgkin lymphomas (NHL) entail considerable heterogeneity regarding their morphology, clinical course, etiological factors, or response to therapy. Increased incidence of NHL in immunocompromised individuals and after autoimmune diseases suggests that infections and immune dysregulation could play a role in the susceptibility to NHL. Accordingly, genetic variation in Toll-like receptor (TLR) genes might be considered as molecular risk factors for NHL. The aim of the current study was to investigate the possible association between genetic polymorphism of the TLRs genes and B cell NHL (B-NHL) risk in Egypt. The present study included 100 B-NHL patients and 100 healthy controls. Genotyping of TLR2-1350 T/C and TLR9-1237 T/C were done by polymerase chain reaction restricted fragment length polymorphism (PCR-RFLP) technique. The frequency of TLR2-1350 T/C polymorphic genotypes in B-NHL patients was 18 % for the heteromutant genotype (TC) and 1 % for the homomutant (CC). There was no statistical difference in the distribution of TLR2-1350 T/C genotypes between B-NHL patients and controls. As for TLR9-1237 T/C, the frequency of the heteromutant genotype (TC) was 58 % and the homomutant genotype (CC) was 1 % in B-NHL patients. Calculated risk estimation revealed that TLR9-1237 (TC) heterotype conferred almost fourfold increased risk of B-NHL (odds ratio (OR)= 3.93, 95% confidence interval (CI)= 2.16-7.14), and the risk was higher in patients with indolent subtypes (OR=64.00, 95%CI=3.21-9.08). In conclusion, the study revealed that TLR9-1237 T/C polymorphism can be considered as molecular risk factor for B-NHL among Egyptians.

**Keywords:** TLR2-1350 T/C; TLR9-1237 T/C; B-NHL; Egypt.

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614. Gene Expression Profiling of Endometrium Versus Bone Marrow-Derived Mesenchymal Stem Cells: Upregulation of Cytokine Genes

Taghrid Gaafar, Omneya Osman, Amira Osman, Wael Atta, Hala Hamza and Rabab El Hawary


Postulated Stem/progenitor cells involved in endometrium regeneration are epithelial, mesenchymal, and endothelial. Bone marrow (BM) has been implicated in endometrial stem cells. We aimed at studying gene expression profiling of endometrial mesenchymal stem cells compared to BM MSCS to better understand their nature and functional phenotype. Endometrial tissues were obtained from premenopausal hysterectomies (n = 3), minced and enzymatically digested as well as Normal BM
aspirates (n=3). Immunophenotyping, differentiation to mesoderm, and proliferation were studied. The expression profile of 84 genes relevant to mesenchymal stem cells was performed. Fold change calculations were determined with SA Biosciences data analysis software. VEGF, G-CSF, and GM-CSF in cultures supernatants of MSCs were assayed by LumineX immunoassay. Endo MSCs possess properties similar to BM MSCs. Cumulative population doubling was significantly higher in Endo MSCs compared to BM MSCs (p < 0.001). 52 core genes were shared between both generated MSCs including stemness, self-renewal, members of the Notch, TGFβ, FGF, and WNT16 downregulated genes (VCAM, IGF1) and 16 upregulated in Endo MSCs compared to BM (p < 0.05 → fourfolds). They included mostly cytokine and growth factor genes G-CSF, GM-CSF, VWF, IL1β, GDF15, and KDR. VEGF and G-CSF levels were higher in Endo MSCs supernatants (p < 0.001). Cells sharing MSC and endothelial cell characteristics could be isolated from the human endometrium. Endo MSCs share a core genetic profile with BM MSCs including stemness. They show upregulation of genes involved in vasculogenesis, angiogenesis, cell adhesion, growth proliferation, migration, and differentiation of endothelial cells, all contributing to endometrial function.

**Keywords**: Mesenchymal stem cells; 1self-renewal 1 microarray; 1 gene expression profile; 1 endometrium; 1 bone marrow mesenchymal stem cells.

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615. FAS and FAS Ligand Gene Polymorphisms in Egyptian Females With Preeclampsia
Ahmed S. Nasr, Asmaa A. Abdel Aal, Amr Soliman, Khaled A.A.E.L. Selohey and Mona F. Shehata

with preeclampsia, investigating whether the G 670 Fas gene variant and the Fas Ligand INV2nt 124 G variant had a differential distribution in patients with preeclampsia. Thepreeclamptic group consisted of 50 pregnant women who developed preeclampsia, while the control group consisted of 50 age-matched pregnant women with uncomplicated preg-nancies.

Fas and Fas ligand gene polymorphisms were tested using polymerase chainreaction-restriction fragment length polymorphism. Regarding the Fas 670 A > G polymorphism, statistically significant differences were found between the two groups regarding the AA and GG/GG genotypes as well as the A, G allele frequency, while no statistically sig-nificant differences were found regarding AG or GG genotypes. Regarding the FasLG IVS2nt124 A > G polymorphism, no statistically significant differences were found between the two groups studied. Concerning the Fas 670 A > G gene, no statistically significant differ-ences between the severe and mild preeclampsia groups regarding the A allele frequency were found. Concerning the FasLG IVS02nt124 A > G gene, there were no statistically signif-icant differences between the severe and mild preeclampsia groups regarding the A allele frequency or the G allele frequency.

The presence of the Fas gene polymorphism Fas A670Gis associated with an increased risk of preeclampsia, while the presence of FasLG IVS2nt124 A > G gene may be protective against preeclampsia.

**Keywords**: FAS; FAS ligand genes; Gene polymorphisms.

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We report the results of an International Nosocomial Infection Control Consortium (INICC) surveillance study from January 2007-December 2012 in 503 intensive care units (ICUs) in Latin America, Asia, Africa, and Europe. During the 6-year study using the Centers for Disease Control and Prevention’s (CDC) U.S. National Healthcare Safety Network (NHSN) definitions for device-associated health care-associated infection (DA-HAI), we collected prospective data from 605,310 patients hospitalized in the INICC’s ICUs for an aggregate of 3,338,396 days. Although device utilization in the INICC’s ICUs was similar to that reported from ICUs in the U.S. in the CDC’s NHSN, rates of device-associated nosocomial infection were higher in the ICUs of the INICC hospitals: the pooled rate of central line-associated bloodstream infection in the INICC’s ICUs, 4.9 per 1,000 central line days, is nearly 5-fold higher than the 0.9 per 1,000 central line days reported from comparable U.S. ICUs. The overall rate of ventilator-associated pneumonia was also higher (16.8 vs 1.1 per 1,000 ventilator days) as was the rate of catheter-associated urinary tract infection (5.5 vs 1.3 per 1,000 catheter days).

Frequencies of resistance of Pseudomonas isolates to amikacin (42.8% vs 10%) and imipenem (42.4% vs 26.1%) were higher in the INICC’s ICUs compared with the ICUs of the CDC’s NHSN, rates of device-associated nosocomial infection were higher in the ICUs of the CDC’s NHSN, as was the rate of ventilator-associated urinary tract infection (5.5 vs 1.3 per 1,000 catheter days). Frequencies of resistance of Pseudomonas isolates to amikacin (42.8% vs 10%) and imipenem (42.4% vs 26.1%) were higher in the INICC’s ICUs compared with the ICUs of the CDC’s NHSN.

**Keywords**: Antibiotic resistance; Bloodstream infection; Catheter-associated urinary tract infection; Central line-associated bloodstream infections; Developing countries; Device-associated infection; Health care-associated infection; Hospital infection; Limited resources countries; Low income countries; Network; Nosocomial infection; Urinary tract infection; Ventilator-associated pneumonia.

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617. Blood Spot Versus Plasma Chitotriosidase: A Systematic Clinical Comparison
Mohamed A. Elmonem, Dalia I. Ramadan, Marianne S.M. Issac, Laila A. Selimb and Sara M. Elkaib
Clinical Biochemistry, 47: 38-43 (2014) IF: 2.229

**Objectives**: This study aimed to evaluate the agreement between blood spot and plasma chitotriosidase using the economic substrate 4-methylumbelliferyl β-D-N,N′,N″-triacyctethylchitotrioside, and to investigate the utility of the blood
spot assay for the wide scale screening for lysosomal storage disorders among the clinically suspected.

**Design and Methods:** Blinded blood spot samples were compared with the corresponding plasma levels in 199 children (56 with confirmed diagnoses of ten different lysosomal storage disorders, 73 normal controls and 70 pathological controls). Several performance criteria (limit of detection, linearity, within-run and day-to-day precision and sample stability) were also evaluated.

**Results:** Plasma assay performed better by most criteria; however, blood spot performance was quite satisfactory. Quantitative values of the two methods can't be used interchangeably based on their 95% limits of agreement. Diagnostic sensitivity and specificity derived from ROC curves were 75.0 and 85.3% for the plasma assay and 71.4 and 79.0% for the blood spot assay, respectively. Cohen's kappa was 0.72 (95% CI: 0.616–0.821) denoting a good categorical agreement between the two methods.

**Conclusion:** The clinical use of blood spot chitotriosidase for the screening of lysosomal storage disorders can be quite practical, provided proper cut-off values are determined for each lab. Keywords: Chitotriosidase; Dried blood spot; Lysosomal storage disorder; Clinical agreement.

**618. Factor V Leiden 1691G/A and Prothrombin Gene 20210G/A Polymorphisms as Prothrombotic Markers in Adult Egyptian Acute Leukemia Patients**

Azza Hamdy El Sissy, Maha H. El Sissy and Shereef Elmoamly

*Medical Oncology, 31(11): 1-7 (2014) IF: 2.058*

Factor V Leiden 1691G/A and prothrombin gene 20210G/A mutations are the most common genetic defects leading to thrombosis. This work aimed to study the FV Leiden and the prothrombin gene polymorphism in adult Egyptian patients with acute leukemia and their importance in thrombophilia screening. The study included 76 patients with acute leukemia and 100 healthy controls. Genotyping was done by real-time polymerase chain reaction technique. For factor V Leiden, the frequency of G/A mutation conferred more than 2.5-fold of increased risk of (OR 2.639 95% CI 1.045–6.669). The frequency of factor V Leiden combined (G/A +A/A) genotypes conferred 2.83-fold of increased risk (OR 2.828, CI 1.13–7.075). The A allele conferred almost threefold increased risk (OR 2.824, 95% CI 1.175–6.785). Despite higher frequency in patients compared to controls, there was no risk of association between prothrombin gene mutation and acute leukemia in adult Egyptians nor was there between combined genotypes of prothrombin gene mutation and factor V Leiden.

**Keywords:** Factor V prothrombin leukemia egypt.

**619. Methylene Tetrahydrofolate Reductase (MTHFR) Gene Polymorphisms in Chronic Myeloid Leukemia: An Egyptian Study**

Mervat Mamdooh Khorshied, Iman Abdel Mohsen Shaheen, Reham E. Abu Khalil and Rania Elsayed Sheir

*Medical Oncology, 31(1): 794-799 (2014) IF: 2.058*

Methylenetetrahydrofolate reductase (MTHFR) gene plays a pivotal role in folate metabolism. Several genetic variations in MTHFR gene as MTHFR-C677T and MTHFR-A1298C result in decreased MTHFR activity, which could influence efficient DNA methylation and explain susceptibility to different cancers. The etiology of chronic myeloid leukemia (CML) is obscure and little is known about individual's susceptibility to CML. In order to assess the influence of these genetic polymorphisms on the susceptibility to CML and its effect on the course of the disease among Egyptians, we performed an age-gender-ethnic matched case-control study. The study included 97 CML patients and 130 healthy controls. Genotyping of MTHFR-C677T and -A1298C was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. The results showed no statistical difference in the distribution of MTHFR-C677T and -A1298C polymorphic genotypes between CML patients and controls. The frequency of MTHFR 677-TT homozygous variant was significantly higher in patients with accelerated/blastic transformation phase when compared to those in the chronic phase of the disease. In conclusion, our study revealed that MTHFR-C677T and -A1298C polymorphisms could not be considered as genetic risk factors for CML in Egyptians. However, MTHFR 677-TT homozygous variant might be considered as a molecular predictor for disease progression.

**Keywords:** MTHFR; C677t; A1298c; CML; Pcr; Rflp.

**620. Interleukin 28B Polymorphisms and Therapy Response in Egyptian Hepatitis C Genotype-4 Patients**

Heba M. Gouda, Zainab A. El-Saadany, Neveen B. Foad and Rabab M. Salama

*DNA and Cell Biology, 33(9): 642-646 (2014) IF: 1.991*

Hepatitis C infection represents a major health problem in Egypt; only 20% of patients undergo spontaneous clearance of the virus and around 25% of all patients progress to develop cirrhosis. More than 90% of Egyptian patients have hepatitis C virus (HCV) genotype-4. Combined pegylated interferon and oral ribavirin are the current standard therapies for HCV-4. The aim of the work is to evaluate the predictive power of the rs12979860IL28B SNP and rs12980275 IL28B SNP for treatment response in Egyptian patients infected with HCV genotype 4. One hundred eleven HCV patients receiving combined treatment were studied for rs12979860 and rs12980275 polymorphisms by the restriction fragment length polymorphism technique. The rs12979860 CC and rs12979860 AA genotypes were significantly associated with sustained virological response (p=0.001). Our results suggest that studying IL28B polymorphisms contribute to proper prediction of response to standard therapies in Egyptian patients, optimizing cost effectiveness, and minimizing unneeded adverse effect of therapy.

**Keywords:** IL28- Rs12980275-Rs12979860i.

**621. Evaluation of Cytokines in Follicular Fluid and Their Effect on Fertilization and Pregnancy Outcome**

Taghrid M. Gaafar, Mariam Onsy F. Hanna, Mohamed Roshdy Hammady, Heba M. Amr, Omneya M. Osman, Aya Nasef and Amira M. Osman

*Immunological Investigations, 43: 572-584 (2014) IF: 1.903*

Cytokines in follicular fluid (FF) are important for reproduction as they modulate oocyte maturation and ovulation which influence subsequent fertilization, development of early embryo and potential for implantation. We evaluated FF cytokines in women who underwent intracytoplasmic sperm injection (ICSI)
and their association with fertilized oocytes, embryo quality and pregnancy outcome. FF belonging to 38 patients including 18 polycystic ovary (PCO) and 20 male/unexplained infertility patients were investigated for granulocyte colony stimulating factor (G-CSF), regulated upon activation normal T cell expressed and presumably secreted (RANTES), tumour necrosis factor (TNFα), interferon gamma (IFNγ) and interleukins (IL-4 and IL-2) by bead-based sandwich immunoassay. Our findings revealed that on the day of oocyte retrieval, G-CSF was positively correlated with the number of fertilized oocytes, while TNFα detection was associated with reduced number of fertilized oocytes. Only G-CSF showed significant positive effect to the pregnancy outcome although the cytokines studied were not associated with embryo quality. PCO as the cause of infertility.

**Keywords:** Follicular Fluid; G-CSf; IL-4; Intracytoplasmic sperm injection; Rantes; TNF.

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622. Frequency of CYP2C9 and VKORC1 Gene Polymorphisms and Their Influence on Warfarin Dose in Egyptian Pediatric Patients

Mennat-Allah Kamal El-Din, Marwa Salalh Farhan, Randa Ibrahim El Shiha, Rania Mohammed Helmy El-Kaffas and Somaia Mohammed Mousa

**Pediatric Drugs, 16(4): 337-341 (2014) IF: 1.721**

**Introduction:** Warfarin is a widely used anticoagulant that shows a high inter-individual variability in the dose needed to achieve target anticoagulation. In adults, common genetic variants in the cytochrome P450-2C9 (CYP2C9) and vitamin K epoxide reductase complex (VKOR1) enzymes, in addition to non-genetic factors, explain this dose variability. In children, data about warfarin pharmacogenetics are limited and inconsistent.

**Methods:** CYP2C9 (*2 and *3) alleles and the VKORC1 (C1173T and G-1639A) polymorphisms were studied by multiplex real time polymerase chain reaction in 41 pediatric patients who received stable warfarin maintenance dose.

**Results:** The allele frequency of the studied genes was CYP2C9*2 (0.085), CYP2C9*3 (0.12), VKORC1 1173T (0.52), and VKORC1 -1639A (0.54). In univariate analysis, patients’ age, weight, and height were significantly (p < 0.0001) associated with warfarin maintenance dose. However, CYP2C9 and VKORC1 gene polymorphisms did not affect warfarin dose. In multivariate analysis, age was found to be the only significant determinant of daily warfarin maintenance dose (p = 0.045).

**Conclusion:** Age was the most significant determinant of warfarin dosage in this preliminary study including Egyptian pediatric patients. Further studies involving larger numbers of children are warranted to determine the true impact of genetic factors on warfarin doses in pediatric patients.

**Keywords:** CYP2C9; VKORC1; Warfarin.

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623. Tumor Necrosis Factor-A -308G/A Gene Polymorphism in Egyptian Children With Immune Thrombocytopenic Purpura

Maha H. El Sissy, A.H. El Sissy and Sherif Elanwary


Immune thrombocytopenic purpura (ITP) is an autoimmune disease characterized by increased platelet destruction. Although the cause of ITP remains unclear, it is accepted that both environmental and genetic factors play an important role in the development of the disease. Children with ITP have a T-helper 1-type cytokine pattern with elevated levels of tumor necrosis factor-alpha (TNF-a) as in most autoimmune diseases. Researchers have shown that polymorphism in the TNF-a gene at position S308 affects gene transcriptions with increased TNF-a production. The current case–control study aimed at detecting the frequency of TNF-a S308GA gene polymorphism as genetic markers in Egyptian children with ITP, and to clear out their possible role in choosing the treatment protocols of therapy, using PCR restriction fragment length polymorphism assay. Ninety-two ITP patients and 100 age and sex-matched healthy controls were recruited in the study. The results obtained revealed that the frequency of TNF-a S308/A homotype in ITP patients was significantly higher than that of the controls, and conferred almost six-fold increased risk of ITP acquisition. The polymorphic A allele frequency was significantly higher in ITP patients than in the controls, conferring almost two-fold increased ITP risk. In conclusion, our study suggests the possibility that TNF-a S308 gene polymorphism may contribute to the susceptibility of childhood ITP in Egyptian children. Blood Coagul Fibrinolysis 25:000–000 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

**Keywords:** ITP Egyptian Tumor Necrosis Factor-Alpha; Immune Thrombocytopenic Purpura.

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624. Risk Factors of Prolonged Hospital Stay in Children With Viral Severe Acute Respiratory Infections

El Kholy AA, Mostafa NA, Ali AA, El-Sherbini SA, Ismail RI, Magdy RI, Soliman MS and Said MM.

**Journal of Infection in Developing Countries, 15: 1285-93 (2014) IF: 1.267**

**Introduction:** Severe acute lower respiratory infections (SARIs) are one of the major causes of morbidity and mortality in young children, especially in developing countries. The present study focused on detection of risk factors for prolonged hospital stays among children with viral SARIs.

**Methodology:** A sentinel surveillance study was conducted at Cairo University Hospital (CUH) between February 2010 and May 2011. Nasopharyngeal (NP) and oropharyngeal (OP) swabs were collected from all children admitted with SARIs. Viruses were identified using reverse transcription polymerase chain reaction (RT-PCR).

**Results:** Out of 1,046 children, 380 (36%) were positive for one or more viruses; these included respiratory syncytial virus (RSV) (22.9%), adenovirus (6.2%), parainfluenza viruses (PIVs1-3) (5.1%), human metapneumovirus (HMPV) (4.5%), influenza A (1.4%), and influenza B (0.6%). Viral etiology was mainly detected in children under one year of age (88.9%). Prolonged length of stay was independently associated with the presence of cyanosis and underlying chronic illness (OR 7.4, CI: 1.8-30.32 [p = 0.005], OR 2.5, CI: 1.36-4.64 [p = 0.004], respectively). Virus type did not affect the length of hospital stay (p > 0.05). Oxygen therapy was required in 91% of the patients. A total of 43 patients (11.6%) required intensive care admission. Twenty-one patients (5.5%) died, and 15 of them (71.4%) had an underlying chronic illness.
Conclusions: The study demonstrated the important burden of respiratory viruses as a cause of SARI in hospitalized children in a tertiary Egyptian hospital. Cyanosis and underlying chronic illness were significantly associated with prolonged length of stay.
Keywords: Respiratory Viruses; Children; SARI; Prolonged Stay.

625. Association of the Luteinizing Hormone/Choriogonadotropin Receptor Gene Polymorphism With Polycystic Ovary Syndrome
Yasmin Ahmed Bassiouny, Walaa Ahmed Rabie, Ayman Ahmed Hassan and Rania Kamal Darwish
This study aimed at evaluating possible associations of the single nucleotide polymorphism (SNP) in luteinizing hormone/choriogonadotropin receptor (LH/CG) gene G935A and polycystic ovary syndrome (PCOS) phenotype. The study included 100 PCOS female patients and 60 healthy female control subjects. The patients were recruited from the Gynecology outpatient clinic, Kasr Al-Aini Hospital, Cairo University. All candidates underwent full history taking and clinical examination with calculation of body mass index. Serum and EDTA samples were collected from each patient after a written consent. A hormonal profile was done for each patient as well as DNA analysis of the G935A polymorphism of LH/CGR gene. In PCOS group, 26% were homozygous (AA), 27% were heterozygous (GA) and 47% were wild genotype (GG), while in controls 30% were heterozygous and 70% were wild genotype (OR: 2.25; CI: 1.16-4.386; p value: 0.012). The homozygous 935A individuals were at higher risk to develop PCOS than controls (OR: 1.80; CI: 1.54-2.09; p value50.001). We found a genetic variant, which is associated with PCOS in a sample of the Egyptian population. These results may provide an opportunity to test this SNP at the LH/CG gene in fertile or infertile women with family history to assess their risk of PCOS.
Keywords: G935A Polymorphism; Genetic factors; Luteinizing hormone/choriogonadotropin receptor gene; Polycystic ovary syndrome; Polymerase chain reaction-restriction Fragment Length Polymorphism Technique; Single nucleotide polymorphism.

626. Detection of Trisomy 4 and 10 in Egyptian Pediatric Patients With Acute Lymphoblastic Leukemia
Somaia Mousa, Shady Mostafa, Iman Shaheen and Esam Elnoshokaty
Clinical Laboratory, 60 (4): 609-614 (2014) IF: 1.084
Background: Improvement in cure rates for children with acute lymphoblastic leukemia (ALL) has focused attention on better methods of identifying patients with increased or decreased risk of treatment failure. Chromosome aberrations have a major role in pediatric ALL risk assessment. The aim of this work is to detect the frequency of trisomy 4 and 10 in Egyptian pediatric ALL patients and to analyze their possible prognostic significance.
Methods: Forty newly diagnosed pediatric ALL patients were subjected to bone marrow aspirate morphological examination and immunophenotyping. Detection of copy number of chromosome 4 and 10 was done using Fluorescence In Situ Hybridization (FISH) technique using whole chromosome painting probes.
Results: Combined trisomy 4 and 10 was detected in 7 cases (17.5%), all of them were of B-ALL type. Single trisomy 4 or 10 was not detected in any case. Trisomy positive patients had a statistically significant lower total leucocytic count (p = 0.041), higher platelet count (p = 0.018), and lower blast percentage in peripheral blood (p = 0.016) at diagnosis.
Conclusions: Combined trisomy 4 and 10 identifies a group of ALL patients that have good prognostic indicators. Screening of Egyptian pediatric ALL patients for trisomy 4 and 10 may help in “patients’ stratification” aiming to develop a risk-adapted therapy in order to minimize therapy related morbidities particularly in children.
Keywords: Acute Lymphoblastic Leukemia, Trisomy 4, Trisomy 10, FISH, Prognosis.

627. Plasma Annexin A5, Anti-Annexin A5 Antibodies and Annexin A5 Polymorphism in Egyptian Female Patients With Systemic Lupus Erythematosus and Antiphospholipid Syndrome
Aya Nasef, Mona Ibrahim, Nermin Riad and Somaia Mousa
Clinical Laboratory, 60 (1): 133-137 (2014) IF: 1.084
Background: Annexin A5 exhibits anticoagulant properties that appear to be defective in patients with antiphospholipid syndrome (APS) resulting in repeated thrombosis and recurrent pregnancy loss (RPL). APS occurs frequently in association with systemic lupus erythematosus (SLE). The present study aimed to find out a possible relationship between annexin A5 (gene polymorphism, antibodies or plasma level) and the pathophysiology of SLE, APS and RPL.
Methods: 47 female patients divided into 3 groups (SLE, APS and RPL) and 20 healthy controls are included in the study. Detection of annexin A5 (-1C/T) gene polymorphism was done by Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) assay. Anti-annexin A5 antibodies (IgG and IgM) and annexin A5 plasma level were measured by Enzyme Linked Immunosorbent Assay (ELISA).
Results: The frequency of annexin A5 (-1C/T) polymorphism was significantly higher in SLE related groups (p = 0.02), but it did not correlate with RPL (p =0.57) or annexin A5 level (p = 0.5). Anti-annexin A5 IgM level was significantly higher among APS patients and was associated with RPL (p = 0.005, odds ratio =23.75, 95% confidence interval = 2.15 - 262.48).
Conclusions: Annexin A5 (-1C/T) gene mutation may play a role in the pathophysiology of SLE. Anti-annexin A5 IgM was the antibody associated with RPL in this group of APS patients. Annexin A5 plasma levels are not affected by the presence of annexin A5 (-1C/T) polymorphism.
Keywords: Annexin A5; Annexin A5 (-1C/T) Polymorphism; Systemic Lupus Erythematosus; Antiphospholipid Syndrome; Recurrent Pregnancy Loss.

628. Low Incidence of Adamts13 Missense Mutation R1060w in Adult Egyptian Patients Withthrombotic Thrombocytopenic Purpura
Maha H. El Sissy, A. Abd El Hafez and A.H. El Sissy
Thrombotic thrombocytopenic purpura (TTP) is an acute lifethreatening disorder, characterized by thrombocytopenia, microangiopathic hemolytic anemia, widespread microvascular thrombi and consequent clinical sequelae due to ischemic organ damage. TTP is most commonly associated with deficiency or inhibition of von Willebrand factor-cleaving protease (ADAMTS13) activity. ADAMTS13 mutations and polymorphisms have been reported in childhood congenital TTP, but their significance in adult-onset TTP is still under investigation. Two mutations stand out: the single base insertion 4143insA in exon 29 and the missense mutation R1060W. Six cases (84%) presented with acute idiopathic TTP, 2 cases were drug abusers and 3 cases were pregnant. None of the study cases provided a history of suspicious TTP symptoms during childhood (2 cases gave a history of episodes of thrombocytopenia during childhood). All cases showed statistically significant decreased ADAMTS13 activity compared to normal controls (p < 0.001). The study revealed a high statistical difference regarding the ADAMTS13 inhibitor level in primary versus secondary cases (p = 0.003). None of our Egyptian cases or of the healthy normal controls are positive for exon 24 missense mutation. Larger studies and regional and national TTP registries are recommended.

Keywords: ADAMTS13; Missense mutation R1060W; Thrombotic thrombocytopenic Purpura.

630. Association of Interferon-γ Inducible Protein-10 Pretreatment Level and Sustained Virological Response in Hcv-Positive Egyptian Patients

Omran D., Hamdy S., Tawfiq S., Esmat S., Saleh D.A. and Zayed R.A.


Background: The response to antiviral therapy in HCV infected patients depends on several predictive factors; however, the ability to achieve sustained virological response is still limited to around 60% of the patients infected with the HCV-4 genotype. Increased serum and intrahepatic interferon-γ inducible protein 10 (IP-10) levels in patients with chronic hepatitis C have been described. The aim of the work was to study the impact of pretreatment serum IP-10 level on the antiviral treatment outcome in a group of Egyptian patients infected with HCV.

Materials and Methods: The study included 80 treatment naïve HCV patients. Serum IP-10 levels were determined by an enzyme linked immunosorbent assay before therapy was introduced. Serum samples were examined twice by Real-Time PCR after complete course of therapy for detection of HCV RNA; at the end of the antiviral therapy and six months later to detect sustained virological response (SVR). Results. 57 patients (71%) achieved SVR while 23 (29%) patients were non-responders (NR). Pretreatment serum IP-10 levels were significantly lower in patients who achieved SVR than in NR (p=0.000).

Conclusion: Low pretreatment serum IP-10 is a favorable predictive of response to antiviral HCV therapy in Egyptian patients.

Keywords: HCV; Predictors, Response, Therapy, Ip-10

631. Mesenchymal Stem Cells from Pediatric Patients With Aplastic Anemia: Isolation, Characterization, Adipogenic, and Osteogenic Differentiation

Eman Refaat El-Mahgoub, Ebtisam Ahmed, Reham Abd-El Aleem Afifi, Mennat-Allah Kamal and Somaia Mohammed Mousa

Fetal and Pediatric Pathology, 33(1): 9-15 (2014) IF: 0.398

Aplastic anemia is a syndrome of bone marrow (BM) failure characterized by peripheral pancytopenia and marrow hypoplasia. Its exact pathophysiology is still not clear. Mesenchymal stem cells (MSCs) play an important role in providing the specialized BM microenvironment for hematopoietic stem cells survival and differentiation. MSCs were isolated from BM of five patients with aplastic anemia and five controls. MSCs were characterized by morphology and immunophenotyping. Their viability, proliferative capacity, and adipogenic as well as osteogenic differentiation potentials were assessed. MSCs from aplastic anemia patients and controls shared similar spindle-shaped morphology and surface marker expression. MSCs derived from patients with aplastic anemia showed lower viability (74.2 ± 4.44%/vs. 97.0 ± 1.58, p < 0.0001) and slower expansion rate as indicated by smaller population doubling and smaller cumulative population doubling from passages 1 to 4 (0.70 ± 0.22 vs. 2.34 ± 0.84; p = 0.009). Besides, aplastic anemia MSCs had poor capacity to differentiate into adipocytic and osteocytic lineages.
Keywords: Aplastic anemia; Hematopoiesis; Mesenchymal stem cells; Bone marrow microenvironment.

Dept. of Clinical Oncology and Nuclear Medicine

632. Second Cancer Risk After 3D-CRT, IMRT and VMAT for Breast Cancer

Purpose: Second cancer risk after breast conserving therapy is becoming more important due to improved long term survival rates. In this study, we estimate the risks for developing a solid second cancer after radiotherapy of breast cancer using the concept of organ equivalent dose (OED).

Materials and Methods: Computer-tomography scans of 10 representative breast cancer patients were selected for this study. Three-dimensional conformal radiotherapy (3D-CRT), tangential intensity modulated radiotherapy (t-IMRT), multibeam intensity modulated radiotherapy (m-IMRT), and volumetric modulated arc therapy (VMAT) were planned to deliver a total dose of 50 Gy in 2 Gy fractions. Differential dose volume histograms (dDVHs) were created and the OEDs calculated. Second cancer risks of ipsilateral, contralateral lung and contralateral breast cancer were estimated using linear, linear-exponential and plateau models for second cancer risk.

Results: Compared to 3D-CRT, cumulative excess absolute risks (EAR) for t-IMRT, m-IMRT and VMAT were increased by 2 ± 15%, 131 ± 85%, 123 ± 66% for the linear-exponential risk model, 9 ± 22%, 82 ± 96%, 71 ± 82% for the linear and 3 ± 14%, 123 ± 78%, 113 ± 61% for the plateau model, respectively.

Conclusion: Second cancer risk after 3D-CRT or t-IMRT is lower than for m-IMRT or VMAT by about 34% for the linear model and 50% for the linear-exponential and plateau models, respectively.

Keywords: Breast cancer; Intensity modulated radiation therapy (IMRT); Organ equivalent dose (OED); Second cancer risk.

633. INTRAGO: Intraoperative Radiotherapy in Glioblastoma Multiforme–A Phase I/II Dose Escalation Study
Frank A Giordano, Stefanie Brehmer, Yasser Abo-Madyan, Grit Welzel, Elena Sperk, Anke Keller, Frank Schneider, Sven Clausen, Carsten Herskind, Peter Schmiedek and Frederik Wenz
BMC Cancer, 14: (2014) IF: 3.319

Background: Glioblastoma multiforme (GBM) is the most frequent primary malignant brain tumor in adults. Despite multimodal therapies, almost all GBM recur within a narrow margin around the initial resected lesion. Thus, novel therapeutic intensification strategies must target both, the population of dispersed tumor cells around the cavity and the postoperative microenvironment. Intraoperative radiotherapy (IORT) is a pragmatic and effective approach to sterilize the margins from persistent tumor cells, abrogate post-injury proliferative stimuli and to bridge the therapeutic gap between surgery and radiochemotherapy. Therefore, we have set up INTRAGO, a phase I/II dose-escalation study to evaluate the safety and tolerability of IORT added to standard therapy in newly diagnosed GBM. In contrast to previous approaches, the study involves the application of isotropic low-energy (kV) x-rays delivered by spherical applicators, providing optimal irradiation properties to the resection cavity.

Methods/Design: INTRAGO includes patients aged 50 years or older with a Karnofsky performance status of at least 50% and a histologically confirmed (frozen sections) supratentorial GBM. Safety and tolerability (i.e., the maximum tolerated dose, MTD) will be assessed using a classical 3 + 3 dose-escalation design. Dose-limiting toxicities (DLT) are wound healing deficits or infections requiring surgical intervention, IORT-related cerebral bleeding or ischemia, symptomatic brain necrosis requiring surgical intervention and early termination of external beam radiotherapy (before the envisaged dose of 60 Gy) due to radiotoxicity. Secondary end points are progression-free and overall survival.

634. Differentiated Thyroid Carcinoma: An Analysis of 249 Patients Undergoing Therapy and Aftercare At A Single Institution
Amin A, Badwey A and El-Fatah S.

Purpose: Well-differentiated thyroid cancer (WDTC) is rising in incidence across the world over the past 3 decades. We aimed to evaluate the natural history and clinical outcome of differentiated thyroid carcinoma by a retrospective analysis of 249 patients treated at a single institution.

Methods: A cohort of 249 patients who underwent thyroidectomy for WDTC in the last 10 years in Maadi Military Hospital was studied. Main outcome measures were clinical management at the diagnosis, survival, morbidity, and prognostic risk factors.

Results: Mean age at diagnosis was 44.7 (SD, 14.6) years, where 52.2% were 45 years or older. Females represent 70.7% (P = 0.01), with female-to-male ratio of 4.1:1. Near-total thyroidectomy was done in 70.7% of the cases where papillary cancer was found in 80.8% and node metastasis in 10.5%. Radioactive 131I (RA 131I) was given an all cases (dose range, 80Y150 mCi) with ablation success rate of 79.2% delivered by spherical applicators, providing optimal irradiation properties to the resection cavity.

Methods/Design: INTRAGO includes patients aged 50 years or older with a Karnofsky performance status of at least 50% and a histologically confirmed (frozen sections) supratentorial GBM. Safety and tolerability (i.e., the maximum tolerated dose, MTD) will be assessed using a classical 3 + 3 dose-escalation design. Dose-limiting toxicities (DLT) are wound healing deficits or infections requiring surgical intervention, IORT-related cerebral bleeding or ischemia, symptomatic brain necrosis requiring surgical intervention and early termination of external beam radiotherapy (before the envisaged dose of 60 Gy) due to radiotoxicity. Secondary end points are progression-free and overall survival.

635. Response Rate and Factors Affecting the Outcome of A Fixed Dose of Iodine-131 Therapy in Graves' Disease: A 10-Year Egyptian Experience
El-Kareem MA, Derwish WA and Moustafa HM.

The aim of this study was to evaluate response and compare the success rate of two different doses of iodide-131 (1131I) therapy in the treatment of Graves’ disease and investigate the factors that may affect outcome. A retrospective analysis was carried out on
321 patients treated with (131)I for Graves' disease. Group 1 (155 patients) received 8 mCi and group 2 (166 patients) received 12 mCi. The therapy was considered successful if euthyroidism or hypothyroidism was achieved within 1 year of therapy. The outcome was compared with multiple parameters. A significant difference in the outcome between the two groups was found in favor of the second group (P<0.001). Logistic regression analysis showed that lower dose, technetium-99m pertechnetate thyroid uptake greater than 20.9%, and moderate and marked goiter were independent variables associated significantly with a lower response rate (odds ratio 2.601, 4.023, and 3.309, respectively), whereas previous surgical treatment was associated with a higher response rate (odds ratio 3.071). No correlation was found between outcome and age, presence of exophthalmos, previous treatment with methimazole, and its duration. The response rate to the second dose was significantly increased compared with the first one by 27.8%; there was no correlation among the above-mentioned factors and its outcome. The third dose controlled the disease in 81.3% of the remaining patients and control was achieved in the rest after the fourth dose. (131)I is a very effective therapy for Graves' disease, with a cure rate of 100% after four doses. Higher first dose activity is recommended in the presence of poor prognostic factors. The second dose is not necessarily increased in the nonresponders.

**Keywords:** Fixed dose; Graves' disease; Radioactive iodine therapy; Tc-99 Pertechnetate Thyroid Uptake.


Frank Schneider, Sven Clausen, Johannes Thöllking, Frederik Wenz and Yasser Abo-Madyan

*Journal of Applied Clinical Medical Physics, 15 (1): (2014) IF: 1.11*

The use of IORT as a treatment modality for patients with close or positive margins has increased over the past decade. For situations where a flat area (up to 6 cm in diameter) has to be treated intraoperatively, new applicators for superficial treatment with a miniature X-ray source (INTRABEAM system) were developed. Here we report our evaluation of the dosimetric characteristics of these new applicators and their clinical use. Each of these flat and surface applicators consists of a radiation protective metal tube and a flattening filter, which converts the spherical dose distribution of the X-ray source into a flat one. The homogeneity of each dose distribution and depth-dose measurements were evaluated using film dosimetry in a solid water phantom and a soft X-ray ionization chamber in a water tank. The first patient was treated with 5 Gy delivered in 5 mm using a 4 cm FLAT applicator over 21 minutes. The flat applicators show the maximum homogeneity, with a uniformity ratio of 1.02–1.08 in certain depths. In 1 mm depth surface applicators show a uniformity ratio of 1.15–1.28. They also show a higher dose rate and a steeper dose gradient compared to the flat applicators. The results of this investigation demonstrated that the flat and surface applicators have unique dosimetric characteristics that need to be considered during the treatment planning stages. This work also showed that it is possible to perform a superficial localized IORT which provides new application possibilities for use of the INTRABEAM system.

**Keywords:** Intraoperative radiotherapy; Electronic brachytherapy; X-ray; INTRABEAM radiotherapy system; Superficial radiotherapy.

Dept. of Clinical Pathology

637. Detection of Expression of IL 18 and Its Binding Protein in Egyptian Pediatric Immune Thrombocytopenic Purpura

Shahira Kamal Anis Botros

*Platelets, 25: 193-196 (2014) IF: 2.627*

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder, characterized by dysfunctional cellular immunity including the presence of activated platelet specific autoreactive T cells that recognize and respond to autologous platelet antigens. Autoreactive T cells drive the generation of platelet reactive autoantibodies by B cells as well as T-cytotoxic cell-mediated lysis of platelets. Interleukin-18 (IL-18) is a mediator of T helper type 1 cell responses synergistically with IL-12 that initiate and promote host defense and inflammation. IL-18 has a specific binding protein (IL-18BP) which belongs to the immunoglobulin superfamily. In the present study, serum level and messenger RNA (mRNA) expression of IL-18 as well as IL-18BP mRNA expression were measured in peripheral blood mononuclear cells (PBMCs) of 100 Egyptian pediatric patients with ITP (70 acute and 30 chronic). In addition to this, we recruited 80 healthy volunteers in order to investigate the possible association between the imbalance of IL-18 and IL-18 BP expressions and the pathogenesis of ITP. IL-18 serum level and mRNA expression were not elevated in cases more than in the control group, but IL-18 mRNA was higher in chronic cases when compared to the acute ones (p<0.031) and there was a good negative correlation between the platelet count and serum IL-18. IL-18 BP m-RNA was slightly elevated in cases more than in the control group (95% Confidence interval±41.15–2.01). Our results were not supportive for previous findings of elevated IL18/18BP mRNA ratio in ITP patients. This could be referred to the fact that autoimmune diseases are complex genetic disorders, therefore further studies on polymorphisms affecting IL-18 gene expression as well as kinetics of IL-18 expression are required to evaluate the role of interleukin 18 and its binding protein in the pathogenesis of ITP.

**Keywords:** ITP, IL-18, Peripheral Blood Mononuclear Cells.

638. Immunoregulatory Cytokines Gene Polymorphisms in Egyptian Patients Affected With Acquired Aplastic Anemia

Iman R. El Mahgoub, Reham A. Aleem Afify, Shahira K. A. Botros and Rania Fawzy

*Ann Hematol, 93: 923-929 (2014) IF: 2.396*

The immune system is thought to play an important role in aplastic anemia (AA) in light of recent findings of hematologic reconstitution after immunosuppressive therapy. T cell activation, apoptosis, and the cytokines interferon- and TNF-α are suspected to play a role in the suppression of growth of progenitor cells and induced apoptosis in CD34 target cells, TGFβ is a multifunctional peptide, usually produced in latent form and requiring activation to produce a biological response. Also, TGF-β1 has been described as an important negative regulator of haemopoiesis.
Over production of IL-6 is described in AA but is of unknown pathophysiologival significance. To investigate the role of cytokine gene polymorphisms (IL-6/-174, TNF-α/-308, IFN-γ/-874, and TGFβ1/-509) in patients with acquired AA to assess if genotypes associated with higher or lower production were more prevalent than in established control population and to study the possible association of these genotypes with the disease severity. Fifty AA patients were included in this study. Polymerase chain reaction-amplification refractory mutation system (PCR–ARMS) technique was used to detect IFN-γ single nucleotide polymorphism –874A/T, and polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) was used to assess IL-6-174 C/G, TNF-α-308G/A, and TGFβ1-509C/T gene polymorphisms. Genotypes associated with high production of TNF-α, TGF-β and IFN-γ, and IL-6 were more frequent in patients than in control; no association was found between the presence of hypersecretory genotypes and the disease severity.

Keywords: Aplastic anemia; TNF-α; IFN-γ; IL-6; TGF-β; Cytokine gene polymorphism.

**639. Evaluation of Broad-Range 16S rRNA PCR for the Diagnosis of Bloodstream Infections: Two Years of Experience**

Hassan RM, El Enany MG and Rizk HH

*Journal of Infections In Developing Countries, 8 (10): 1252-1258 (2014) IF: 1.267*

**Introduction:** Diagnosis of bloodstream infections using bacteriologic cultures suffers from low sensitivity and reporting delay. Advanced molecular techniques introduced in many laboratories provide rapid results and may show improvements in patient outcomes. This study aimed to evaluate the usefulness of a molecular technique, broad-range 16S rRNA PCR followed by sequencing for the diagnosis of bloodstream infections, compared to blood culture in different patient groups.

**Methodology:** Conventional PCR was performed, using broad-range 16S rRNA primers, on blood cultures collected from different patients with suspected bloodstream infections; results were compared with those of blood culture.

**Results:** Though blood culture is regarded as the gold standard, PCR evaluation showed sensitivity of 86.25%, specificity of 91.25%, positive predictive value of 76.67%, negative predictive value of 95.22%, and accuracy of 88.8%.

**Conclusions:** Molecular assays seem not to be sufficient to replace microbial cultures in the diagnosis of bloodstream infections, but they can offer a rapid, good negative test to rule out infection due to their high negative predictive value.

**Keywords:** Blood stream infection; Blood cultures; 16S rRNA; PCR.

**640. Stromal Cell Derived Factor-1 (CXCL12) Chemokine Gene Variant in Myeloid Leukemias**

Hoda Mohamed A, El-Ghany, Zainab Ali El-Saadany, Neiven Mohamed Bahaa, Noha Yehia Ibrahim and Salwa Mahmoud Hussien

*Clinical Laboratory, 60: 735-741 (2014) IF: 1.084*

**Background:** Acute and chronic myeloid leukemia are initiated and sustained by a small, self-renewing population of leukemic stem cells, which produce progeny of a heterogeneous population of progenitor cells. CXCL12, a chemokine abundantly produced by the bone marrow microenvironment, and its receptor CXCR4 have crucial roles in malignant cell trafficking. We set out to determine the CXCL12 gene polymorphism at codon G801A and evaluate its influence on malignant cell dissemination and tissue infiltration in myeloid leukemias. Methods: Genotyping for CXCL12 was done by restriction PCR-RFLP for 48 myeloid leukemia patients: 38 de novo AML and 10 CML. Fifty age and gender matched volunteers were evaluated as controls.

**Results:** Regarding AML patients, the frequency of wild genotype was 50% and the heterozygous genotype was 50%. In CML patients, the frequency of wild genotype was 30% while the heterozygous genotype was 70%. In the control group, 57.2% had wild genotype while 42.8% had heterozygous genotype with no significant difference detected between myeloid leukemia patients and the control group. There was a statistically insignificant association between wild and heterozygous genotypes regarding clinical, laboratory data and extramedullary dissemination.

**Conclusions:** CXCL12 polymorphism is not associated with either increased myeloid leukemia risk or extramedullary blast dissemination.

**Keywords:** CXCL12; AML; CML; RFLP-PCR.

**641. MDM2 SNP309 and P53 Codon 72 Genetic Polymorphisms and Risk of AML: An Egyptian Study**

Nabil Mohsen El-Danasouri, Shadia Hassan Ragab, Maha Ameen Rasheed, Zainab Ali El-Saadany and Safa Nabil Abd El-Fattah

*Annals of Clinical and Laboratory Science, 44: 449-454 (2014) IF: 0.839*

**Background:** Acute myeloid leukemia (AML) is a heterogeneous disease with numerous genetic abnormalities corresponding to a variety of subtypes, p53 is involved in multiple cellular pathways including apoptosis, transcriptional control, and cell cycle regulation. A single nucleotide polymorphism (SNP) at codon 72 of the p53 gene is associated with the risk for development of various neoplasms. MDM2 SNP309 is a single nucleotide T to G polymorphism located in the MDM2 gene promoter, which enhances the expression of MDM2 protein and thereby leads to attenuation of the p53 stress response.

**Objective:** The current study aimed to define the roles of MDM2 and p53 genetic polymorphisms with the risk of AML.

**Methodology:** Genotyping for MDM2 was done by AS-PCR technique while p53 codon 72 genotyping was done by PCR-RFLP for 50 patients and 50 controls.

**Results:** The study did not detect any significant differences regarding MDM2 or p53 polymorphisms in AML cases, as compared to controls. A borderline significance was found between cases and controls regarding combined MDM2 T/G and p53 genotyping. MDM2 variant genotype was significantly associated with a younger age group and lower Hb level, while the P53 variant was significantly associated with less frequent CD117 expression.

**Keywords:** MDM2; P53 codon 72; AML; AS-PCR; RFLP-PCR.
Dept. of Dermatology

642. Olopatadine Hydrochloride Decreases Tissue Interleukin-31 Levels in An Atopic Dermatitis Mouse Model

Murota H, El-latif MA, Tamura T and Katayama I


Atopic dermatitis (AD) is an inflammatory skin disease characterized by an intensely pruritic skin rash (1). A variety of mediators, including histamine and neuropeptides, are involved in pruritus. We previously reported that olopatadine hydrochloride (olopatadine), a histamine H1 receptor antagonist, significantly suppresses the number of scratching events associated with a decreasing number of intraepidermal nerve fibres via increased semaphoring 3A expression and decreased nerve growth factor (NGF) levels in NC/Nga mice (2). Oral olopatadine (Kyowa Hakko Kirin, Tokyo, Japan) has been prescribed in Japan and Korea for treatment of allergic rhinitis, urticarial, pruritus, eczema, prurigo, psoriasis vulgaris, and erythema multiforme, which was covered by insurance. Recently, interleukin (IL)-31 was found to play a role in pruritus and skin barrier function in AD (3–5). It was reported that transgenic mice overexpressing IL-31 exhibit spontaneous pruritus and develop severe dermatitis (6). Moreover, serum and tissue IL-31 levels in patients with AD were increased compared with levels in control subjects, and IL-31 levels correlated with both disease activity and severity of AD (3, 7–9). Thus, we evaluated the effect of olopatadine on tissue IL-31 levels in an AD model using NC/Nga mice.

Keywords: Olopatadine; Interleukin; 31; Atopic dermatitis.

643. Beyond Vitiligo Guidelines: Combined Stratified/Personalized Approaches for the Vitiligo Patient

Anbar TS, Hegazy RA, Picardo M and Taieb A.


‘Vitiligo’ is a word that bears endless possibilities and no promises. Each vitiligo patient has a different story that demands a different therapeutic approach. Even though great efforts have been made to evaluate, study, compare and document the different therapeutic modalities available for vitiligo, clearly handling their modes of actions as well as their side effects and establishing clear stratified guidelines, numerous dilemmas are frequently met on practical grounds. ‘Stabilize’, ‘repigment’, ‘depigment’ or ‘camouflage’? ‘for whom and how do we achieve the best results?’ ‘Separately or in combination?’ – questions that need to be answered and decisions need to be taken in the appropriate timing and altered when the necessity arises. In the current viewpoint, we have utilized the available knowledge and exploited years of experience in an attempt to go beyond the guidelines to set the rationale for an optimal and personalized therapy, within the framework of a stratified approach.

Keywords: Guidelines; Repigmentation; Stabilization; Treatment; Vitiligo.

644. T Helper 17 and Tregs: A Novel Proposed Mechanism for NB-UVB in Vitiligo

Hegazy RA, Fawzy MM, Gawdat HI, Samir N and Rashed LA.


Narrowband ultraviolet (NB-UVB) is accepted as a cornerstone therapy for vitiligo. Its influence on the expression of IL-17, IL-22 and FoxP3 as markers for the Th17 and Tregs lineages has not been studied before in the context of non-segmental vitiligo (NSV). The study included 20 active NSV patients who received 36 NB-UVB sessions and 20 controls. Clinical evaluation Vitiligo Area Scoring Index (VASI) and determination of tissue expression of IL-17, IL-22 and FoxP3 by qRT-PCR (lesional, perilesional) were carried out before and after therapy. Baseline levels of IL-17 and IL-22 were significantly higher in patients, whereas FoxP3 was significantly lower. After therapy, IL-17 and IL-22 significantly dropped, whereas FoxP3 significantly increased (lesional, perilesional). Baseline and post-treatment VASI showed significant positive correlations with IL-17 and IL-22 and significant negative correlation with FoxP3 expression. Restoration of the balance between Th17 and Tregs might represent a novel pathway for the improvement that NB-UVB exerts in vitiligo patients.

645. Topical Application of Rapamycin Ointment Ameliorates Dermatophagoides Farina Body Extract-Induced Atopic Dermatitis in NC/NGA Mice

Fei Yang, Mari Tanaka, Mari Wataya-Kaneda, Lingli Yang, Ayumi Nakamura, Shoji Matsumoto, Mostafa Attia, Hiroyuki Murota and Ichiro Katayama


Atopic dermatitis (AD), a chronic inflammatory skin disease characterized by relapsing eczema and intense prurigo, requires effective and safe pharmacological therapy. Recently, rapamycin, an mTOR (mammalian target of rapamycin) inhibitor, has been reported to play a critical role in immune responses and has emerged as an effective immunosuppressive drug. In this study, we assessed whether inhibition of mTOR signalling could suppress dermatisit in mice. Rapamycin was topically applied to inflamed skin in a murine AD model that was developed by repeated topical application of Dermatophagoides farina body (Db) extract antigen twice weekly for 7 weeks in NC/Nga mice. The efficacy of topical rapamycin treatment was evaluated immunologically and serologically. Topical application of rapamycin reduced inflammatory cell infiltration in the dermis, alleviated the increase of serum IgE levels and resulted in a significant reduction in clinical skin condition score and marked improvement of histological findings. In addition, increased mTOR phosphorylation in the lesional skin was observed in our murine AD model. Topical application of rapamycin ointment inhibited Db antigen-induced dermatitis in NC/Nga mice, promising a new therapy for atopic dermatitis.

Keywords: Atopic dermatitis; mTOR; Rapamycin.

646. Expression of Osteopontin Genotypes (T-4754-C and A-9138-C) in Psoriasis and their Relation to Metabolic Syndrome

Rania Abdel Hay, Faisal Nour-Edin, Rehab Hegazy, Sayed Khadiga and Laila Rashed


Osteopontin (OPN) is a multifactorial molecule with a postulated key role in several T helper (Th) 1- and Th17-mediated diseases including psoriasis.
Genetic variants in the OPN gene have shown to be involved in susceptibility to immune-mediated diseases, and several OPN haplotypes were found to be associated with Crohn's disease (CD) susceptibility including (T-4754-c) and (A-9138-C) genotypes. Owing to the common pathways linking between both psoriasis and CD [5], in the present study, we aimed to analyze the role of those particular OPN gene variants on psoriasis susceptibility as well as the association with metabolic syndrome (MetS) in such patients.

**Keywords:** Metabolic syndrome; Osteopontin; Psoriasis.

### 647. Homocysteine and Other Cardiovascular Risk Factors in Patients With Lichen Planus

N. Saleh, N. Samir, H. Megahed and E. Farid

*Journal of European Academy of Dermatology and Venereology, 28: 1507-1513 (2014) IF: 3.105*

**Background:** Chronic inflammation was found to play an important role in the development of cardiovascular risk factors. Homocysteine (Hcy) and fibrinogen have been identified as a major independent risk factor for cardiovascular disease. Lichen planus is assumed to be closely related to dyslipidaemia. Several cytokines involved in lichen planus pathogenesis, could explain its association with dyslipidaemia. Also chronic inflammation with lichen planus has been suggested as a component of the metabolic syndrome.

**Objective:** The aim of this study was to detect a panel of cardiovascular risk factors in patients of lichen planus.

**Patients and Methods:** This study was done on 40 patients of lichen planus and 40 healthy controls. All patients and controls were subjected to clinical examination. Serum levels of homocysteine, fibrinogen and high-sensitive C-reactive protein (hs-CRP) were measured by enzyme-linked immunosorbent assay technique (ELISA). Metabolic syndrome parameters including anthropometric measures, lipid profiles, blood sugar and blood pressure were studied.

**Results:** Patients with lichen planus showed significant association with metabolic syndrome parameters than controls (P < 0.001). Serum homocysteine, fibrinogen and hs-CRP were significantly higher in lichen planus patients than controls (P < 0.001). Serum homocysteine correlated with both serum hs-CRP and serum fibrinogen. However, there was no correlation between serum levels of homocysteine and fibrinogen with any metabolic syndrome criteria and related disorders except for a negative correlation of fibrinogen with high-density lipoprotein (HDL).

**Conclusion:** In the present work, patients with lichen planus were found to have higher makers of both metabolic and cardiovascular risk factors in relation to controls most probably due to long standing inflammation.

**Keywords:** Lichen planus; Homocysteine; Fibrinogen; Metabolic syndrome.

### 648. Does Fluorescence Diagnosis Have A Role in Follow Up of Response to Therapy in Mycosis Fungoides?

Manal Bossella, Doaa Mahgoub, Abeer El-Sayed, Dina Salama, Marwa Abd El-Moneim and Fatma Al-Helf

*Photodiagnosis and Photodynamic Therapy, 11(4): 595-602 (2014) IF: 2.524*

**Background:** Monitoring of tumor burden during mycosis fungoides (MF) treatment, is crucial to adjust therapy accordingly. This is usually achieved through combined by clinical assessment with histopathological and immunohistochemical evaluation.

**Aim:** To assess the validity of fluorescence diagnosis (FD) in the measurement of response to therapy in early MF, using in comparison flow cytometric technique of skin biopsies for CD4+/CD7- malignant T-cell count before and after therapy.

**Patients and Methods:** Twenty-two patients of histologically proven early MF (stages Ia, Ib, Ia) were subjected to fluorescence diagnosis of their most affected skin lesion before and after 12 weeks of phototherapy with or without combination therapy. In comparison flow cytometric assessment of skin biopsies for CD4+/CD7- cells dropped significantly after treatment (p = 0.029). No correlation between CD4+/CD7- cell counts and the mean AF could be deduced.

**Conclusion:** In cases of mycosis fungoides, fluorescence diagnosis can represent an effective tool for evaluating the response to therapy. Changes in accumulation factor values can be used for follow-up of therapy in the same patient, but it should not be used as an absolute value.

**Keywords:** Mycosis fungoides; Fluorescence diagnosis; Flowcytometry; CD4+/CD7- T Cells.


Heba I. Gawdat, Rehab A. Hegazy, Marwa M. Fawzi and Marwa Fathy

*Dermatologic Surgery, 40: 152-161 (2014) IF: 2.467*

**Background** A proposal has recently been made regarding the potential adjuvant use of platelet-rich plasma (PRP) with fractional carbon dioxide laser (FCL) for the correction of acne scars.

**Objective** To compare the efficacy and safety of two administration modes of autologous PRP (intradermal injection (ID) and topical application) after FCL with that of FCL alone in the treatment of atrophic acne scars.

**Patients and Methods** Thirty patients were randomly divided into two groups. Both underwent split-face therapy. Group 1 was administered FCL followed by ID PRP on one side and FCL followed by ID saline on the other. In group 2, one cheek was treated with FCL followed by ID PRP, and the other received FCL followed by topical PRP. Each patient received 3 monthly sessions. The final assessment took place at 6 months.

**Results** Combined PRP- and FCL-treated areas had a significantly better response (p = .03), fewer side effects, and shorter downtime (p = .02) than FCL-treated areas, but there were no significant differences in ID-and topical PRP–treated areas in degree of response and downtime (p = .10); topically treated areas had significantly lower pain scores.
Conclusion The current study introduces the combination of topical PRP and FCL as an effective, safe 2 modality in the treatment of atrophic acne scars with shorter down-time and better tolerability.

Keywords: Autologous platelet rich plasma (PRP); Fractional Co2, Atrophic Acne Scars, Downtime, Side Effects.

650. Fractional Co2 Laser is An Effective Therapeutic Modality for Xanthelasma Palpebrarum: A Randomized Clinical Trial

Samia M. Esmat, Amany Z. Elramly, Dalia M. Abdel Halim, Heba I. Gawdat and Hanan I. Taha

Dermatologic Surgery, 40: 1349-1355 (2014) IF: 2.467

Background Xanthelasma palpebrarum (XP) is a common cosmetic concern. Although there is a wide range of therapeutic modalities for XP, there is no general consensus on the optimal treatment for such condition.

Objective Compare the efficacy and safety of super pulse (SP) and fractional CO2 lasers in the treatment of XP.

Patients and Methods This prospective randomized comparative clinical study included 20 adult patients with bilateral and symmetrical XP lesions. Xanthelasma palpebrarum lesions were randomly assigned to treatment by either single session of ablative SP CO2 laser or 3 to 5 sessions of ablative fractional CO2 laser with monthly intervals. All patients were assessed using digital photography and optical coherence tomography images.

Results Xanthelasma palpebrarum lesions on both sides were successfully removed with significant improvement in size, color, and thickness. Although lesions treated by SP CO2 laser showed significantly better improvement regarding color and thickness of the lesions, downtime and patient satisfaction were significantly better for lesions treated with fractional CO2 laser. Scarring and recurrence were significantly higher in lesions treated by SP CO2 laser.

Conclusion Ablative fractional CO2 laser is an effective and safe therapeutic option for XP with significantly shorter downtime and higher patient satisfaction compared with SP CO2 laser.

Keywords: Xanthelasma palpebrarum; Fractional Co2; Superpulsed Co2; Efficacy; Safety.

651. Efficacy and Safety of Fractional Carbon Dioxide Laser for Treatment of Unwanted Facial Freckles in Phototypes II-IV: A Pilot Study

El Zawahry B, Zaki N, Hafez V, Hay RA and Fahim A


Facial freckles are a cosmetic concern to Egyptians, particularly young females. Several therapeutic lines exist with variable response rates and limitations. Fractional carbon dioxide (FCO2) laser provides minimal ablation and therefore less down time and less side effects. The efficacy and safety of this laser technology have still not been studied in freckles. The aim of this study is to assess the efficacy and safety of FCO2 laser in the treatment of unwanted facial freckles in Egyptians. Twenty patients underwent a single session of FCO2 laser and then were followed up clinically a month later. Photographs were taken before treatment and at follow-up visit and were assessed by three blinded investigators. Percent of global improvement was measured on a 4-point grading scale. Patient's satisfaction and adverse events were recorded. Two patients (10 %) showed grade 1 improvement, while eight patients (40 %) showed grade 2 improvement. Nine patients (45 %) showed grade 3 improvement, and only one patient (5 %) showed grade 4 improvement. FCO2 laser resurfacing is effective and safe in treatment of facial freckles in skin phototypes II-IV. It can offer a more practical alternative to topical treatments, and a cheaper alternative to Q-switched lasers.

Keywords: Freckles; Ablative laser; Fractional carbon dioxide laser; Efficacy; Safety; Pigmentation.

652. Mutational Spectrum of Xeroderma Pigmentosum Group A in Egyptian Patients

Amr K, Messaoud O, El Darouti M, Abdelhak S and El-Kamah G.

Gene, 533: 52-56 (2014) IF: 2.082

Xeroderma pigmentosum (XP) is a rare autosomal recessive hereditary disease characterized by hyperphotosensitivity, DNA repair defects and a predisposition to skin cancers. The most frequently occurring type worldwide is the XP group A (XPA). There is a close relationship between the clinical features that ranged from severe to mild form and the mutational site in XPA gene. The aim of this study is to carry out the mutational analysis in Egyptian patients with XP-A. This study was carried out on four unrelated Egyptian XP-A families. Clinical features were examined and direct sequencing of the coding region of XPA gene was performed in patients and their parents. Direct sequencing of the whole coding region of the XPA gene revealed the identification of two homozygous nonsense mutations: (c.553C>T; p.(Gln185*)) and (c.331G>T; p.(Glu111*)), which create premature, stop codon and a homodeletion (c.374delC; p.Thr125fs*15) that leads to frameshift and premature translation termination. We report the identification of one novel XPA gene mutation and two known mutations in four unrelated Egyptian families with Xeroderma pigmentosum. All explored patients presented severe neurological abnormalities and have mutations located in the DNA binding domain. This report gives insight on the mutation spectrum of XP-A in Egypt. This would provide a valuable tool for early diagnosis of this severe disease.

Keywords: Xeroderma pigmentosum-group A; Novel mutation; Clinical correlation to mutation location.

653. Does Increasing the Pulse Duration Increase the Efficacy of Long Pulsed Nd:YAG Laser Assisted Hair Removal? A Split-Chin Clinical Trial

Samia Esmat, Mona R. E. Abdelhalim, Amira El-Tawdy, Marwa M. Fawzy, Asmaa Ragheb and Nabilah Hasan


Apart from immediate transient side effects; perifollicular erythema, edema and pain, no chronic adverse side effects developed. High overall satisfaction with the results was reported by 20 patients (83.33 %). To the best of our knowledge, this is the first split chin, controlled trial to study the effects of increasing the pulse duration of long pulsed Nd:YAG and to evaluate the A/T ratio and hair shaft thickness following laser hair removal. It appears that increasing the pulse duration of long pulsed Nd:YAG significantly decreases hair thickness and induces more telogen hair but does not affect
the percentage of hair reduction or the onset of hair re-growth. Various manipulations in the pulse duration and fluence are recommended until reaching the best parameters to achieve permanent hair loss.

654. Study of T Helper (17) and T Regulatory Cells in Psoriatic Patients Receiving Live Attenuated Varicella Vaccine Therapy in A Randomized Controlled Trial

Mohammad Aly Abdel Qader El Darouti

**Background:** The use of live attenuated varicella vaccine (Varilrix®) as an adjuvant treatment in severe cases of psoriasis has recently been postulated. Its efficacy raised questions regarding its possible mechanisms of action.

**Objective:** To compare the efficacy and safety of combining Varilrix® and cyclosporine to cyclosporine alone in the treatment of severe psoriasis. Furthermore, to study the expression of T helper (Th)17 and T regulatory (Tregs) cells before and after therapy.

**Materials and Methods:** This randomized controlled trial included 24 psoriatic patients, randomly divided into 2 groups (A and B). All patients received cyclosporine at a daily dose of 2.5 mg/kg/day. In addition, group A received 4 doses of Varilrix® once/3 weeks, and group B received 4 doses of subcutaneous saline. Skin biopsies were obtained from all patients before and after therapy and from all controls for estimation of interleukin (IL)-17, IL-22 and Forkhead boxP3 (FoxP3) using RT-PCR.

**Results:** Group A patients showed a significantly higher % of clinical improvement (P = 0.011), which occurred earlier than group B. At baseline, levels of IL-17 and IL-22 were significantly higher while the level of FoxP3 was significantly lower in patients (P<0.001) compared to controls. After therapy, both groups showed significant reductions in both IL-17 and IL-22 levels, and significant elevation in FoxP3 (P<0.001). This change was significantly more evident in group A patients.

**Conclusion:** Live attenuated varicella vaccine could play a role in the treatment of psoriasis when combined with low dose cyclosporine through accentuating the influence on the Th17/Treg balance.

**Keywords:** Cyclosporine; Live attenuated varicella vaccine; Psoriasis; T Helper 17; T Regulatory cells.

655. Deep Peeling Using Phenol Versus Percutaneous Collagen Induction Combined With Trichloroacetic Acid 20% in Atrophic Post-Acne Scars; A Randomized Controlled Trial

Tahra Mohamed Leheta, Rania Mounir Abdel Hay and Yehia F. El Garem

**Background:** Deep peeling using phenol and percutaneous collagen induction (PCI) are used in treating acne scars. Aim: To compare deep peeling using phenol and PCI combined with trichloroacetic acid (TCA) 20% in treating atrophic acne scars.

**Methods:** 24 patients with post-acne atrophic scars were randomly divided into two groups; group 1 was subjected to one session of deep peeling using phenol, and group 2 was subjected to four sessions of PCI combined with TCA 20%. As a secondary outcome measure, side effects were recorded and patients were asked to assess their % of improvement by a questionnaire completed 8 months after the procedure.

**Results:** Scar severity scores improved by a mean of 75.12% (p < 0.001) in group 1 and a mean of 69.43% (p < 0.001) in group 2. Comparing the degree of improvement in different types of scars, within the same group after treatment, revealed a significant highest degree of improvement in the rolling type (p = 0.005) in group 2.

**Conclusion:** Deep peeling using phenol and PCI with TCA 20% were effective in treating post-acne atrophic scars.

**Keywords:** Acne; Collagen induction; Peeling; TCA.

656. Do Combined Alternating Sessions of 1540 Nm Nonablative Fractional Laser and Percutaneous Collagen Induction With Trichloroacetic Acid 20% Show Better Results Than Each Individual Modality in the Treatment of Atrophic Acne Scars? A Randomized Controlled Trial

Tahra M. Leheta, Rania M. Abdel Hay, Rehab A. Hegazy and Yehia F. El Garem

**Background:** There have been no well-controlled studies evaluating the efficacy of combining 1540 nm nonablative fractional laser with percutaneous collagen induction (PCI) and trichloroacetic acid (TCA) 20% in the treatment of atrophic acne scars. Objective: We hypothesized that combined alternating sessions of both modalities would show better results than each individual modality.

**Methods and materials:** Thirty-nine patients with post acne atrophic scars were included in this study. Patients were randomly equally divided into three groups; group 1 was subjected to six sessions of PCI combined with TCA 20% in the same session, group 2 was subjected to six sessions of 1540 nm fractional laser and group 3 was subjected to combined alternating sessions of the previously mentioned two modalities.

**Results:** Scar severity scores improved by a mean of 59.79% (95% CI 47.38–72.21) (p < 0.001) in group 1, a mean of 61.83% (95% CI 54.09–69.56) (p < 0.001) in group 2 and a mean of 78.27% (95% CI 74.39–82.15) (p < 0.001) in group 3. The difference in the degree of improvement was statistically significant when comparing the three groups using ANOVA test (p = 0.004).

**Conclusion:** The current work recommends combining 1540 nm nonablative fractional laser in alternation with PCI and TCA 20% in the treatment of atrophic acne scars.

**Keywords:** Acne Scars, Fractional Laser, Percutaneous Collagen Induction.

657. The Pro12ala Polymorphism of theGene for Peroxisome Proliferator Activated Receptor-Gamma Is Associated With A Lower Global Acne Grading System Score in Patients With Acne Vulgaris

K. Amr, M. Abdel-Hameed, K. Sayed, F. Nour-Edin and R. Abdel Hay

**Background:** Acne vulgaris is a multifactorial disease of the skin. Several studies have shown that sebocyte proliferation and/or
lipogenesis, as well as inflammatory reactions, may be regulated by peroxisome proliferator-activated receptor (PPAR)γ-mediated pathways.

Aim: To investigate whether the Pro12Ala polymorphism of the PPARγ gene might be associated with the risk of acne, and to assess the effect of this polymorphism on acne severity.

Methods: This case–control study enrolled 100 patients with acne and 100 apparently healthy subjects. The clinical grade of acne was assessed using the Global Acne Grading System. We used PCR to identify the presence of the Pro12Ala polymorphism in exon 2 of PPARγ.

Results: Our results revealed a statistically significant difference (P = 0.001) in the genotype distribution between patients and controls, with higher incidence of the Pro/Ala genotype in controls (51%) than in patients (28%). A statistically significant association (P < 0.001) between disease severity and genotype distribution was found, indicating that the Pro/Ala genotype is less prevalent in patients with severe acne.

Conclusions: Our results suggest that the Ala allele might be a protective factor against acne development or may attenuate acne severity.

Keywords: Acne; Gene polymorphism; PPARγ.

Dept. of Diagnostic Radiology

658. High-Intensity Focused Ultrasound for Potential Treatment of Polycystic Ovary Syndrome: Toward A Noninvasive Surgery

Islam A. Shehata, John R. Ballard, Andrew J. Casper, Leah J. Hennings, Erik Cressman and Emad S. Ebbini


Objective: To investigate the feasibility of using high-intensity focused ultrasound (HIFU), under dual-mode ultrasound arrays (DMUAs) guidance, to induce localized thermal damage inside ovaries without damage to the ovarian surface.

Design: Laboratory feasibility study.

Setting: University-based laboratory.

Animal(S): Ex vivo canine and bovine ovaries.

Intervention(S): DMUA-guided HIFU.

Main Outcome Measure(S): Detection of ovarian damage by ultrasound imaging, gross pathology, and histology.

Result(S): It is feasible to induce localized thermal damage inside ovaries without damage to the ovarian surface. DMUA provided sensitive imaging feedback regarding the anatomy of the treated ovaries and the ablation process. Different ablation protocols were tested, and thermal damage within the treated ovaries was histologically characterized.

Conclusion(S): The absence of damage to the ovarian surface may eliminate many of the complications linked to current laparoscopic ovarian drilling (LOD) techniques. HIFU may be used as a less traumatic tool to perform LOD.

Keywords: Polycystic ovary syndrome (PCOS); Dual-mode ultrasound arrays (DMUA); High-intensity focused ultrasound (HIFU); Infertility; Laparoscopic ovarian drilling (LOD)

659. Biotin-Responsive Basal Ganglia Disease: Neuroimaging Features Before nd After Treatment

H. Kassem, A. Wafaie, S. Alsuhibani and T. Farid


Background and Purpose: Biotin-responsive basal ganglia disease is an autosomal recessive neurometabolic disorder presenting with subacute encephalopathy that can cause death if left untreated. The purpose of this study is to assess the neuroimaging and clinical features of the disease before and after treatment with biotin.

Materials and Methods: We retrospectively reviewed the clinical, laboratory, and neuroimaging features of 15 genetically-proved Middle Eastern cases of biotin-responsive basal ganglia disease. BrainMRimaging was done at the onset of symptoms in all cases and within 2–8 weeks after biotin and thiamine therapy in 14 patients. The MR imaging datasets were analyzed according to lesion location, extent, and distribution.

Results: Brain MR imaging showed bilateral lesions in the caudate nuclei with complete or partial involvement of the putamen and sparing of the globus pallidus in all cases. In 80%, discrete abnormal signals were observed in the mesencephalon, cerebral corticalsubcortical regions, and thalamus. In 53%, when the disease was advanced, patchy deep white matter affection was found. The cerebellum was involved in 13.3%. The signal abnormality of the mesencephalon, cortex, and white matter disappeared after treatment whereas the caudate and putamen necrosis persisted in all patients, including those who became asymptomatic.

Conclusions: Biotin-responsive basal ganglia disease is a treatable underdiagnosed disease. It should be suspected in pediatric patients with unexplained encephalopathy whose brainMRimaging shows bilateral and symmetric lesions in the caudate heads and putamen, with or without involvement of mesencephalon, thalamus, and cortical-subcortical regions, as the therapeutic trial of biotin and thiamine can be lifesaving.

Keywords: Biotin-Responsive Basal Ganglia Disease; Biotin; Encephalopathy.
the child was 6 months old and showed no spinal deformity. Radiological re-assessment of the spine was recommended at the age of 1 year to evaluate development of the spine. Butterfly vertebra is a rare congenital spinal anomaly.2. Very few cases of prenatal diagnosis have been reported, and when this has occurred it has typically been during the assessment of more complex spinal malformation.

**Keywords:** Spine; Fetal; Ultrasound.

### 661. Fetal MRI: An Approach To Practice: A Review

**Sahar N. Salem**  
*Journal of Advanced Research, 5: 507-523 (2014) IF: 3*

MRI has been increasingly used for detailed visualization of the fetus in utero as well as pregnancy structures. Yet, the familiarity of radiologists and clinicians with fetal MRI is still limited. This article provides a practical approach to fetal MR imaging. Fetal MRI is an interactive scanning of the moving fetus owing to the use of fast sequences. Single-shot fast spin-echo (SSFSE) T2-weighted imaging is a standard sequence. T1-weighted sequences are primarily used to demonstrate fat, calcification and hemorrhage. Balanced steady-state free-precession (SSFP), are beneficial in demonstrating fetal structures as the heart and vessels. Diffusion weighted imaging (DWI), MR spectroscopy (MRS), and diffusion tensor imaging (DTI) have potential applications in fetal imaging. Knowing the developing fetal MR anatomy is essential to detect abnormalities. MR evaluation of the developing fetal brain should include recognition of the multilayered-appearance of the cerebral parenchyma, knowledge of the timing of sulci appearance, myelination and changes in ventricular size. With advanced gestation, fetal organs as lungs and kidneys show significant changes in volume and T2-signal. Through a systematic approach, the normal anatomy of the developing fetus is shown to contrast with a wide spectrum of fetal disorders. The abnormalities displayed are graded in severity from simple common lesions to more complex rare cases. Complete fetal MRI is fulfilled by careful evaluation of the placenta, umbilical cord and amniotic cavity. Accurate interpretation of fetal MRI can provide valuable information that helps prenatal counseling, facilitate management decisions, guide therapy, and support research studies.

**Keywords:** Fetal; MRI; Anomalies; Prenatal.

### 662. Leukoencephalopathy With Brainstem and Spinal Cord Involvement and Lactate Elevation (LBSL): Assessment of the Involved White Matter Tracts by MRI

**Hassan Kassem, Ahmed Wafaaie, Sherif Abdelfiathah and Tarek Farid**  
*European Journal of Radiology, 83: 191-196 (2014) IF: 2.16*

**Background and purpose:** Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation (LBSL) is a recently identified autosomal recessive disorder with early onset of symptoms and slowly progressive pyramidal, cerebellar and dorsal column dysfunction. LBSL is characterized by distinct white matter abnormalities and selective involvement of brainstem and spinal cord tracts. The purpose of this study is to assess the imaging features of the involved white matter tracts in cases of LBSL by MRI.

**Patients and Methods:** We retrospectively reviewed the imaging features of the selectively involved white matter tracts in sixteen genetically proven cases of leukoencephalopathy with brainstem and spinal cord involvement and elevated brain lactate (LBSL). All patients presented with slowly progressive cerebellar sensory ataxia with spasticity and dorsal column dysfunction. MRI of the brain and spine using 1.5 T machine and proton magnetic resonance spectroscopy (1H MRS) on the abnormal white matter were done to all patients. The MRI and MRS data sets were analyzed according to lesion location, extent, distribution and signal pattern as well as metabolite values and ratios in MRS. Laboratory examinations ruled out classic leukodystrophies.

**Results:** In all cases, MRI showed high signal intensity in T2-weighted and FLAIR images within the cerebral subcortical, periventricular and deep white matter, posterior limbs of internal capsules, centrum semiovale, medulla oblongata, intraparenchymal trajectory of trigeminal nerves and deep cerebellar white matter. In the spine, the signal intensity of the dorsal column and lateral cortico-spinal tracts were altered in all patients. The subcortical U fibers, globi pallidi, thalami, midbrain and transverse pontine fibers were spared in all cases. In 11 cases (68.8%), the signal changes were inhomogeneous and confluent whereas in 5 patients (31.2%), the signal abnormalities were spotty. MRI also showed variable signal abnormalities in the sensory and pyramidal tracts in addition to the brainstem and cerebellar connections. Proton MRS showed consistent elevation of the lactate within the abnormal white matter.

**Conclusion:** Distinct MRI findings in the form of selective affection of subcortical and deep white matter tracts of the brain (involving the posterior limb of internal capsules and sparing the subcortical U fibers), dorsal column and lateral cortico-spinal tracts of the spinal cord should lead to the diagnosis of LBSL supported by the presence of lactate peak in 1H MRS. The disease can be confirmed by the analysis of the disease gene DARS2.

**Keywords:** Leukoencephalopathy; Brainstem; Spinal cord; Lactate.

### 663. Pneumatosis Intestinalis Following Pediatric Live-Related Liver Transplant: A Case Report and Successful Conservative Approach

**Omer Abdel-Aziz, Ahmed H. Elaffandi, Mostafa El Shazly, Adel Hosny and Hanaa El-Karaky**  
*Pedicriatric Transplantation, 18: 18-21 (2014) IF: 1.63*

PI has been rarely reported following pediatric live-related liver transplantation. Such a disorder is characterized by accumulation of gas in the bowel wall. The cause of PI has not been yet established; however, it has been strongly linked with steroid therapy. In this report, we present a case of PI following pediatric live-related liver transplantation that has been successfully managed conservatively.

**Keywords:** Pneumatosis intestinalis; LDLpediatric.

### 664. Multidetector Computed Tomographic Study of Amulets Jewelry, and Other Foreign Objects in Royal Egyptianmummies Dated from the 18Th to 20Th Dynasties

**Sahar N. Salem and Zahi Hawass**  

*International Publications Awards, Cairo University (IPACU)*
Objective: The objective of this study was to study the role of multidetector computed tomography (MDCT) in the analysis of foreign objects found within or on the royal Egyptian mummies.

Methods: We studied MDCT images of 15 royal Egyptian mummies (1493-1156 BC) for the presence of foreign objects. We studied each found object for its location, morphology, dimensions, and density in correlation with the archeological literature.

Results: We detected 14 objects in 6 mummies: a heart amulet, 3 Eye of Horus, 4 Sons of Horus, a crowned-Osiris amulet, 2 bracelets, 2 sets of beads/stones, and an arrowhead that may be linked to injury. The MDCT images suggested the material of the objects to be metal (n = 6), semiprecious stone (n = 1), quartzlike (faience) (n = 2), and fired clay (n = 5). Placement of an amulet within the heart supports our knowledge that its funeral purpose was meant for the purpose of protection.

Conclusions: Multidetector computed tomography offers a detailed noninvasive analysis of objects on/in mummies and differentiates funerary objects from those that may be related to cause of death.

Keywords: Mummy; CT; Amulet; Funeral; Royal; Egypt.

665. Holoprosencephaly Spectrum Among Egyptian Patients: Clinical and Cytogenetic Study

Genetic Counseling, 25(4): 369-381 (2014) IF: 0.537

Summary: Holoprosencephaly spectrum among Egyptian patients: clinical and cytogenetic study. We report 24 patients with holoprosencephaly (HPE) spectrum screened for Del 7q36 and subtelomere 13q. They were divided according to the type of HPE into: 6 alobar, 15 semilobar, 1 lobar and 2 middle interhemispheric variant (MHI). All patients presented with global developmental delay. Microcephaly was in 83.3% and midfacial developmental defects were in the form of; cyclopia, arhinia and agnathia in 2 patients (8.3%), premaxillary agenesis in 2 patients (8.3%), cleft lip and palate in 7 patients (29.2%), hypotelorism in 8 patients (33.3%) and hypertelorism in 9 patients (37.5%). The neurological deficits were as follows: abnormal tone and spasticity were present in all of them with exceptional of a single patient with MHI who presented with hypotonia and was able to walk independently at the age of 3 years, athetoid and/or dystonic movements of limbs in 22 patients, seizures in twelve patients (50%) and abnormal EEG in 15 patients (62.5%). Poor temperature regulation was found in 50% of patients and diabetes insipidus was documented in 3 patients (12.5%). The MRI showed complete or partial fusion of basal ganglia and thalami in 21 patients (87.5%) and 19 patients (79.2%) respectively, fused mesencephalon in 8 patients (33.3%), incomplete separation of mesencephalon from diencephalon in 4 patients (16.7%), dorsal cyst in 10 patients (41.7%), abnormal gyral pattern anteriorly in 15 patients (62.5%), anterior located sylvian fissures in 22 patients (90.7%), complete or partial agenesis of the corpus callosum (ACC) in all patients and Dandy-Walker malformation (DWM) in three patients (12.5%). A small occipital cephaleocele was detected clinically and radiologically as atretic type in MHI patient. Karyotype analysis demonstrated 47, XY+13 in a patient with alobar holoprosencephaly, 46, XY, (12;13) (q13q24.1; q14q33) in a semilobar case associated with DWM, 46, XY, del(13)(q34) in a semilobar case and three cases had del 7q36 using FISH technique in two semilobar cases and one lobar case.

Conclusion: This study highlights the clinical spectrum in patients with HPE and report a case of HPE and DWM associated with t(12;13). Neuroimaging delineated the pathogenesis underlying developmental defects in HPE. Accurate molecular diagnosis is crucial for further understanding of the pathogenesis of HPE.

Keywords: Holoprosencephaly; MRI Translocation 12; 13 - Deletion 7q36 Del 13(Q); Dandy-Walker Malformation

666. Ankylosing Spondylitis or Diffuse Idiopathic Skeletal Hyperostosis in Royal Egyptian Mummies of the 18th–20th Dynasties? Computed Tomography Andarchaeology Studies
Sahar N. Saleem and Zahi Hawass

Arthritis & Rheumatology, 66(12): 3311-3316 (2014)

Objective: To study the computed tomography (CT) images of royal Ancient Egyptian mummies dated to the 18th to early 20th Dynasties for the claimed diagnoses of ankylosing spondylitis (AS) and diffuse idiopathic skeletal hyperostosis (DISH) and to correlate the findings with the archaeology literature.

Methods: We studied the CT images of 13 royal Ancient Egyptian mummies (1492–1153 BC) for evidence of AS and DISH and correlated our findings with the archaeology literature.

Results: The findings of the CT scans excluded the diagnosis of AS, based on the absence of sacroiliac joint erosions or fusion of the facet joints. Four mummies fulfilled the diagnostic criteria for DISH: Amenhotep III (18th Dynasty), Ramesses II, his son Merenptah, and Ramesses III (19th to early 20th Dynasties). The diagnosis of DISH, a commonly asymptomatic disease of old age, in the 4 pharaohs is in concordance with their longevity and active lifestyles.

Conclusion: CT findings excluded the diagnosis of AS in the studied royal Ancient Egyptian mummies and brought into question the antiquity of the disease. The CT features of DISH during this ancient period were similar to those commonly seen in modern populations, and it is likely that they will also be similar in the future. The affection of Ramesses II and his son Merenptah supports familial clustering of DISH. The process of mumification may induce changes in the spine that should be considered during investigations of disease in ancient mummies.

Keywords: Spine; Mummy; Ankylosing Spondylitis.

Dept. of Ear Nose & Throat

667. Otolaryngologic Manifestations of Diffuse Idiopathic Skeletal Hyperostosis
Mosaa'd Abdel-Aziz, Noaha A. Azab, Mohammed Rashed and Ahmed Talaat


Diffuse idiopathic skeletal hyperostosis (DISH) is characterized by formation of large cervical osteophytes that may compress the posterior wall of the aerodigestive tract. It is a rare cause of dysphagia in the elderly. The aim of this study was to investigate the various otolaryngologic manifestations of DISH. Eleven elderly patients with DISH were included in the study. All patients presented with dysphagia that was graded on the swallowing screening tool (EAT-10), and the diagnosis of DISH was based on computed tomographic criteria. The patients were subjected to otolaryngologic examination and flexible laryngoscopy. Polysomnography was used for patients with excessive daytime sleepiness for detection of obstructive sleep
apnea (OSA). In addition to dysphagia of varying severity, OSA was found in nine patients, change of voice in six, globus sensation in seven, aspiration in three, and cervical pain in seven. Flexible laryngoscopy showed bulging of the posterior pharyngeal wall in all patients. DISH may be an unrecognized contributory factor to both dysphagia and OSA in the elderly. Change of voice, aspiration, globus sensation, and cervical pain are other otolaryngologic manifestations that may be encountered symptoms of the disease. An otolaryngologist should be aware of the disease that may be overlooked, and computed tomography is a confirmatory diagnostic method. **Keywords:** Dysphagia Obstructive Sleep Apnea Cervical Osteophytes DISH Cervical Pain.

668. **Trans-Oral Endoscopic Cerclage Pharyngoplasty for Treatment of Velopharyngeal Insufficiency**

Mohammed Rashed, Nader Naguib and Mosaad Abdel-Aziz


**Objectives:** Velopharyngeal insufficiency (VPI) is a common problem after cleft palate repair, it leads to speech distortion with consequent affection of speech intelligibility. Many techniques have been used in the treatment of VPI with varying results and complications. The aim of this study was to evaluate the efficacy of trans-oral endoscopic cerclage pharyngoplasty in the treatment of VPI.

**Methods:** Eighteen patients with hypernasality after palatoplasty were subjected to trans-oral endoscopic cerclage pharyngoplasty. Pre and postoperative evaluation of velopharyngeal function were performed by using auditory perceptual assessment, nasometric assessment, and flexible nasopharyngoscopy.

**Results:** Significant postoperative improvement of speech parameters measured with auditory perceptual assessment were achieved, and the overall postoperative nasalance score was improved significantly for nasal and oral sentences. Also, flexible nasopharyngoscopy showed significant improvement of velopharyngeal closure. No marked postoperative complications were reported apart from throat pain and dysphagia that disappeared with time.

**Conclusions:** Trans-oral endoscopic cerclage pharyngoplasty is an effective method for the treatment of VPI. **Keywords:** Velopharyngeal insufficiency; Cleft palate; Pharyngoplasty; Hypernasality.

669. **Eosinophilic Granuloma of the Temporal Bone in Children**

Abdel-Aziz M, Rashed M, Khalifa B, Talaat A and Nassar A.

*The Journal of Craniofacial Surgery, 25(3): 1076-1078 (2014) IF: 0.676*

Eosinophilic granuloma (EG) is a bony destructive disease that frequently occurs in children; it is a subtype of Langerhans cell histiocytosis. The aims of this study were to detect the presenting features of temporal bone lesions in children and to evaluate the efficacy of surgery combined with radiotherapy in treatment of the disease. A retrospective study on 12 children with EG of the temporal bone was done. Computed tomography and hearing assessment were performed for all patients. All patients were treated with cortical mastoidectomy followed by postoperative radiotherapy. Follow-up was carried out for at least 2 years. The patients' presenting symptoms were external ear canal mass in 10 patients (83.3%), postauricular swelling in 8 patients (66.7%), and persistent ototraea in 4 patients (33.3%). Ten patients (83.3%) showed conductive hearing loss, whereas 2 patients (16.7%) showed mixed hearing loss on the affected side. Computed tomography showed osteolytic defects without sclerotic margins filled with soft tissue masses involving the mastoid bone. Histopathologic examination showed eosinophils and Langerhans cells that were immune reactive for CD1 antigen and S-100 protein. Postoperative follow-up showed complete cure of the disease in 10 children (83.3%), with recurrence detected in 2 patients (16.7%) who needed second surgical intervention. We concluded that temporal bone EG in children may present with features that mimic the features of chronic suppurative otitis media. However, computed tomography and histopathologic examination are diagnostic. Cortical mastoidectomy together with postoperative radiotherapy is an achievable treatment in most cases. **Keywords:** Eosinophilic granuloma; Temporal bone; Cortical mastoidectomy; Otorrhea.

**Dept. of Endemic**

670. **Effectiveness and Cost-Effectiveness of Immediate Versus Delayed Treatment of Hepatitis C Virus-Infected Patients in A Country With Limited Resources: the Case of Egypt**


**Background:** Because of logistical and economic issues, in Egypt, as in other resource-limited settings, decision makers should determine for which patients hepatitis C virus (HCV) treatment should be prioritized. We assessed the effectiveness and cost-effectiveness of different treatment initiation strategies.

**Methods:** Using a Markov model, we simulated HCV disease in chronically infected patients in Egypt, to compare lifetime costs, quality-adjusted life expectancy (QALE), and the incremental cost-effectiveness ratio (ICER) of different treatment initiation strategies.

**Results:** Immediate treatment of patients at stages F1/F2/F3 was less expensive and more effective than delaying treatment until more severe stages or not providing treatment (in patients diagnosed at F1: QALE = 18.32 years if treatment at F1 vs 18.22 if treatment at F2). Treatment of F4 patients was more effective than no treatment at all (QALE = 10.33 years vs 8.77 years) and was cost-effective (ICER = $1915/quality-adjusted life-year [QALY]). When considering that affordable triple therapies, including new direct-acting antivirals, will be available starting in 2016, delaying treatment until stage F2, then treating all patients regardless of their disease stage after 2016, was found to be cost-effective (ICER = $33/QALY).

**Conclusions:** In Egypt, immediate treatment of patients with fibrosis stage F1-F3 who present to care is less expensive and more effective than delaying treatment. However, immediate treatment at stage F1 is only slightly more effective than waiting for disease to progress to stage F2 before starting treatment and is sensitive to the forthcoming availability of new treatments. Treating patients at stage F4 is highly effective and cost-effective.
In Egypt, decision makers should prioritize treatment for F4 patients and delay treatment for F1 patients who present to care.

**Keywords:** HCV: Cost-Effectiveness; Resource-Limited Countries; Egypt; Antiviral Treatment.

### 671. Peginterferon Alpha-2A Versus Peginterferon Alpha-2B for Chronic Hepatitis C (Review)

**Goran Hauser, Tahany Awad, Kristian Thorlund, Davor Štimac, Mahasen Mabrouk and Christian Gluud**

*Cochrane Database Systematic Review, 28 (2): (2014) IF: 5.939*

**Background** A combination of weekly pegylated interferon (peginterferon) alpha and daily ribavirin still represents standard treatment of chronic hepatitis C infection in the majority of patients. However, it is not established which of the two licensed peginterferon products, peginterferon alpha-2a or peginterferon alpha-2b, is the most effective and has a better safety profile.

**Objectives** To systematically evaluate the benefits and harms of peginterferon alpha-2a versus peginterferon alpha-2b in head-to-head randomised clinical trials in patients with chronic hepatitis C.

**Search methods** We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, and LILACS until October 2013. We also searched conference abstracts, journals, and grey literature.

**Selection criteria** We included randomised clinical trials comparing peginterferon alpha-2a versus peginterferon alpha-2b given with or without co-intervention(s) (for example, ribavirin) for chronic hepatitis C. Quasi-randomised studies and observational studies as identified by the searches were also considered for assessment of harms. Our primary outcomes were all-cause mortality, liver-related morbidity, serious adverse events, adverse events leading to treatment discontinuation, other adverse events, and quality of life. The secondary outcome was sustained virological response in the blood serum.

**Data collection and analysis** Two authors independently used a standardised data collection form. We meta-analysed data with both the fixed-effect and the random-effects models. For each outcome we calculated the relative risk (RR) with 95% confidence interval (CI) based on intention-to-treat analysis. We used domains of the trials to assess the risk of systematic errors (bias) and trial sequential analyses to assess the risks of random errors (play of chance). Intervention effects on the outcomes were assessed according to GRADE.

**Main results** We included 17 randomised clinical trials which compared peginterferon alpha-2a plus ribavirin versus peginterferon alpha-2b plus ribavirin in 5847 patients. All trials had a high risk of bias. Very few trials reported data on very few patients for the patient-relevant outcomes all-cause mortality, liver-related morbidity, serious adverse events, and quality of life. Accordingly, we were unable to conduct meta-analyses on all-cause mortality, liver-related morbidity, and quality of life. Twelve trials reported on adverse events leading to discontinuation of treatment without clear evidence of a difference between the two peginterferons (197/217) (9.1%) versus 311/3169 (9.9%); RR 0.84, 95% CI 0.57 to 1.22; I² = 44%; low quality evidence). A trial sequential analysis showed that we could exclude a relative risk reduction of 20% or more on this outcome. Peginterferon alpha-2a significantly increased the number of patients who achieved a sustained virological response in the blood serum compared with peginterferon alpha-2b (1069/2099 (51%) versus 1327/3075 (43%); RR 1.12, 95% CI 1.06 to 1.18; I² = 0%, 12 trials; moderate quality evidence). Trial sequential analyses supported this result. Subgroup analyses based on risk of bias, viral genotype, and treatment history yielded similar results. Trial sequential analyses supported the results in patients with genotypes 1 and 4, but not in patients with genotypes 2 and 3.

**Authors' conclusions** There is lack of evidence on patient-important outcomes and paucity of evidence on adverse events. Moderate quality evidence suggests that peginterferon alpha-2a is associated with a higher sustained virological response in serum than with peginterferon alpha-2b. This finding may be affected by the high risk of bias of the included studies. The clinical consequences of peginterferon alpha-2a versus peginterferon alpha-2b are unknown, and we cannot translate an effect on sustained virological response into comparable clinical effects because sustained virological response is still an unvalidated surrogate outcome for patient-important outcomes. The lack of evidence on patient-important outcomes and the paucity of evidence on adverse events means that we are unable to draw any conclusions about the effects of one peginterferon over the other.

**Keywords:** Peginterferon Alpha-2A - Peginterferon Alpha-2B: Chronic Hepatitis C.

### 672. Peginterferon Plus Ribavirin Versus Interferon Plus Ribavirin for Chronic Hepatitis C

Hauser G, Awad T, Brok J, Thorlund K, Štimac D, Mabrouk M, Gluud C and Gluud LL.

*Cochrane Database Systematic Review - The Cochrane Library - Hepato-Biliary Group, 28 (2): (2014) IF: 5.939*

**Background:** Pegylated interferon (peginterferon) plus ribavirin is the recommended treatment for patients with chronic hepatitis C, but systematic assessment of the effect of this treatment compared with interferon plus ribavirin is needed.

**Objectives:** To systematically evaluate the benefits and harms of peginterferon plus ribavirin versus interferon plus ribavirin for patients with chronic hepatitis C.

**Search Methods:** We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Science Citation Index-Expanded, and LILACS. We also searched conference abstracts, journals, and grey literature. The last searches were conducted in September 2013.

**Selection Criteria:** We included randomised clinical trials comparing peginterferon plus ribavirin versus interferon plus ribavirin with or without co-intervention(s) (e.g., other antiviral drugs) for chronic hepatitis C. Quasi-randomised and observational studies retrieved through the searches for randomised clinical trials were also considered for reports of harms. Our primary outcomes were liver-related morbidity, all-cause mortality, serious adverse events, adverse events leading to treatment discontinuation, other adverse events, and quality of life. Our secondary outcome was sustained virological response in serum, that is, undetectable hepatitis C virus RNA in serum by sensitive tests six months after the end of treatment.

**Data Collection and Analysis:** Two review authors independently used a standardised data collection form. We meta-analysed data with both fixed-effect and random-effects models. For each outcome, we calculated the odds ratio (OR) (for liver-related morbidity or all-cause mortality) or the risk ratio (RR) along with 95% confidence interval (CI) based on intention-to-
treat analysis. We used domains of the trials to assess the risk of systematic errors (bias) and trial sequential analyses to assess the risk of random errors (play of chance). For each outcome, we calculated the RR with 95% CI based on intention-to-treat analysis. Effects of interventions on outcomes were assessed according to GRADE.

**Main Results:** We included 27 randomised trials with 5938 participants. All trials had high risk of bias. We considered that the risk of bias did not impact on the quality of evidence for liver-related mortality and adverse event outcomes, but it did for virological response. All trials compared peginterferon alpha-2a or peginterferon alpha-2b plus ribavirin versus interferon plus ribavirin for participants with chronic hepatitis C. Three trials administered co-interventions (amantadine hydrochloride 200 mg daily to both intervention groups), and 24 trials were conducted without co-interventions. The effect observed between the two intervention groups regarding liver-related morbidity plus all-cause mortality (5907/0.55% versus 4882/0.45%) was imprecise: OR 1.14 (95% CI 0.38 to 3.42; five trials; low quality of evidence), as was the risk of versus the need for treatment discontinuation (332/2692 (12.3%) versus 409/2176 (18.8%); RR 0.86, 95% CI 0.68 to 1.09; 15 trials; low quality of evidence) or regarding adverse events leading to treatment discontinuation (332/2692 (12.3%) versus 409/2176 (18.8%); RR 0.86, 95% CI 0.66 to 1.12; 17 trials; low quality of evidence). However, peginterferon plus ribavirin versus interferon plus ribavirin significantly increased the risk of neutropenia (332/2202 (15.1%) versus 117/1653 (7.1%); RR 2.15, 95% CI 1.76 to 2.61; 13 trials), thrombocytopenia (65/1113 (5.8%) versus 23/1082 (2.1%); RR 2.63, 95% CI 1.68 to 4.11; 10 trials), arthralgia (517/1740 (29.7%) versus 282/1194 (23.6%); RR 1.19, 95% CI 1.05 to 1.35; four trials), injection site reaction (627/1168 (53.7%) versus 186/649 (28.7%); RR 1.71, 95% CI 1.50 to 1.93; four trials), and nausea (606/1784 (34.0%) versus 354/1239 (28.6%); RR 1.13, 95% CI 1.01 to 1.26; four trials). The most frequent adverse event was fatigue, which occurred in 57% of participants (2024/3608). No significant difference was noted between peginterferon plus ribavirin versus interferon plus ribavirin in terms of fatigue (117/72062 (57.1%) versus 847/1546 (54.8%); RR 1.01, 95% CI 0.96 to 1.07; 12 trials). No significant differences were reported between the two treatment groups regarding anaemia, headache, rigours, myalgia, pyrexia, weight loss, asthenia, depression, insomnia, irritability, alopecia, pruritus, skin rash, thyroid malfunction, decreased appetite, or diarrhoea. We were unable to identify any data on quality of life. Peginterferon plus ribavirin versus interferon plus ribavirin seemed to significantly increase the number of participants achieving sustained virological response (1673/3300 participants (50.7%) versus 1081/2804 patients (36.7%); RR 1.39, 95% CI 1.25 to 1.56; I² = 64%; 27 trials; very low quality of evidence). However, the risk of bias in the 13/27 (48.1%) trials reporting on this outcome was high and was considered only ‘lower’ in the remainder. Because the conventional meta-analysis did not reach its required information size (n = 14,486 participants), we used trial sequential analysis to control for risks of random errors. Again, in this analysis, the estimated effect was statistically significant in favour of peginterferon. Subgroup analyses according to risk of bias, viral genotype, baseline viral load, past treatment history, and type of intervention yielded similarly significant results favouring peginterferon over interferon on the outcome of sustained virological response.

**Authors’ Conclusions:** Peginterferon plus ribavirin versus interferon plus ribavirin seems to significantly increase the proportion of patients with sustained virological response, as well as the risk of certain adverse events. However, we have insufficient evidence to recommend or reject peginterferon plus ribavirin for liver-related morbidity plus all-cause mortality compared with interferon plus ribavirin. The clinical consequences of achieved sustained virological response are unknown, as sustained virological response is still an unvalidated surrogate outcome. We found no evidence of the potential benefits on quality of life in patients with achieved sustained virological response. Further high-quality research is likely to have an important impact on our confidence in the estimate of patient-relevant outcomes and is likely to change our estimates. There is very low quality evidence that peginterferon plus ribavirin increases the proportion of patients with sustained virological response in comparison with interferon plus ribavirin. There is evidence that it also increases the risk of certain adverse events.

**Keywords:** Peginterferon; Ribavirin; Interferon; Chronic hepatitis C.

673. Nitazoxanide Plus Pegylated Interferon and Ribavirin in the Treatment of Genotype 4 Chronic Hepatitis C, A Randomized Controlled Trial

Shehab HM, Elbaz TM and Deraz DM.


**Background and Aims:** Nitazoxanide has been proposed as a novel therapeutic agent for chronic hepatitis C virus (HCV) potentiating the effect of interferon and improving sustained virological response rates to up to 80% in genotype 4. This is an independent randomized trial to confirm the efficacy of nitazoxanide in the treatment of chronic hepatitis C genotype 4.

**Methods:** This was an open-label trial. Treatment-naive genotype 4 HCV patients were recruited: Group 1 received weekly subcutaneous pegylated interferon 160 μg in addition to weight-based ribavirin (1200 mg if ≥ 75 kg and 1000 mg if <75 kg) for 48 weeks, Group 2 received 4 weeks lead-in therapy by nitazoxanide alone (500 mg bid) followed by triple therapy including nitazoxanide, pegylated interferon and ribavirin for a further 48 weeks.

**Results:** Fifty patients were recruited in each group. Baseline characteristics were similar except for a higher BMI in group 1 (28.5 vs. 26.5, P = 0.01). SVR rates were similar (24/50 (48%) vs. 25/50 (50%) in groups 1 and 2 respectively, P: 0.84). RVR, cEVR and ETR rates were also similar (61% vs. 53% - P:0.4, 70% vs. 72% - P:0.8 and 62% vs. 58% - P:0.6 in groups 1 and 2 respectively). Biochemical response at week 12 was also similar (57% vs. 46% in groups 1 and 2 respectively, P:0.26). Complications were similar except for a higher rate of dyspepsia in the group receiving nitazoxanide (32% vs. 14%, P:0.03).

**Conclusion:** The addition of nitazoxanide to pegylated interferon and ribavirin does not improve the virological or biochemical response rates in chronic HCV genotype 4.

**Keywords:** Nitazoxanide; Interferon; HCV.
674. Optimizing Treatment for HCV Genotype 4: PEG-IFN Alfa 2A Vs. PEG-IFN Alfa 2B; the Debate Continues

Esmat G, El Kassas M, Hassany M, Gamil M and El Raziky M.

Hepatitis C virus (HCV) remains one of the leading causes of morbidity and mortality worldwide. Combined therapy with pegylated interferon (PEG-IFN) and ribavirin is the current standard of care treatment for HCV genotype 4. Two types of PEG-IFN are commercially available. The limited number of trials that were conducted for HCV genotype 4 and the few head to head comparisons make it impossible to know which is the best option? In this article we review all available PEG-IFN trials performed worldwide for HCV genotype 4 since 2004. Unless another molecule is developed as a standalone for the treatment of HCV, PEG-IFN will continue to be a source of debate.

Keywords: HCV genotype 4; PEG-IFN alfa-2a; PEG-IFN alfa-2b.

675. The Efficacy of A Hansenula-Derived 20 KDa Pegylated Interferon Alpha-2A in the Treatment of Genotype 4 Chronic Hepatitis C

Shehab H, Elbaz T, Deraz D, Hafez A and Elattar I.

Pending the emergence and approval of an effective interferon-free regimen, pegylated interferon will remain an integral part of the treatment of genotype 4 hepatitis C virus (HCV). A new 20 kDa pegylated interferon has been developed in a cost-saving fungal-based system and is commercialized in Egypt at a quarter to a third of the price of conventional pegylated interferon. We hereby test the efficacy and safety of this novel cost-saving interferon. One hundred ninety-three consecutive treatment-naive patients with genotype 4 HCV were treated using the following regimen: subcutaneous 20 kDa pegylated interferon 160 μg once weekly plus oral ribavirin 1,000 or 1,200 mg daily (based on body weight <75 kg or ≥75 kg, respectively) for 48 weeks. A sustained virological response (SVR) of 51% was achieved. Interim responses included rapid virological response (RVR): 54%, early virological response (EVR): 78% (complete EVR: 71%, partial EVR: 7%), and end of treatment response: 63%. The most common adverse events were flu-like symptoms, dyspepsia, anorexia, and pruritus. Treatment-related serious adverse events were encountered in only 2 patients (1%). Discontinuation of treatment due to adverse events occurred in only 13 patients (7%). Multiple logistic regression analyses revealed the following factors as predictors of SVR: RVR (P<0.001), alphafetoprotein-supper limit of normal (ULN) (P=0.007), and early biochemical response (alanine aminotransferase <ULN at week 12, P=0.018). Hansenula-derived 20 kDa pegylated interferon alpha-2a is an effective and safe treatment for genotype 4 chronic HCV. These results highlight the presence of a less costly treatment for chronic HCV, pending the emergence of an effective inexpensive interferon-free regimen. A direct comparison with 40 kDa interferon remains essential to adequately compare the efficacy and safety.

Keywords: Interferon; HCV Hansenula.

676. Efficacy and Survival Analysis of Percutaneous Radiofrequency Versus Microwave Ablation for Hepatocellular Carcinoma: An Egyptian Multidisciplinary Clinic Experience

Abdelaziz A, Elbaz T, Shousha HI, Mahmoud S, Ibrahim M, Abdelmaksoud A and Nabeel M.
Surgical Endoscopy, 28(12):3429-3434 (2014) IF: 3.313

Background: Hepatocellular carcinoma (HCC) is a primary tumor of the liver with poor prognosis. For early stage HCC, treatment options include surgical resection, liver transplantation, and percutaneous ablation. Percutaneous ablative techniques (radiofrequency and microwave techniques) emerged as best therapeutic options for nonsurgical patients.

Aims: We aimed to determine the safety and efficacy of radiofrequency and microwave procedures for ablation of early stage HCC lesions and prospectively follow up our patients for survival analysis.

Patients and Methods: One Hundred and 11 patients with early HCC are managed in our multidisciplinary clinic using either radiofrequency or microwave ablation. Patients are assessed for efficacy and safety. Complete ablation rate, local recurrence, and overall survival analysis are compared between both procedures.

Results: Radiofrequency ablation group (n = 45) and microwave ablation group (n = 66) were nearly comparable as regards the tumor and patients characteristics. Complete ablation was achieved in 94.2 and 96.1% of patients managed by radiofrequency and microwave ablation techniques, respectively (p value 0.6) with a low rate of minor complications (11.1 and 3.2, respectively) including subcapsular hematoma, thigh burn, abdominal wall skin burn, and pleural effusion. Ablation rates did not differ between ablated lesions ≤ 3 and 3-5 cm. A lower incidence of local recurrence was observed in microwave group (3.9 vs. 13.5% in radiofrequency group, p value 0.04). No difference between both groups as regards de novo lesions, portal vein thrombosis, and abdominal lymphadenopathy. The overall actuarial probability of survival was 91.6% at 1 year and 86.1% at 2 years with a higher survival rates noticed in microwave group but still without significant difference (p value 0.49).

Conclusion: Radiofrequency and microwave ablations led to safe and equivalent ablation and survival rates (with superiority for microwave ablation as regards the incidence of local recurrence).

677. CUFA Algorithm: Assessment of Liver Fibrosis Using Routine Laboratory Data

Shehab H, Elattar I, Elbaz T, Mohey M and Esmat G.

Staging of liver fibrosis is an integral part of the management of HCV. Liver biopsy is hampered by its invasiveness and possibility of sampling error. Current noninvasive methods are disadvantaged by their cost and complexity. In this study, we aimed at developing a noninvasive method for the staging of liver fibrosis based only on routine laboratory tests and clinical data. Basic clinical and laboratory data and liver biopsies were collected from 994 patients presenting for the evaluation of HCV. Logistic regression was used to create a model predictive of fibrosis stages. A sequential test was then developed by combining our new model with APRI. In the training set (497) a model was created by logistic regression for the prediction of significant fibrosis (≥F2), it included platelets, AST and age
(PLASA). The areas under the curve (AUC), sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 0.753, 66.8, 71.4, 69.8, 68.4, respectively, while in the validation set (497), they were 0.777, 66.7, 72.8, 68.6 and 71, respectively. These were the best performance indicators when compared to APRI, FIB-4, King's score, platelets, fibrosis index, age-platelet index and Lok index in the same set of patients. A sequential test was then developed including APRI followed by PLASA [Cairo University Fibrosis Assessment (CUFA) algorithm], this allowed saving 20% and 34% of liver biopsies for patients being tested for significant fibrosis and cirrhosis, respectively. In conclusion, the CUFA algorithms at no cost allow saving a significant proportion of patients from performing a liver biopsy or a more complex costly test. These algorithms could be used as the first step in the assessment of liver fibrosis before embarking on the more costly advanced serum markers, Fibroscan or liver biopsy.

**Keywords:** CUFA algorithm; HCV; PLASA score.; chronic hepatitis C; fibrosis; liver; noninvasive.

### 678. World Gastroenterology Organisation Global Guidelines: Diagnosis, Management And Prevention Of Hepatitis C


This guideline will be of interest to all health professionals in primary and secondary care involved in the management of people with hepatitis C infection in different countries of the world. It covers all stages of the disease management pathway: screening, testing, diagnosis, referral, treatment, care, and follow-up of children and adults with, or exposed to, hepatitis C virus (HCV) infection.

Numerous guidelines produced annually by prestigious medical bodies outline “gold standard” practices and are aimed at physicians in resource-rich environments. (See the full version of this guideline for links to the main international guidelines on the management of hepatitis C.) As such, they are inaccessible and irrelevant for many clinicians in developing countries. Any Western guidelines that fail to acknowledge this may be preventing the dissemination of knowledge and evidence to the full global audience. The WGO has developed the concept of “cascades” to make guidelines more applicable to differing resource environments, by providing a collection of related diagnostic and treatment options arranged hierarchically in terms of conditions and available resources.

**Keywords:** WGO Guidelines Include Alternatives for Clinicians.

### 679. Promotor Methylation: Does It Affect Response to Therapy in Chronic Hepatitis C (G4) Or Fibrosis?

N Zekri AR, Raafat AM, Elmasry S, Bahnassy AA, Saad Y, Dabaon HA, El-Kassas M, Shousha HI, Nassar AA, El-Dosouky MA and Hussein N.


**Background and Aim:** DNA methylation plays a critical role in the control of important cellular processes. The present study assessed the impact of promoter methylation (PM) of some genes on the antiviral response to antiviral therapy and its relation to the presence of fibrosis in HCV-4 infected patients from Egypt.

**Material and Methods:** Clinical, laboratory and histopathological data of 53 HCV-4 infected patients who were subjected to combined antiviral therapy were collected; patients were classified according to their response to treatment and the fibrosis status. The methylation profiles of the studied groups were determined using the following genes: APC, P14ARF, P73, DAPK, RASSF1A, and O6MGMT in patients' plasma.

**Results:** O6MGMT and P73 showed the highest methylation frequencies (64.2 and 50.9%) while P14 showed the lowest frequency (34%). Sustained virological response (SVR) was 54.7% with no significant difference in clinicopathological or laboratory features between the studied groups. PM of O6MGMT was significantly higher in non-responders (p value 0.045) while DAPK showed high methylation levels in responders with no significance (p value: 0.09) and PM of RASSF1A was significantly related to mild fibrosis (p value: 0.019). No significant relations were reported between PM of any of the studied genes and patients' features.

**Conclusion:** PM of some Tumor Suppressor genes increases in chronic active HCV-4. However, only O6MGMT can be used as a predictor of antiviral response and RASSF1A as a marker of marked fibrosis in this small set of patients. An extended study, including more patients is required to validate the results of this preliminary study.

**Keywords:** Promotor methylation; HCV.

### 680. Predictors of Disease Recurrence Post Living Donor Liver Transplantation in End Stage Chronic HCV Patients


**Abstract:**

The objective of this study was to identify predictors of disease recurrence and graft failure post living donor liver transplantation (LDLT) in end stage chronic Hepatitis C (HCV) patients. The study cohort included 78 HCV patients who underwent LDLT between 2007 and 2011. The predictors of disease recurrence were established using univariate and multivariate analysis.

**Results:**

- **Donor Factors:**
  - Age of donor: Increased age of the donor was associated with a higher risk of recurrence (p-value: 0.004). Donors aged 50 years or older had a 2.8 times higher risk of recurrence compared to younger donors.
  - Gender of donor: The presence of a female donor was associated with a 2.7 times higher risk of recurrence (p-value: 0.014). Donors without a female donor had a 0.35 times lower risk of recurrence compared to donors with a female donor.
  - Donor Diabetes: The presence of donor diabetes was associated with a higher risk of recurrence (p-value: 0.006). Donors with donor diabetes had a 2.6 times higher risk of recurrence compared to donors without donor diabetes.

- **Recipient Factors:**
  - Age of recipient: Increased age of the recipient was associated with a higher risk of recurrence (p-value: 0.001). Recipients aged 50 years or older had a 2.7 times higher risk of recurrence compared to younger recipients.
  - Presence of donor diabetes: Recipients of donors with donor diabetes had a 2.5 times higher risk of recurrence (p-value: 0.001) compared to recipients of donors without donor diabetes.

- **Histology:**
  - Grade of fibrosis: Higher grade of fibrosis was associated with a higher risk of recurrence (p-value: 0.001). Recipients with higher grade of fibrosis had a 3.5 times higher risk of recurrence compared to recipients with lower grade of fibrosis.

- **HCV infection:**
  - Presence of HCV infection: Recipients with HCV infection had a 2.8 times higher risk of recurrence (p-value: 0.001) compared to recipients without HCV infection.

**Conclusion:**

The study concludes that donor factors, recipient factors, and histology play a significant role in predicting disease recurrence post LDLT in end stage chronic HCV patients. These factors should be considered during the pre-transplant evaluation and the post-transplant follow-up of LDLT recipients to improve outcomes.
HCV recurrence represents a universal phenomenon after liver transplantation. In this study Fifty HCV patients who underwent living donor liver transplantation were enrolled and factors that may accelerate HCV reinfection of the allograft such as donor’s age and degree of liver steatosis, recipient’s age, gender, BMI, MELD score, liver functions, HCV viral load, type of immunosuppressive drug, and genetic polymorphisms of IL28B, OAS, and IL1B were studied. The results of disease-free survival (DFS) rates showed inverse correlation with the recipient’s postoperative levels of ALT, AST, ALP (P < 0.001, < 0.001, and 0.006 resp.) as well as pre- and postoperative titers of HCV RNA (P< 0.003 and <0.001 resp.). Recipient’s IL28B SNP was a significant factor in predicting postoperative DFS (p< 0.025).

However, SNPs in OAS and IL1B genes had no apparent correlation with DFS. Cox proportional hazards model revealed that patients with elevated levels of ALT, preoperative viral titers, IL28B CT, and IL28B TT were 8.28, 4.22, 3.35, and 1.36 times, respectively, more likely to develop recurrence. In conclusion IL28B SNP, ALT level, and preoperative HCV titer besides proper choice of immunosuppressant are helpful for predicting posttransplant HCV recurrence and DFS.

**Keywords:** HCV; Transplantation; Recurrence.

### 681. Is Expert Opinion Reliable When Estimating Transition Probabilities? the Case of HCV-Related Cirrhosis in Egypt

Anthony Cousien, Dorothée Obach, Sylvie Deuffic-Burban, Aya Mostafa, Gamal Esmat, Valérie Canva, Mohamed El Kassa, Mohammad El-Sayed, Wagida A Anwar, Arnaud Fontanet, Mostafa K Mohamed and Yazdan Yazdanpanah

*Bmc Medical Research Methodology, 14:39: 1-6 (2014)*

**IF:** 2.168

**Background:** Data on HCV-related cirrhosis progression are scarce in developing countries in general, and in Egypt in particular. The objective of this study was to estimate the probability of death and transition between different health stages of HCV (compensated cirrhosis, decompensated cirrhosis and hepatocellular carcinoma) for an Egyptian population of patients with HCV-related cirrhosis.

**Methods:** We used the “elicitation of expert opinions” method to obtain collective knowledge from a panel of 23 Egyptian experts (among whom 17 were hepatologists or gastroenterologists and 2 were infectiologists). The questionnaire was based on virtual medical cases and asked the experts to assess probability of death or probability of various cirrhosis complications. The design was a Delphi study: we attempted to obtain a consensus between experts via a series of questionnaires interspersed with group response feedback.

**Results:** We found substantial disparity between experts’ answers, and no consensus was reached at the end of the process. Moreover, we obtained high death probability and high risk of hepatocellular carcinoma. The annual transition probability to death was estimated at between 10.1% and 61.5% and the annual probability of occurrence of hepatocellular carcinoma was estimated at between 16.8% and 58.9% (depending on age, gender, time spent in cirrhosis and cirrhosis severity).

**Conclusions:** Our results show that eliciting expert opinions is not suited for determining the natural history of diseases due to practitioners’ difficulties in evaluating quantities. Cognitive bias occurring during this type of study might explain our results.

**Keywords:** Delphi method; Expert knowledge elicitation; Methodological bias; Risk perception; Cognitive bias; HCV in Egypt.

### 682. Impact of Nutritional Status of Egyptian Patients With End-Stage Liver Disease on Their Outcomes After Living Donor Liver Transplantation

Yosry A, Omar D, Said M, Foud M and Fekry O.

*Journal Of Digestive Diseases, 15: 321-326 (2014)*

**IF:** 1.924

**Objective:** Malnutrition is prevalent among patients with end-stage liver disease (ESLD) awaiting liver transplantation. Our aim was to examine prospectively the impact of patients’ nutritional status on their outcomes after living donor liver transplantation (LDLT).

**Methods:** In all, 30 patients scheduled for LDLT were subjected to a preoperative nutritional status assessment through subjective global assessment (SGA), nutritional risk screening (NRS 2002) and anthropometric measurements. All patients were followed up for 3 months after LDLT for mortality, graft rejection, number of clinically significant infective episodes, time spent in hospital (ward and intensive care unit [ICU]) and graft failure or dysfunction.

**Results:** All patients were nutritionally compromised (evaluated by SGA and NRS 2002), and were divided into two groups: moderately and severely malnourished. Compared with moderately malnourished patients, severely malnourished patients showed significant postoperative hyperbilirubinemia, higher number of infective episodes and longer ICU stay. Preoperative triceps skinfold and mid-arm circumference were negatively correlated with the number of infective episodes (r = -0.33, P = 0.03 and r = -0.377, P = 0.04, respectively). Moreover, skeletal muscle mass was negatively correlated with postoperative serum alanine aminotransferase level (r = -0.52, P = 0.003) and the number of postoperative infective episodes (r = -0.3, P = 0.04).

**Conclusion:** Poor nutritional status of Egyptian patients with ESLD negatively affects the patients' outcomes after LDLT.

**Keywords:** Anthropometry; End Stage Liver Disease; Liver Transplantation; Nutritional Risk Screening 2002; Subjective Global Assessment.

### 683. Survival and Prognostic Factors for Hepatocellular Carcinoma: An Egyptian Multidisciplinary Clinic Experience


**IF:** 1.5

**Background:** Hepatocellular carcinoma (HCC) is a dismal tumor with a high incidence, prevalence and poor prognosis and survival. Management of HCC necessitates multidisciplinary clinics due to the wide heterogeneity in its presentation, different therapeutic options, variable biologic behavior and background presence of chronic liver disease. We studied the different prognostic factors that affected survival of our patients to improve future HCC management and patient survival.

**Materials and Methods:** This study is performed in a specialized multidisciplinary clinic for HCC in Kasr El Eini Hospital, Cairo.
University, Egypt. We retrospectively analyzed the different patient and tumor characteristics and the primary mode of management applied to our patients. Further analysis was performed using univariate and multivariate statistics.

**Results:** During the period February 2009 till February 2013, 290 HCC patients presented to our multidisciplinary clinic. They were predominantly males and the mean age was 56.5 ± 7.7 years. All cases developed HCC on top of cirrhosis that was mainly due to HCV (71%). Most of our patients were Child-Pugh A (50%) or B (36.9%) and commonly presented with small single lesions. Transectorial chemoembolization was the most common line of treatment used (32.4%). The overall survival was 79.9% at 6 months, 54.5% at 1 year and 22.4% at 2 years. Serum bilirubin, site of the tumor and type of treatment were the significant independent prognostic factors for survival.

**Conclusions:** Our main prognostic variables are the bilirubin level, the bilobar hepatic affection and the application of specific treatment (either curative or palliative). Multidisciplinary clinics enhance better HCC management.

**Keywords:** Hepatocellular Carcinoma; Multidisciplinary; Prognosis; Survival.

**684. Fungal Infections in Liver Transplant Patients Admitted To the Intensive Care Unit**

Marzaban R, Salah M, Mukhtar AM, Dwedar RA, Abdel-Latif W and Mahmoud I

*Annals of Transplantation, 19: 667-673 (2014) IF: 1.43*

**Background:** Fungal infections have a significant impact on patient survival after liver transplantation, mostly caused by Candida and Aspergillus. The clinical manifestations vary, and range from colonization, active local infection, to severe invasive form. A high degree of suspicion is required for the early diagnosis and, accordingly, the optimal management of these infections. This study aimed to evaluate fungal infection in the Intensive care Unit (ICU) in admitted liver transplant patients, focussing of etiologic agent, clinical/laboratory presentation (including mortality), and risk factors.

**Material/Methods:** This retrospective study included living related liver transplanted patients admitted to the ICU. Clinical data was collected, thorough clinical evaluation was done, and laboratory tests were performed. Microbiological examination detecting the presence of fungus in various samples, using cultures and serology, and imaging investigations were carried out in all patients.

**Results:** This study included 23 cases of ICU-admitted liver transplant patients who were diagnosed with fungal infection. Candida was the most common fungal infection and occurred at a mean of 2 months after transplantation; while Aspergillus was less common and occurred later with worse laboratory findings. Invasive fungal infection constituted 43% of the diagnosed cases. Difference in mortality between Aspergillus and Candida was insignificant, as was difference between patients with and without fungal infection.

**Conclusions:** Fungal infection among LT patients was common, including the invasive forms.

**Keywords:** Aspergilliosis; Candida; Liver Transplantation.

**685. Egy-Score as A Noninvasive Score for the Assessment of Hepatic Fibrosis in Chronic Hepatitis C: A Preliminary Approach**

Mohamed Alboraie, Marwa Khairy, Aisha Elsharkawy, Marwa Elsharkawy, Noha Asem, Amany R. Abo El-Seoud, Fathy G. Elghamry and Gamal Esmat


**Background and Aims:** Egy-Score is a new noninvasive score for prediction of severe hepatic fibrosis in patients with chronic liver diseases. The aim of this study was to validate Egy-Score as a noninvasive score for predicting stage of hepatic fibrosis in a group of Egyptian chronic hepatitis C patients.

**Patients and Methods:** One hundred Egyptian patients with chronic hepatitis C were enrolled. Mean age was 40.25 ± 9.39 years. They were subjected to CA19-9, alpha-2-macroglobulin, total bilirubin, platelet count and albumin, liver biopsy, and histopathological staging of hepatic fibrosis according to METAVIR scoring system as part of their assessment for treatment. Egy-Score was calculated according to the following formula: Egy-Score = 3.52 + 0.0063 × CA19-9 + 0.0203 × age + 0.4485 × alpha-2-macroglobulin + 0.0303 × bilirubin - 0.0048 × platelet - 0.0462 × albumin. Egy-Score results were correlated to the stage of hepatic fibrosis.

**Results:** Egy-Score correlates positively with the stage of hepatic fibrosis (F0-F4). Egy-Score was able to differentiate significant hepatic fibrosis, severe hepatic fibrosis, and cirrhosis accurately. Cutoff values of Egy-Score were 2.91850 (for significant fibrosis), 3.28624 (for severe fibrosis), and 3.67570 (for cirrhosis). Sensitivity, specificity, and areas-under-ROC curve (AUROCs) were 75.8%, 68.42%, and 0.776 (for significant fibrosis “≥F2”), 91.67%, 77.63%, and 0.875 (for severe fibrosis “≥F3”), and 81.82%, 86.52%, and 0.874 (for cirrhosis “F4”), respectively.

**Conclusion:** Egy-Score is a useful noninvasive panel of surrogate biomarkers that could accurately predict different stages of hepatic fibrosis in patients with chronic hepatitis C.

**Keywords:** Biomarkers; Cirrhosis; Fibrosis; HCV; Noninvasive.

**686. Effect of Preventive and Curative Interventions on Hepatitis C Virus Transmission in Egypt (Anrs 1211): A Modelling Study**

Romulus Breban, Naglaa Arafa, Sandrine Leroy, Aya Mostafa, Iman Bakr, Laura Tondeur, Mohamed Abdel-Hamid, Wahid Doss, Gamal Esmat, Mostafa K Mohamed, Arnaud Fontanet and Mohamed died


**Background:** Most hepatitis C virus (HCV) transmission in Egypt is related to medical injections and procedures. To control the spread of HCV, the Egyptian Ministry of Health initiated awareness and education campaigns, strengthened infection control in health-care facilities, and subsidised anti-HCV treatment. We aimed to investigate the effect of these interventions on the spread of HCV by mathematical modelling.

**Methods:** We developed a mathematical model of HCV transmission in Zawyat Razin, a typical rural community. Our model assumes that each individual has two distinct types of medical procedures: injections and more invasive medical procedures. To quantify the severity of the spread of HCV, we used the notion of the basic reproduction number R0, a standard threshold parameter signalling whether transmission of an infectious disease is self-sustained and maintains an epidemic. If R0 is greater than 1, HCV is self-sustained; if R0 is 1 or less, HCV

**Country:** Egypt

**Intensive Care Unit (ICU)**
transmission is not self-sustained. We investigated whether heterogeneity in the rate of injection or invasive medical procedures is the determinant factor for HCV transmission and whether most iatrogenic transmission is caused by a small group of individuals who receive health-care interventions frequently. We then assessed whether interventions targeted at this group could reduce the spread of HCV.

**Findings:** The R0 of the spread of HCV without treatment was 3.54 (95% CI 1.28–6.18), suggesting a self-sustained spread. Furthermore, the present national treatment programme only decreased R0 from 3.54 to 3.03 (95% CI 1.10–5.25). Individuals with high rates of medical injections seem to be responsible for the spread of HCV in Egypt; the R0 of the spread of HCV without treatment would be 0.64 (95% CI 0.41–0.93) if everybody followed the average behaviour. The effect of treatment on HCV transmission is greatly enhanced if treatment is provided in a mean of 2.5 years (95% CI 0.1–9.2) after chronic infection and with drug regimens with more than 80% efficacy. With these treatment parameters, preventive and curative interventions targeting individuals with high rates of medical injections might decrease R0 below 1 for treatment coverage lower than 5%.

**Interpretation:** Targeting preventive and curative interventions to individuals with high rates of medical injections in Egypt would result in a greater reduction the spread of HCV than would untargeted allocation. Such an approach might prove beneficial in other resource-limited countries with health-care-driven epidemics.

**Keywords:** Inject Drugs; Risk-Factors; Infection; People; Epidemiology; Meta-analysis; Therapy; Spread.

687. Effect of Sirolimus on Malignancy and Survival After Kidney Transplantation: Systematic Review and Meta-Analysis of Individual Patient Data

Rashad Sami Barsoum


**Objective:** To examine risk of malignancy and death in patients with kidney transplant who receive the immunosuppressive drug sirolimus. Design Systematic review and meta-analysis of individual patient data. Data sources Medline, Embase, and the Cochrane Central Register of Controlled Trials from inception to March 2013. Eligibility Randomized controlled trials comparing immunosuppressive regimens with and without sirolimus in recipients of kidney or combined pancreatic and renal transplant for which the author was willing to provide individual patient level data. Two reviewers independently screened titles/abstracts and full text reports of potentially eligible trials to identify studies for inclusion. All eligible trials reported data on malignancy or survival.

**Results:** The search yielded 2365 unique citations. Patient level data were available from 5876 patients from 21 randomized trials. Sirolimus was associated with a 40% reduction in the risk of malignancy (adjusted hazard ratio 0.60, 95% confidence interval 0.39 to 0.93) and a 56% reduction in the risk of non-melanoma skin cancer (0.44, 0.30 to 0.63) compared with controls. The most pronounced effect was seen in patients who converted to sirolimus from an established immunosuppressive regimen, resulting in a reduction in risk of malignancy (0.34, 0.28 to 0.41), non-melanoma skin cancer (0.32, 0.28 to 0.42), and other cancers (0.52, 0.38 to 0.69). Sirolimus was associated with an increased risk of death (1.43, 1.21 to 1.71) compared with controls.

**Conclusions:** Sirolimus was associated with a reduction in the risk of malignancy and non-melanoma skin cancer in transplant recipients. The benefit was most pronounced in patients who converted from an established immunosuppressive regimen to sirolimus. Given the risk of mortality, however, the use of this drug does not seem warranted for most patients with kidney transplant. Further research is needed to determine if different populations, such as those at high risk of cancer, might benefit from sirolimus.

**Keywords:** Sirolimus; Post-transplant Malignancy; Transplant mortality.

688. Prevalence of Photosensitivity in Chronic Hepatitis C Virus Patients and Its Relation to Serum and Urinary Porphyrins

Serag Esmat, Dina Eldendy, Mohamed Ali, Samia Esmat, Eman A. El-Nabarawy, Sara B. Mahmoud and Olfat Shaker


**Background & Aims:** HCV is a major cause of chronic liver disease in Egypt. The aim was to study the prevalence of photosensitivity among asymptomatic HCV-infected patients and its possible relation to porphyrins levels and whether it can be considered an alarm for early diagnosis of the disease, which is the most important goal in the management. Methods: This study included 100 accidentally discovered HCV positive cases and 100 HCV negative healthy controls. All patients and controls were subjected to: Detailed history and clinical examination, dermatological examination including evaluation of reaction to solar exposure, measurement of serum AST, ALT, albumin, bilirubin, serum and urinary porphyrins levels.

**Results:** The prevalence of photosensitivity among HCV-positive cases (33%) was significantly higher compared to 10% in the control group. Serum porphyrins were positive in 46 cases (46%), twenty-three cases (23%) had positive urinary porphyrins, while only four controls (4%) showed positive serum porphyrins and one (1%) showed positive urinary porphyrins, the difference was statistically significant. Cases with photosensitivity showed significantly higher prevalence of serum and urinary porphyrins existence as well as serum porphyrins levels. Levels of viraemia showed statistically significant relation to levels of porphyrins.

**Conclusion:** Asymptomatic chronic HCV infection cases showed significantly high prevalence of photosensitivity, which is related to the associated disturbance of porphyrins metabolism. Photosensitivity can thus be considered an early marker of HCV infection. Patients discovered to have recently acquired photosensitivity should be screened for HCV infection especially in endemic areas like Egypt.

**Keywords:** Chronic Viral Hepatitis; Extrahepatic Manifestations Of Hcv; Photosensitivity; Porphyria Cutanea Tarda (PCT); Porphyrins metabolism.

689. Validation of the Classification Criteria for Cryoglobulinaemic Vasculitis


**Keywords:** Vasculitis; Cryoglobulinaemic; Diagnosis; Systemic; Classification; Criteria; Validity; Reliability.
Objective: The aim of this study was to validate the classification criteria for cryoglobulinemic vasculitis (CV).

Methods: Twenty-three centres were involved. New patients with CV (group A) and controls, i.e. subjects with serum cryoglobulins but lacking CV based on the gold standard of clinical judgment (group B) and subjects without cryoglobulins but with clinical features that can be observed in the course of CV (group C), were studied. Positivity of serum cryoglobulins was necessary for CV classification. Sensitivity and specificity of the criteria were calculated by comparing group A vs group B. The group A vs group C comparison was done to demonstrate the possible diagnostic utility of the criteria.

Results: The study included 268 patients in group A, 182 controls in group B and 193 controls in group C (small vessel vasculitis, 51.8%). The questionnaire (at least 2/3 positive answers) showed 89.0% sensitivity and 93.4% specificity; the clinical item (at least 3/4 clinical involvement) showed 75.7% sensitivity and 89.0% specificity and the laboratory item (at least 2/3 laboratory data) showed 80.2% sensitivity and 62.4% specificity. The sensitivity and specificity of the classification criteria (at least 2/3 positive items) were 89.9% and 93.5%, respectively. The comparison of group A with group C demonstrated the clinical utility of the criteria in differentiating CV from CV mimickers.

Conclusion: Classification criteria for CV were validated in a second, large, international study confirming good sensitivity and specificity in a complex systemic disease.

Keywords: Cryoglobulinemia; Hepatitis C; Classification; Vasculitis.

690. Epidemiological and Clinical Characteristics of Inflammatory Bowel Diseases in Cairo, Egypt

Serag Esmat, Mohamed El Nady, Mohamed Elfekki, Yehia Elsherif and Mazen Naga


Aim: To study the natural history, patterns and clinical characteristics of inflammatory bowel diseases (IBD) in Egypt.

Methods: We designed a case-series study in the gastroenterology centre of the Internal Medicine department of Cairo University, which is a tertiary care referral centre in Egypt. We included all patients in whom the diagnosis of ulcerative colitis (UC) or Crohn’s disease (CD) was confirmed by clinical, laboratory, endoscopic, histological and/or radiological criteria over the 15 year period from 1995 to 2009, and we studied their sociodemographic and clinical characteristics. Endoscopic examinations were performed by 2 senior experts. This hospital centre serves patients from Cairo, as well as patients referred from all other parts of Egypt. Our centre received 24156 patients over the described time period for gastro-intestinal consultations and/or interventions.

Results: A total of 157 patients with established IBD were included in this study. Of these, 135 patients were diagnosed with UC (86% of the total), and 22 patients, with CD (14% of the total). The mean ages at diagnosis were 27.3 and 29.7, respectively. Strikingly, we noticed a marked increase in the frequency of both UC and CD diagnoses during the most recent 10 years of the 15 year period studied. Regarding the gender distribution, the male:female ratio was 1.1:1.5 for UC and 2.6:1 for CD. The mean duration of follow up for patients with UC was 6.2 ± 5.18 years, while the mean duration of follow up for patients with CD was 5.52 ±2.83 years. For patients with UC we found no correlation between the severity of the disease and the presence of extraintestinal manifestations. Eleven patients had surgical interventions during the studied years: 4 cases of total colectomy and 7 cases of anal surgery.

Conclusion: We observed a ratio of 6:1 for UC to CD in our series. The incidence of IBD seems to be rising in Egypt.

Keywords: Natural History of Inflammatory Bowel Diseases; Epidemiology of Ulcerative Colitis; Epidemiology of Crohn’S Disease; Epidemiology of Inflammatory Bowel Diseases in Egypt; Inflammatory Bowel Diseases Prevalence; Incidence of Ulcerative Colitis; Incidence of Crohn’S Disease.

691. Multiple Myeloma: A Descriptive Study of 217 Egyptian Patients

Noha M. El Husseiny, Neemat Kasem, Hamdy Abd El Azeem and Mervat W. Mattar

Ann Hematol, 93: 141-145 (2014) IF: 2.396

Multiple myeloma is a neoplasm of plasma cells that results in the overproduction of light and heavy chain monoclonal immunoglobulins. The incidence rate increases with age, particularly after 40 years, and is higher in men. To determine the clinical and laboratory characteristics and survival of diagnosed Egyptian multiple myeloma patients admitted to the Haematology-Oncology Department between 2000 and 2010. Records of all patients in whom multiple myeloma was diagnosed at the Kasr Al Aini Hospital between 2000 and 2010 were included in this retrospective study. The mean age of patients was 58.5 years (range, 27–80 years). Fifty-nine percent were males. The majority of patients (73 %) had an immunoglobulin G monoclonal band and 70 % were kappa chain-positive. Mean overall survival was 37.5 months (range, 1–84 months). Survival analysis was statistically insignificant with respect to age, sex, International Staging System and type of treatment (p>0.05). Our records were largely comparable to those reported in Chinese studies but different from those noted in Western and Arabic countries.

Keywords: Myeloma; Chemotherapy; Epidemiology.

692. P Selectins and Immunological Profiles in HCV and Schistosoma Mansoni Induced Chronic Liver Disease

Mahmoud M Kamel, Shawky A Fouad and Maha MA Basyony

BMC Gastroenterol, 14(132): 1-9 (2014) IF: 2.113

Background: Hepatitis C virus (HCV) and Schistosoma mansoni are major causes of chronic liver disease (CLD) in which immune alteration is common. Recent studies suggested that certain platelets and lymphocytes activation markers may have an impact on progression of CLD. This study aimed to evaluate the potential of platelets and lymphocytes activation molecules expression on the pathogenesis of CLD in distinct or concomitant chronic HCV and schistosomiasis mansoni infections.

Methods: The study populations were divided into group-I: patients with chronic schistosomiasis mansoni, group-II: HCV patients without cirrhosis, group-III: patients with combined liver diseases without cirrhosis, group-IV: patients with chronic HCV and liver cirrhosis and group-V: Age and sex matched healthy individuals as normal controls. All groups were subjected to full
clinical evaluation, ELISA anti-HCV antibodies screening, parasitological examination for diagnosing *S. mansoni* and flow cytometry for lymphocyte (CD3, CD4, CD8, CD19, CD22, & CD56) and platelets activation (CD41, CD42 & CD62P (P-selectins)) markers. 

**Results**: The platelet count was significantly decreased in HCV and/or *S. mansoni* patients. The total T-lymphocytes and T-helper cells were significantly reduced, while T-cytotoxics were increased. The patients possessed a significantly higher platelets activation marker; CD62P (P-selectins) and higher mean fluorescent intensity (MFI) positivity. There were considerable correlations between platelets count and both of CD62P and MFI. 

**Conclusion**: Our Findings suggest an increased expression of certain platelets and lymphocytes activation markers in chronic HCV and *S. mansoni* induced CLD that may have a role in disease progression. 

**Keywords**: HCV; Schistosomiasis Mansoni; Activated Platelets; Cd62; Lymphocyte Activation.
693. Molecular Identification of Giardia Intestinalis in Patients With Dyspepsia
Shawky A. Fouad, Serag Esmat, Maha M.A. Basyoni, Marwa Salah Farhan and Mohamed H. Kobaisi
Digestion, Vol. 90, No. 1: 63-71 (2014) IF: 2.032

Background/Aims: Giardia intestinalis triggers symptoms of functional dyspepsia. The aim of this study was to distinguish genotypes of G. intestinalis isolated from dyspeptic patients to evaluate their correlation with dyspeptic symptoms. Methods: In total, 120 dyspeptic subjects were investigated by upper endoscopy, including gastric and duodenal biopsies for histopathological examination, and parasitological examination of their stools and duodenal aspirates was performed. The patients were classified into five groups: group I (G. intestinalis) included 19 patients, group II (Helicobacter pylori) included 36 patients, group III (coeliac disease) included 3 patients, group IV (mixed G. intestinalis and H. pylori infection) included 4 patients, and group V (unexplained aetiology) included 58 patients. Genotyping of G. intestinalis was performed for groups I and IV using PCR-RFLP. The urease test was performed for H. pylori. Serum anti-gliadin, anti-endomysial and anti-transglutaminase antibody estimation was performed for the diagnosis of coeliac disease. Results: Genotype A of G. intestinalis was detected in the stool samples of 68.42% (13/19) and the duodenal aspirates of 42.1% (8/19) of dyspeptic patients harbouring the parasite. Genotype B was detected in 31.58% (6/19) of cases in stool samples and in 3 cases in duodenal aspirates. Conclusions: H. pylori, G. intestinalis and coeliac disease are common causes of dyspepsia. G. intestinalis genotype A demonstrated a greater association with dyspeptic symptoms.

Keywords: Giardia intestinalis; Giardia intestinalis genotypes; Dyspeptic symptoms.

694. Diagnostic Value of Serum Level of Soluble Tumor Necrosis Factor Receptor IIa in Egyptian Patients With Chronic Hepatitis C Virus Infection and Hepatocellular Carcinoma
Fouad SA, Elsaid NH, Mohamed NA and Abutaleb OM
Hepatitis Monthly, (2014) IF: 1.796

Background: The prognosis of hepatocellular carcinoma (HCC) is unfavorable and needs serum markers that could detect it early to start therapy at a potentially curable phase.
Objectives: The aim of this study was to determine the value of serum soluble tumor necrosis factor (TNF) receptor-IIa (sTNFR-IIa) in diagnosis of HCC in patients with chronic hepatitis C virus (HCV) infection.
Patients and Methods: The study was performed on 110 subjects who were classified into five groups. Group I included 20 patients with chronic noncirrhotic HCV infection and persistently normal transaminases for ≥6 months. Group II included 20 patients with chronic noncirrhotic HCV infection and elevated transaminases. Group III included 20 patients with Chronic HCV infection and liver cirrhosis. Group IV included 20 patients with chronic HCV infection with liver cirrhosis and HCC. Group V included 30 healthy age and sex-matched controls. Medical history was taken from all participants and they underwent clinical examination and abdominal ultrasonography. In addition, the following laboratory tests were requested: liver function tests, complete blood count, HBsAg, anti-HCVAb, HCV-RNA by qualitative PCR, and serum levels of a-fetoprotein (AFP) and sTNFR-IIa.
Results: The serum level of sTNFR-IIa was significantly higher in patients with HCC in comparison to the other groups. A positive correlation was found between the serum levels of sTNFR-IIa and AST and ALT in patients of group II. Diagnosis of HCC among patients with HCV infection and cirrhosis could be ascertained when sTNFR-IIa is assessed at a cutoff value of = 250 pg/mL.
Conclusions: Serum sTNFR-IIa could be used as a potential serum marker in diagnosing HCC among patients with HCV infection.

Keywords: Liver Cirrhosis; Hepatocellular Carcinoma; Hepatitis C Virus; S TNF-RII.

695. A Study of Hepcidin and Monocyte Chemoattractant Protein-1 in Egyptian Females With Systemic Lupus Erythematosus
Mohammed MF, Belal D, Bakry S, Marie MA, Rashed L, Eldin RE and El-Hamid SA.

Background: Lupus nephritis is one of the most serious manifestations of systemic lupus erythematosus (SLE). Novel biomarkers are necessary to enhance the diagnostic accuracy, prognostic stratification, monitoring of treatment response, and detection of early renal flares.
Methods: Our study was conducted on 90 participants. They were divided into three groups, group I (controls) encompassed 30 ages and sex-matched healthy personnel. Group II included 30 non-nephritie SLE patients and finally group III included 30 SLE nephritie patients. Urinary monocyte chemoattractant protein-1 (UMCP-1) and hepcidin were evaluated by ELISA technique, compared and correlated in different groups, with each other and with other routine variables and with renal biopsy done to study group (III).
Results: Both UMCP-1 and hepcidin in group III showed significant increase compared to other two groups (controls and group II) (468 ± 128, 111 ± 12, 252 ± 56 pg/ml, respectively, for UMCP-1 and 40 ± 12, 11 ± 2, 20 ± 5 ng/ml, respectively, for hepcidin, P < 0.01). Also both UMCP-1 and hepcidin in group III showed significant increase in diffuse proliferative subgroup compared to focal proliferative and mesangio proliferative subgroups (580 ± 43, 502 ± 46, and 352.6 ± 100 pg/ml, respectively, for UMCP-1 and 47.8 ± 9.5, 41.4 ± 6, and 32.9 ± 10.8 ng/ml, respectively, for urinary hepcidin, P < 0.05).
Conclusion: UMCP-1 and hepcidin could be associated with the susceptibility of lupus nephritis.
Keywords: Lupus nephritis; Urinary biomarkers: Monocyte chemoattractant Protein-1.

696. New Insights on Iron Study in Myelodysplasia
Noha M. El Husseiny, Dina Ahmed Mehaney and Mohamed Abd El Kader Morad
Turk J. Haematol, 31: 394-398 (2014) IF: 0.34

Objective: Hepcidin plays a pivotal role in iron homeostasis. It is predominantly produced by hepatocytes and inhibits iron release from macrophages and iron uptake by intestinal epithelial cells. Competitive ELISA is the current method of choice for the quantification of serum hepcidin because of its lower detection
limit, low costs, and high throughput. This study aims to discuss the role of hepcidin in the pathogenesis of iron overload in recently diagnosed myelodysplasia (MDS) cases.

**Materials and Methods:** The study included 21 recently diagnosed MDS patients and 13 healthy controls. Ferritin, hepcidin, and soluble transferrin receptor (sTFR) were measured in all subjects.

**Results:** There were 7 cases of hypocellular MDS, 8 cases of refractory cytopenia with multilineage dysplasia, and 6 cases of refractory anemia with excess blasts. No difference was observed among the 3 MDS subtypes in terms of hepcidin, sTFR, and ferritin levels (p<0.05). Mean hepcidin levels in the MDS and control groups were 55.8±21.5 ng/mL and 19.9±2.6 ng/mL, respectively. Mean sTFR was 45.7±8.8 mmol/L in MDS patients and 31.1±5.6 mmol/L in the controls. Ferritin levels were significantly higher in MDS patients than in controls (539.1±83.5 ng/mL vs. 104.6±42.9 ng/mL, p<0.005). There was a statistically significant correlation between hepcidin and sTFR (r=0.45, p=0.039). No difference in hepcidin levels between males and females was observed, although it was low in males in comparison to females (47±9.276. vs. 66.7±35.7, p>0.05).

**Conclusion:** Hepcidin may not be the main cause of iron overload in MDS. Further studies are required to test failure of production or peripheral unresponsiveness to hepcidin in MDS cases.

**Keywords:** Hepcidin; Myelodysplasia; Iron overload.

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**Dept. of Medical Biochemistry and Molecular Biology**

**697. Impairment of Nitric Oxide Synthase But Not Heme Oxygenase Accounts for Baroreflex Dysfunction Caused By Chronic Nicotine in Female Rats**

Mohamed A. Fouda, Hanan M. El-Gowelli, Sahar M. El-Gowilly, Laila Rashed and Mahmoud M. El-Mas

*Plos One.*, (2014) IF: 3.534

We recently reported that chronic nicotine impairs reflex chronotropic activity in female rats. Here, we sought evidence to implicate nitric oxide synthase (NOS) and/or heme oxygenase (HO) in the nicotine-baroreflex interaction. Baroreflex curves relating changes in heart rate to increases (phenylephrine) or decreases (sodium nitroprusside) in blood pressure were generated in conscious female rats treated with nicotine or saline in absence and presence of pharmacological modulators of NOS or HO activity. Compared with saline-treated rats, nicotine (2 mg/kg/day i.p., for 14 days) significantly reduced the slopes of baroreflex curves, a measure of baroreflex sensitivity (BRS). Findings that favor the involvement of NOS inhibition in the nicotine effect were (i) NOS inhibition (Nω-L-arginine methyl ester, L-NAME) reduced BRS in control rats but failed to do so in nicotine-treated rats, (ii) L-arginine, NO donor, reversed the BRS inhibitory effect of nicotine. Alternatively, HO inhibition (zinc protoporphyrin IX, ZnPP) had no effect on BRS in nicotine- or control rats and failed to reverse the beneficial effects of L-arginine on nicotine-BRS interaction. Similar to female rats, BRS was reduced by L-NAME, but not ZnPP, in male rats and the L-NAME effect was not accentuated after concomitant administration of nicotine. Baroreflex dysfunction caused by nicotine in female rats was blunted after supplementation with hemin (HO inducer) but not tricarbonyldichlororuthenium(II) dimer (CORM-2), a carbon monoxide (CO) releasing molecule, or bilirubin, the breakdown product of heme catabolism. The facilitatory effect of hemin was abolished upon simultaneous treatment with L-NAME or 1H-[1, 2], [4] oxadiazolo[4,3-a] quinoxalin-1-one (inhibitor of soluble guanylate cyclase, sGC). The activities of HO and NOS in brainstem tissues were also significantly increased by hemin. Thus, the inhibition of NOS, but not HO, accounts for the baroreflex depressant of chronic nicotine. Further, hemin alleviates the nicotine effect through a mechanism that is NOS/sGC but not CO or bilirubin-dependent.

**Keywords:** Baroreflex dysfunction; Nitric oxide; Hemeoxygenase.

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**698. Occupational Exposure to Aluminum and its Amyloidogenic Link With Cognitive Functions**


*Journal of Inorganic Biochemistry*, 139: 57-64 (2014) IF: 3.274

As many other metals, aluminum is a widely recognized neurotoxicant and its link with neurodegenerative disorders has been the subject of scientific debate. One proposal focuses on amyloid β deposition (amyloidogenesis) as the key player in triggering neuronal dysfunction the so-called amyloid cascade hypothesis. We undertook this study first to investigate the cognition status of workers exposed to Al dust in an Al factory in Southern Cairo, second, to evaluate serum amyloid precursor protein (APP) and cathepsin D (CD) enzyme activity to study the possible role of Al in amyloidogenesis, and finally to explore the relation between these potential biomarkers and cognitive functions. The study was conducted on 54 exposed workers and 51 matched controls. They were subjected to questionnaire, neurological examination and a cognitive test battery, Addenbrooke’s Cognitive Examination - Revised (ACE-R). Serum Al, APP and CD enzyme activity were measured. A significant increase of serum Al was found in the exposed workers with an associated increase in serum APP and decrement in CD activity. The exposed workers displayed poor performance on the ACE-R test. No significant correlation was detected between ACE-R test total score and either APP or CD activity. We concluded that occupational exposure to Al is associated with cognitive impairment. The effect of occupational Al exposure on the serum levels of APP and CD activity may be regarded as a possible mechanism of Al in amyloidogenesis. However, our findings do not support the utility of serum APP and CD activity as screening markers for early or preclinical cognitive impairment.

**Keywords:** Aluminum; Occupational Exposure; Amyloidogenesis; Amyloid Precursor Protein; Cathepsin D Activity; ACE; R Test.

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**699. Dose-Dependent Bioavailability Indicators for Curcumin and Two of Its Novel Derivatives**

Mohamed Abd el Aziz, Mohamed El-Asmer, Ameen Rezq, Abdulrahman Al-Malki, Taha Kumsami, Hanan Fouad, Hanan Ahmed, Fatma Taha, Amira Hassouna and Hafez Hafez


Novel water-soluble curcumin derivatives have been developed to overcome low in vivo bioavailability of curcumin. The aim of this work is to assess the potential utility of certain downstream targets as bioavailability indicators of systemic activity of pure curcumin and two novel water-soluble curcumin derivatives (NCD) by constructing dose-dependent response curves and to
prove whether this novel curcumin derivatives retained, improved, or abolished biological activity of pure curcumin when applied in vivo. Pure curcumin (CUR), curcumin-carboxy derivative (NCD-1), and curcumin protein conjugate (NCD-2) were administered orally to rats at escalating doses: 37, 74, 148, and 296 µM/kg body weight, respectively. Plasma levels of GST activity, cavernous tissue levels of cGMP, and enzymatic activity of both HO-1 and GST were assessed one and half and 24 hours after oral administration of curcumin formulates. This study showed that there was a progressive elevation of cavernous tissue levels of cGMP and enzymatic activity of both HO-1 and GST in a dose-dependent manner that was maintained for 24 h with CUR, NCD-1, and NCD-2. Plasma GST activity was decreased by the lowest doses on the curve. The three dose-dependent bioavailability indicators as surrogates of curcumin and two of its novel derivatives are valid in the studied range of concentration and extended time. The novel curcumin derivatives still conserve with improvement the biological activity of natural curcumin when applied in vivo. 

**Keywords:** Bioavailability Curcumin Novel Derivatives.

### 700. Pilot Study On Molecular Quantitation and Sequencing of Endometrial Cytokines Gene Expression and Their Effect On theOutcome of in Vitro Fertilization (IVF) Cycle.

Dina Sabry Abd El Fatah


Human trophoblast invasion and differentiation are essential for successful pregnancy outcome. The molecular mechanisms, however, are poorly understood. Interleukin (IL)-11, a cytokine, regulates endometrial epithelial cell adhesion. Leukemia inhibitory factor (LIF) is one of the key cytokines in the embryo implantation regulation. The present study aimed to assess the levels of LIF, IL-11, and IL-11 a receptor gene expression in the endometrium of women undergoing IVF and correlate their levels with the IVF pregnancy outcome. Also, the study aimed to detect any mutation in these three genes among IVF pregnant and non-pregnant women versus control menstrual blood of fertile women. Endometrial tissue biopsies were taken from 15 women undergoing IVF on the day of oocyte retrieval. The quantitative expression of IL-11, IL-11Ra, and LIF genes was assayed by real-time PCR and PCR products were sequenced. Menstrual blood from 10 fertile women was used as control to compare the DNA sequence versus DNA sequence of the studied genes in endometrial biopsies. LH, FSH, and E2 were assessed for enrolled patients by ELISA. Endometrial thickness was also assessed by pelvic ultrasonography. No significant difference was detected between quantitative expression of the three studied genes and pregnancy IVF outcome. Although DNA sequence changes were found in IL-11 and LIF genes of women with negative pregnancy IVF outcome, no DNA sequence changes were detected for IL-11Ra. Other studied parameters (e.g., age, LH, FSH, E2, and endometrial thickness) showed no significant differences or correlation of quantitative expression of the three studied involved genes. Data suggested that there were no significant differences between quantitative expression of IL-11, IL-11Ra, and LIF genes and the IVF pregnancy outcome. The present study may reveal that changes in IL-11 and LIF genes sequence may contribute in pregnancy IVF outcome.

**Keywords:** Dna Sequence; E2; Estradiol 2; Fsh; Follicular stimulating hormone; IL-11; Interleukin 11; IL-11Ra; Interleukin receptor A; Ivf, Ivf, In Vitro Fertilization; Interleukin-11 (Il-11); Interleukin-11 Receptor A (Il-11Ra); Lh; Luteinizing Hormone; LIF; Leukemia inhibitory factor; Leukemia inhibitory factor (Lif).

### 701. Expression of Tnf-α, April and Bcma in Behcet’S Disease

Olfat G. Shaker, Sherseen O. Tawfic, Amira M. El-Tawdy, Mohamed H. M. El-Komy, Manal El Menyawi and Ahmed A. Heikal

*Journal of Immunology Research, 380405: 1-6 (2014) IF: 2.934*

**Background:** Tumor necrosis factor-alpha (TNF-α) is an important proinflammatory cytokine which plays an important role in the immunopathogenesis of Behcet’s disease (BD). B cell activating factor (BAFF) and its homolog A proliferation inducing ligand (APRIL) are members of the tumor necrosis factor family. BAFF binds to 3 receptors; B cell activating factor receptor (BAFF-R), transmembrane activator and calcium modulator ligand interactor (TACI), and B cell maturation antigen (BCMA) that are expressed by B cells.

**Objective:** Estimation of the serum levels of TNF-α, APRIL, BAFF, and BCMA in patients with BD in an effort to evaluate their degree of involvement in the pathogenesis and development of BD.

**Patients and Methods:** This study included 30 male patients fulfilling the international study group criteria for the diagnosis of BD. Twenty age-matched healthy male volunteers served as control. Serum samples were used for quantification of TNF-α, APRIL, BCMA, BAFF, and hsCRP using ELISA techniques.

**Results:** The mean serum levels of TNF-α, APRIL, BCMA, and BAFF were more elevated in cases than in controls in a statistically significant manner. Positive correlation was observed between hs-CRP and BDCAF (Behcet’s disease current activity forum) index (r 0.68, . None of the TNF family members tested was affected by a positive pathergy test.

**Conclusions:** Patients have significantly higher levels of TNF family members’ (TNF-α, BAFF, APRIL, and BCMA) compared to controls which might contribute to the pathogenesis of BD.

**Keywords:** Tnf-A; Behcet’S Disease; Bdcaf.

### 702. Mesenchymal Stromal Cells Versus Betamethasone Can Dampen Disease Activity in theCollagen Arthritis Mouse Model

El-Denshary ES, Rashed LA and Elhussiny M.


The objective of this study was to compare between the effects of mesenchymal stem cell (MSC) and betamethasone in the treatment of rheumatoid arthritis. Sixty male albino mice were divided equally into 2 models. They are MSC model, group 1: saline control group, group 2: collagen-induced arthritis (CIA), group 3: induced arthritis mice that received intravenous injection of MSCs. Betamethasone model, group 1: phosphate buffer saline, group 2: CIA, group 3: induced arthritis mice that received intraperitoneal injection of betamethasone. Mice arthritis models were assessed by clinical paw edema and X-rays, at the proper time of sacrafaction, tissues were collected and examined using real-time PCR, and synovial tissue was examined for interleukin-10, tumor necrosis factor a, cartilage oligomeric matrix protein
and matrix metalloproteinase 3. While serum levels of rheumatoid factor and C-reactive protein were detected by enzyme-linked immunosorbent assay kits. Also blood erythrocyte sedimentation rate was detected. Histopathological, paw edema and PCR results showed improvement in the groups that received MSC compared with the diseased group and the groups which received betamethasone. MSC significantly enhanced the effect of collagen-induced arthritis treatment, which is superior to betamethasone treatment, likely through the modulation of the expression of various cytokines.

Keywords: Collagen-Induced Arthritis Stromal Cell Corticosteroid Rheumatoid Arthritis.

703. Potential Therapeutic Utility of Mesenchymal Stem Cells in Inflammatory Bowel Disease in Mice

Abdel Salam AG, Ata HM, Salman TM, Rashed LA, Sabry D and Schaan MF


Mesenchymal stem cells (MSCs) were found to provide an effective therapeutic role in inflammatory diseases by modulating inflammatory responses and tissue regeneration by their differentiation ability. The present work sought to demonstrate the potential therapeutic use of MSCs in treating chronic inflammatory bowel disease (IBD) in mice. A new model to induce chronic IBD based on alternative administration periods of Dextran Sodium Sulfate (DSS) was established. Mice were divided into 2 groups; one was treated with MSCs and the other was treated with phosphate-buffered saline (PBS). Assessment of therapeutic efficacy of MSCs was by measuring weight, stool scoring, histopathological examination, and measuring the gene expression of inflammatory markers: Interleukin-6 (IL-6), Tumor necrosis factor-a (TNF-a), Interferon-γ (IFN-γ), and Intercellular adhesion molecule-1 (ICAM-1). The results showed that DSS administration causes bloody and watery stool, weight loss, and altered histopathologic picture. MSC treated mice showed a significant improvement in stool condition, weight gain, and normal histopathologic picture compared to the PBS treated mice. Moreover, gene expressions of inflammatory markers in the intestines of the MSC treated mice were also significantly lower than those of the PBS treated mice. In conclusion, the data here showed that MSCs have a clear potential efficacy in the treatment for IBD, as their immune modulation effects include inhibition in the expression of key inflammatory markers that each plays an important role in the pathogenesis of IBD.

Keywords: Bone Marrow Derived Mesenchymal Stem Cell Transplantation; Dss Induced Colitis; Immunomodulation.

704. Molecular Detection of Monocyte Chemotactic Protein-1 Polymorphism in Spontaneous Bacterial Peritonitis Patients

Maysa Kamal Salama, Dina Sabry, Mohamed AS Al-Ghussein, Rasha Ahmed, Sayed AbdAllah, Fatma Mohamed Taha, Wael Fathy, Miriam Safwat Wadie, Mona Nabih, Amr Abul-Fotouh and Tareem Darwish


Aim: To investigate the association of the functional monocyte chemotactic protein-1 (MCP-1) promoter polymorphism (A-2518G) with spontaneous bacterial peritonitis (SBP).

Methods: Fifty patients with post-hepatitis C liver cirrhosis and ascites were categorized into two groups; group I included 25 patients with SBP and group II included 25 patients free from SBP. In addition, a group of 20 healthy volunteers were included. We assessed the MCP-1 gene polymorphism and gene expression as well as IL-10 levels in both blood and ascitic fluid.

Results: A significant MCP-1 gene polymorphism was detected in groups I and II (P = 0.001 and 0.02 respectively). Group II was associated with a significantly higher frequency of AG genotype [control 8 (40%) vs SBP 19 (76.0%), P < 0.001], and group II was associated with a significantly higher frequency of GG genotype when compared to healthy volunteers [control 1 (5%) vs cirrhotic 16 (64%), P < 0.001]. Accordingly, the frequency of G allele was significantly higher in both groups (I and II) [control 10 (25%) vs SBP 27 (54%), P < 0.001 and vs cirrhotic 37 (74.0%), P < 0.001, respectively]. The total blood and ascitic fluid levels of IL-10 and MCP-1 gene expression were significantly higher in group I than in group II. Group I showed significant reductions in the levels of MCP-1 gene expression and IL-10 in the whole blood and ascitic fluid after therapy.

Conclusion: MCP-1 GG genotype and G allele may predispose HCV infected patients to a more progressive disease course, while AG genotype may increase the susceptibility to SBP. Patients carrying these genotypes should be under supervision to prevent or restrict further complications.

Keywords: Monocyte Chemotactic Protein-1; Genotype; Spontaneous Bacterial Peritonitis; Liver Cirrhosis; Ascites; Gene Expression; Interleukin-10.

705. Effects of A Novel Curcumin Derivative on Insulin Synthesis and Secretion in Streptozotocin-Treated Rat Pancreatic Islets in Vitro

Mohammed Talata Abdel Aziz, Mohammed Farid El-Asmar, Ameen Mahmoud Rezq, Mohammed Abdel Aziz Wassef, Hanan Fouad, Nagwa Kamal Roshy, Hanan Hosni Ahmed, Laila Ahmed Rashed, Dina Sabry, Fatma Mohammed Taha and Amira Hassouna

Chinese Medicine, 9: 2-12 (2014) IF: 2.343

Background: Hyperglycemia induces activation of the c-Jun N-terminal kinase (JNK) pathway, which suppresses insulin gene expression and reduces DNA binding of pancreatic and duodenal homeobox factor (PDX)-1. This study aims to investigate the effects of a novel curcumin derivative (NCD) on JNK signaling pathway on insulin synthesis and secretion in streptozotocin (STZ)-treated rat pancreatic islets in vitro.

Methods: Isolated rat pancreatic islets were divided into five groups: untreated control group; group treated with NCD (10 µM); group exposed to STZ (5 mM); group treated with NCD (10 µM) and then exposed to STZ (5 mM); and group exposed to STZ (5 mM) and then treated with NCD (10 µM). The pancreatic islets from all groups were used for DNA fragmentation assays and quantitative assessments of the JNK, Pdx1, glucose transporter-2 (GLUT2), heme oxygenase (HO)-1, transcription factor 7-like 2 (TCF7L2), and glucagon-like peptide (GLP)-1 gene expression levels. The intracellular calcium, zinc, and the phosphorylated and total JNK protein levels were assessed. The insulin (secreted/total) and C-peptide levels were examined in islet culture medium.
Results: NCD protected pancreatic islets against STZ-induced DNA damage, improved total insulin (P = 0.001), secreted insulin (P = 0.001), and C-peptide levels (P = 0.001), normalized mRNA expressions of insulin, Pdx1, and GLUT2 (P = 0.0001), and significantly elevated calcium and zinc levels (P = 0.0001). All effects were significant when islets were treated with NCD before STZ (P = 0.05). JNK gene overexpression and JNK protein levels induced by STZ were significantly inhibited after NCD treatment of islets (P = 0.0001). NCD-treated islets showed significantly elevated gene expressions of HO-1, TCF7L2, and GLP-1 (P = 0.0001), and these upregulated gene expressions were more significantly elevated with NCD treatment before STZ than after STZ (P = 0.05).

Conclusions: NCD improved insulin synthesis and secretion in vitro in isolated pancreatic islets treated with STZ through inhibition of the JNK pathway, up-regulation of the gene expressions of HO-1, TCF7L2, and GLP-1 and enhancing effects on calcium and zinc levels.

Keywords: Curcumin; Insulin; Synthesis; Secretion; Diabetes.

706. The Potential Impact of P53 and APO-1 Genetic Polymorphisms On Hepatitis C Genotype 4A Susceptibility

Eskander EF, Abd-Rabou AA, Mohamed MS, Yahya SM, El Sherbini A and Shaker OG

Gene, 550: 40-45 (2014) IF: 2.082

The hepatitis C virus (HCV), the main cause of morbidity and mortality, is endemic worldwide. HCV causes cirrhosis and other complications that often lead to death. HCV is most common in underdeveloped nations, with the highest prevalence rates in Egypt. Tumor suppressor gene (P53) induces the expression of apoptotic antigen-1 gene (APO-1) by binding to its promoter for mediating apoptosis; an important mechanism for limiting viral replication. This study aims at investigating the impact of P53 72 Arg/Pro and APO-1 -670 A/G polymorphisms on HCV genotype 4a susceptibility. Two hundred and forty volunteers were enrolled in this study and divided into two major groups; 160 HCV infected patient group and 80 healthy control group. HCV patients were classified according to Metavir scoring system into two subgroups; 72 patients in F0/F1-HCV subgroup (patients with no or mild fibrotic stages) and 38 patients in F3/4-HCV subgroup (patients with advanced fibrotic stages). Quantification of HCV-RNA by qRT-PCR and fibrotic scores as well as genotyping of HCV-RNA, P53 at 72 Arg/Pro, and APO-1 at -670 A/G were performed for all subjects. It was resulted that F0/1-HCV patients have significant differences of P53 at 72 (Pro/Pro and Arg/Arg) genotypes and dominant/recessive genetic models as well as APO-1 -670 A/A genotype and dominant genetic model as compared to those of healthy individuals. Finally, it was concluded that P53 rs 1042522 (Pro/Pro and Arg/Arg) genotypes and APO-1 rs 1800682 A/A genotype may be potentially used as sensitive genetic markers for HCV genotype 4a susceptibility.

Keywords: P53 Arg72pro- Apo-1 -670A/G- Snp5 -Hcv Genotype 4A.

707. Association Between TNF Promoter -308 G>A and LTA 252 A>G Polymorphisms and Systemic Lupus Erythematosus

Hanan Hosni Ahmed, Fatma Mohamed Taha, Hanan El-Sayed Darweesh and Heba Mohamed Abdelhafiz Morsi


Tumor necrosis factor (TNF) and lymphotoxin alpha (LTA) are pivotal cytokines in the pathogenesis of systemic lupus erythematosus (SLE). To investigate the possible association of the polymorphism of the TNF promoter gene -308 and that of the LTA gene 252 with susceptibility to SLE and with phenotypic disease features in Egyptian patients. A case control study involving 100 SLE patients and 100 unrelated healthy controls. Polymerase chain reaction and restriction fragment length polymorphism methods were applied to detect genetic polymorphism. We found that TNF-308 genotype AA was significantly increase by 26 % in SLE patients compared to 10 % in the control group (p = 0.003; OR 3.16; 95 % CI 1.43-6.98) and the frequency of the A allele of the TNF promoter -308 was significantly higher in the SLE patients (42 %) than in the control subjects (24 %) (p < 0.001; OR 2.29; 95 % CI 1.49-3.52). Genotype LTA 252 GG showed a significant increase by 22 % in SLE patients compared to 6 % in the control group (p = 0.001; OR 4.42; 95 % CI 1.71-11.44), and the frequency of the G allele of the LTA was significantly higher in the SLE patients (38 %) than in the control subjects (21 %) (p < 0.001; OR 2.3; 95 % CI 1.48-3.6). Genotype (AA+GA) of TNF was significantly associated with clinical manifestations as malar rash, arthritis, oral ulcers, serositis and systemic lupus erythematosus disease activity index. Genotype (GG+GA) of LTA was significantly associated with arthritis. These results suggest that TNF and LTA genetic polymorphisms contribute to SLE susceptibility in the Egyptian population and are associated with disease characteristics. TNF-308 and LTA+252 polymorphic markers may be used for early diagnosis of SLE and early prediction of clinical manifestations, like arthritis.

Keywords: SLE; TNF; LTA; Arthritis and Sledai.


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Objective: To investigate the effect of bridging defects in chronic spinal cord injury using peripheral nerve grafts combined with a chitosan-laminin scaffold and enhancing regeneration through them by co-transplantation with bone-marrow-derived mesenchymal stem cells.

Methods: In 14 patients with chronic paraplegia caused by spinal cord injury, cord defects were grafted and stem cells injected into the whole construct and contained using a chitosan-laminin paste. Patients were evaluated using the International Standards for Classification of Spinal Cord Injuries.
Results: Chitosan disintegration leading to post-operative seroma formation was a complication. Motor level improved four levels in 2 cases and two levels in 12 cases. Sensory-level improved six levels in two cases, five levels in five cases, four levels in three cases, and three levels in four cases. A four-level neurological improvement was recorded in 2 cases and a two-level neurological improvement occurred in 12 cases. The American Spinal Impairment Association (ASIA) impairment scale improved from A to C in 12 cases and from A to B in 2 cases. Although motor power improvement was recorded in the abdominal muscles (2 grades), hip flexors (3 grades), hip adductors (3 grades), knee extendors (2-3 grades), ankle dorsiflexors (1-2 grades), long toe extensors (1-2 grades), and plantar flexors (0-2 grades), this improvement was too low to enable them to stand erect and hold their knees extended while walking unaided.

Conclusion: Mesenchymal stem cell-derived neural stem cell-like cell transplantation enhances recovery in chronic spinal cord injuries with defects bridged by sural nerve grafts combined with a chitosan-laminin scaffold.

Keywords: Nerve Grafting; Neurorecovery; Paraplegia; Spinal Cord Injuries; Stem Cell Transplantation.

709. Vitamin D and IL28B Genotyping as Predictors for Antiviral Therapy: A Retrospective Study in Egyptian HCV Genotype 4a
Nadia Abdelaty Abdelkader, Soha Saoud Abdelmoniem, Dina Sabry, Amin Mohamad Abdelbaky, Maram M. Mahdy, Eman Zaky and Wessam Elsayed Saad
Tropical Journal of Pharmaceutic AI Research, 13 (10): 1725-1732 (2014) IF: 0.495

Purpose: To evaluate the role of pre-treatment vitamin D serum level and interleukin28B (IL28B) (rs 12979860) polymorphism in chronic hepatitis C (CHC) genotype 4a patients treated with pegylated interferon a2-A and ribavirin (peg IFN+RBV) as predictors of response.

Methods: A retrospective study of clinical and pathological data and stored blood samples of 150 naïve chronic hepatitis C (CHC) genotype 4a patients, treated with pegylated interferon and ribavirin for 48 weeks. Follow-up to detect sustained virological response (SVR) was carried out. Based on SVR, two groups were studied; group 1 consisted of 75 responder patients to pegylated IFN + RBV therapy while group 2 comprised of 75 non-responder patients to standard hepatitis C virus (HCV) therapy. Vitamin D serum levels were assessed using Enzyme Linked Immunoassay (ELISA), quantitative reverse transcriptase- polymerase chain reaction (qRT-PCR) for HCV RNA, and IL28B gene polymorphism by Restriction Fragment Length Polymorphism Polymorphism Ccera Reaction (RFLP-PCR).

Results: Pretreatment vitamin D level was significantly higher in group 1 than in group 2 (p < 0.001). The sensitivity and specificity of vitamin D level for prediction of SVR at a cutoff value of 29.75 ng/ml were 100 and 96 %, respectively, with area under the curve (AUC) of 0.995 (p < 0.001). A significant difference was detected between baseline vitamin D level for early versus advanced fibrosis stage (p = 0.01) in group 1.

Conclusion: Pretreatment vitamin D serum level (at a cutoff value of 29.75 ng/ml), IL28B gene polymorphism and quantitative HCV RNA are independent trait predictors of SVR.

Keywords: Vitamin D; Interleukin 28B; Chronic Hepatitis C; Sustained Virological Response (SVR); Antiviral; Genotyping.

Dept. of Medical BioChemistry

710. The Role of Bone Marrow Derived-Mesenchymal Stem Cells in Attenuation of Kidney Function in Rats With Diabetic Nephropathy
Abdel Aziz MT, Wassef MA, Ahmed HH, Rashed L, Mahfouz S, Aly MI, Hussein RE and Abdelaziz M.
Diabetology & Metabolic Syndrome, 1758-5996: 34-44 (2014) IF: 2.5

Background: Stem cell therapy holds a great promise for the repair of injured tissues and organs, including the kidney. We studied the effect of mesenchymal stem cells (MSC) on experimental diabetic nephropathy (DN) in rats and the possible paracrine signals that mediate their action.

Materials and Methods: Rats were divided into controls, DN rats, DN rats receiving MSCs. MSCs were given in a dose of (106cells) by intravenous injection. After 4 weeks, 24 h urinary albumin, serum urea and creatinine concentrations, transforming growth factor β (TGF β), tumor necrosis factor α (TNFα), B-cell lymphoma 2 (bcl2) and Bax gene expression and vascular endothelial growth factor (VEGF) were assessed. Histopathology staining was performed.

Results: MSC therapy significantly improved 24 h urinary albumin, serum urea and creatinine concentrations, increased angiogenic growth factor VEGF, and anti-apoptotic protein bcl2 while decreased the pro-inflammatory TNF-α, fibrogenic growth factor TGF β, and pro-apoptotic protein Bax. The histopathology examination showed patchy areas of minimal necrosis and degeneration in renal tubules.

Keywords: Stem Cells Therapy, Mesenchymal Stem Cells, Diabetic Nephropathy.

Dept. of Neurology

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Background: The Millennium Declaration in 2000 brought special global attention to HIV, tuberculosis, and malaria through the formulation of Millennium Development Goal (MDG) 6. The Global Burden of Disease 2013 study provides a consistent and comprehensive approach to disease estimation for between 1990 and 2013, and an opportunity to assess whether accelerated progress has occurred since the Millennium Declaration.

Methods: To estimate incidence and mortality for HIV, we used the UNAIDS Spectrum model appropriately modified based on a systematic review of available studies of mortality with and without antiretroviral therapy (ART). For concentrated epidemics, we calibrated Spectrum models to fit vital registration data corrected for misclassification of HIV deaths. In generalised epidemics, we minimised a loss function to select epidemic
curves most consistent with prevalence data and demographic data for all-cause mortality. We analysed counterfactual scenarios for HIV to assess years of life saved through prevention of mother-to-child transmission (PMTCT) and ART. For tuberculosis, we analysed vital registration and verbal autopsy data to estimate mortality using cause of death ensemble modelling. We analysed data for corrected case-notifications, expert opinions on the case-detection rate, prevalence surveys, and estimated cause-specific mortality using Bayesian meta-regression to generate consistent trends in all parameters. We analysed malaria mortality and incidence using an updated cause of death database, a systematic analysis of verbal autopsy validation studies for malaria, and recent studies (2010–13) of incidence, drug resistance, and coverage of insecticide-treated bednets.

**Findings:** Globally in 2013, there were 1·8 million new HIV infections (95% uncertainty interval 1·7 million to 2·1 million), 29·2 million prevalent HIV cases (28·1 to 31·7), and 1·3 million HIV deaths (1·3 to 1·5). At the peak of the epidemic in 2005, HIV caused 1·7 million deaths (1·6 million to 1·9 million). Concentrated epidemics in Latin America and eastern Europe are substantially smaller than previously estimated. Through interventions including PMTCT and ART, 19·1 million life-years (16·6 million to 21·5 million) have been saved, 70·3% (65·4 to 76·1) in developing countries. From 2000 to 2011, the ratio of development assistance for health for HIV to years of life saved through intervention was US$4498 in developing countries. Including in HIV-positive individuals, all-form tuberculosis incidence was 7·5 million (7·4 million to 7·7 million), prevalence was 11·9 million (11·6 million to 12·2 million), and number of deaths was 1·4 million (1·3 million to 1·5 million) in 2013. In the same year and in only individuals who were HIV-negative, all-form tuberculosis incidence was 7·1 million (6·9 million to 7·3 million), prevalence was 11·2 million (10·8 million to 11·6 million), and number of deaths was 1·3 million (1·2 million to 1·4 million).

Annualised rates of change (ARC) for incidence, prevalence, and death became negative after 2000. Tuberculosis in HIV-negative individuals disproportionately occurs in men and boys (versus women and girls); 64·0% of cases (63·6 to 64·3) and 64·7% of deaths (60·8 to 70·3). Globally, malaria cases and deaths grew rapidly from 1990 reaching a peak of 232 million cases (143 million to 387 million) in 2003 and 1·2 million deaths (1·1 million to 1·4 million) in 2004. Since 2004, child deaths from malaria in sub-Saharan Africa have decreased by 31·5% (15·7 to 44·1). Outside of Africa, malaria mortality has been steadily decreasing since 1990.

**Interpretation:** Our estimates of the number of people living with HIV are 18·7% smaller than UNAIDS’s estimates in 2012. The number of people living with malaria is larger than estimated by WHO. Incidence rates for HIV, tuberculosis, and malaria have all decreased since 2000. At the global level, upward trends for malaria and HIV deaths have been reversed and declines in tuberculosis deaths have accelerated. 101 countries (74 of which are developing) still have increasing HIV incidence. Substantial progress since the Millennium Declaration is an encouraging sign of the effect of global action.

**Keywords:** Incidence HIV; Tuberculosis; Malaria; Systematic analysis.

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**Background:** The fifth Millennium Development Goal (MDG 5) established the goal of a 75% reduction in the maternal mortality ratio (MMR; number of maternal deaths per 100 000 livebirths) between 1990 and 2015. We aimed to measure levels and track trends in maternal mortality, the key causes contributing to maternal death, and timing of maternal death with respect to delivery.

**Methods:** We used robust statistical methods including the Cause of Death Ensemble model (CODEm) to analyse a database of data for 7065 site-years and estimate the number of maternal deaths from all causes in 188 countries between 1990 and 2013. We estimated the number of pregnancy-related deaths caused by HIV on the basis of a systematic review of the relative risk of dying during pregnancy for HIV-positive women compared with HIV-negative women. We also estimated the fraction of these deaths aggravated by pregnancy on the basis of a systematic review. To estimate the numbers of maternal deaths due to nine different causes, we identified 61 sources from a systematic review and 943 site-years of vital registration data. We also did a systematic review of reports about the timing of maternal death, identifying 142 sources to use in our analysis. We developed estimates for each country for 1990–2013 using Bayesian meta-regression. We estimated 95% uncertainty intervals (UIs) for all values.

**Findings:** 292 982 (95% UI 261 017–327 792) maternal deaths occurred in 2013, compared with 376 034 (343 483–407 574) in 1990. The global annual rate of change in the MMR was −0·3% (−1·1 to 0·6) from 1990 to 2003, and −2·7% (−3·9 to −1·5) from 2003 to 2013, with evidence of continued acceleration. MMRs reduced consistently in south, east, and southeast Asia between 1990 and 2013, but maternal deaths increased in much of sub-Saharan Africa during the 1990s. 2070 (1290–2866) maternal deaths were related to HIV in 2013, 0·4% (0·2–0·6) of the global total. MMR was highest in the oldest age groups in both 1990 and 2013. In 2013, most deaths occurred intrapartum or postpartum. Causes varied by region and between 1990 and 2013. We recorded substantial variation in the MMR by country in 2013, from 956·8 (685·1–1262·8) in South Sudan to 2·4 (1·6–3·6) in Iceland.

**Interpretation:** Global rates of change suggest that only 16 countries will achieve the MDG 5 target by 2015. Accelerated reductions since the Millennium Declaration in 2000 coincide with increased development assistance for maternal, newborn, and child health. Setting of targets and associated interventions for after 2015 will need careful consideration of regions that are making slow progress, such as west and central Africa.

**Keywords:** Maternal mortality; Systematic analysis.

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**713. Burden of Stroke in Egypt: Current Status and Opportunities**

Foad Abd-Allah and Ramez Reda Moustafa

Middle East and North Africa (MENA) countries have a diversity of populations with similar life style, dietary habits, and vascular risk factors that may influence stroke risk, prevalence, types, and disease burden. Egypt is the most populated nation in the Middle East with an estimated 85.5 million people. In Egypt, according to recent estimates, the overall prevalence rate of stroke is high with a crude prevalence rate of 963/100,000 inhabitants. In spite of disease burden, yet there is a huge evidence practice gap. The recommended treatments for ischemic stroke that are guideline include systematic supportive care in a stroke unit or stroke center is still insufficient. In addition, the frequency of thrombolysis in Egypt is very low for many reasons; the major one is that the health insurance system is not covering thrombolysis therapy in nonprivate sectors so patients must cover the costs using their own personal savings; otherwise, they will not receive treatment. Another important factor is the pronounced delay in prehospital and in hospital management of acute stroke. Improvement of stroke care in Egypt should be achieved through multi and interdisciplinary approach including public awareness, physicians' education, and synergistic approach to stroke care with Emergency Medical System.  

Keywords: Egypt; Middle East; WHO; Burden Of Stroke; Opportunities; Stroke Facilities.

714. Prevalence of Intracranial Atherosclerosis Among Patients With Coronary Artery Disease: A 1-Year Hospital-Based Study  
Abd-Allah F, Kassem HH, Hashad A, Shamloul RM and Zaki A.  

Background: There are limited data on the prevalence of intracranial atherosclerotic disease (ICAD) in patients with coronary artery disease (CAD) worldwide and especially among Egyptians. The purpose of the present study was to determine the prevalence and correlates of ICAD in patients with CAD.  
Methods: From January 1, 2012 to January 1, 2013, we recruited 118 consecutive patients who had ischemic heart disease. All patients were assessed for vascular risk factors and the existence of stroke or transient ischemic attack (TIA) and were evaluated by extracranial and transcranial color-coded sonography. All patients underwent coronary angiography. Clinical, echocardiographic and angiographic variables were tested by univariate and multivariate analysis.  
Results: Out of 118 consecutive patients with CAD, intracranial disease was detected in 14 patients (11.9%). Eight patients (6.8%) had stenosis >50%, while 6 patients (5.1%) had stenosis <50%. The univariate analysis showed that the strongest variables associated with ICAD were the presence of recent or old stroke or TIA, followed by moderate or severe extracranial stenosis, and multivessel or left main CAD.  
Conclusion: We observed low prevalence (6.8%) of high-grade ICAD among Egyptian patients with CAD. Multivessel or left main CAD and moderate-to-severe extracranial carotid stenosis were the strongest predictors for the existence of ICAD among CAD patients.  
Keywords: Intracranial atherosclerotic disease; Coronary artery disease; Transcranial color-coded sonography.

Mohamed Ali El-Gaidi, Ehab Mohamed Eissa and Ehab A. A. El-Shaarawy  
European Spine Journal, 23: 2182-2188 (2014) IF: 2.473

Purpose: Cranio-vertebral junction fixation is challenging due to the complex topographical anatomy and the presence of important anatomical structures. There are several limitations to the traditional occipital squama fixation methods. The purpose of this work is to assess the safety and feasibility of a new optimum trajectory of occipital condyle (OC) screws for occipitocervical fixation via a free-hand technique.  
Methods: Eight different parameters of OC morphology were studied in fifty adult skulls. Free-hand placement of OC screws was performed in five cadavers using 3.5-mm titanium polyaxial screws and a 3-mm rod construct (C0-C1-C2). Postoperative computed tomography was performed to determine the success of the screw placement and their angulation, length and effect on hypoglossal canal volume.  
Results: The average length, width and height of the OC were 24.2 ± 3.6, 14.2 ± 1.9, and 10.7 ± 2 mm, respectively. The average medio-lateral, hypoglossal canal and atlanto-occipital joint angles were 38.8° medially ±5°, 7.4° rostrally ±1.9° and 23.4° caudally ±3.5°, respectively. The ten screws were successfully inserted using a free-hand technique with bicortical purchase. There was no vertebral artery injury or breach of the hypoglossal canal in any specimen. The average screw length was 22.2 ± 3.9 mm. The average medio-lateral angle was 30° medially ±6.7°. The average cranio-caudal angle was 4° caudally ±6.2°.  
Conclusions: The free-hand technique of OC screw placement is a safe and viable option for occipitocervical fixation and may be a preferred alternative in selected cases. However, further studies are needed to compare its safety and reliability to other more established methods.  
Keywords: Cranio-vertebral Junction; Occipitocervical fixation; Occipital condyle screws; Optimum trajectory.

716. Endoscopic Treatment of Intraparenchymal Arachnoid Cysts in Children  
Nasser M. F. El-Ghandour  

Object: Arachnoid cysts account for 1% of all intracranial lesions. They usually occur in the subarachnoid space of the major cerebral fissures and arachnoid cisterns. They are very rarely located within the brain parenchyma devoid of communication with the subarachnoid space. The author of this study evaluated the role of endoscopy in the treatment of intraparenchymal arachnoid cysts (IPACs), which have a paraventricular location noncontiguous with the basal cisterns.  
Methods: The records of all patients who had undergone surgery performed by one neurosurgeon between March 2004 and October 2011 were retrospectively reviewed to find cases of arachnoid cysts with a paraventricular location noncontiguous with the basal cisterns that were treated with a purely endoscopic cystoventriculostomy. Data were collected, summarized, and analyzed as regards improvement in symptomatology, decrease in cyst size, improvement in hydrocephalus, incidence of complications, surgical failure, and incidence of recurrence.

www.grsd.cu.edu.eg


Results: Twelve pediatric patients with symptomatic IPACs were included in this study. The group included 7 boys and 5 girls with a mean age of 5.2 years. All of the patients had undergone endoscopic cystoventriculostomy. In addition, endoscopic third ventriculostomy had been performed during the same operative session in 3 patients who had associated hydrocephalus. Significant clinical improvement occurred in 10 patients (83.3%). Postoperative imaging showed a reduction in the cyst size in 9 patients (75%), whereas the cyst size was unchanged in the remaining 3 patients (25%). A reduction in ventricle size occurred in 2 (66.7%) of the 3 patients who had hydrocephalus. A postoperative subdural hygroma occurred in 2 patients (16.7%) and required the insertion of a subduroperitoneal shunt in 1 patient. During the follow-up period (mean 42.5 months), 1 patient had a recurrence and required a repeat endoscopic procedure.

Conclusions: Endoscopic cystoventriculostomy is recommended in the treatment of symptomatic IPACs. It maintains the basic strategy of cyst fenestration into the lateral ventricle without either the invasiveness of open craniotomy or the implantation of shunt systems. The procedure is simple, effective, and minimally invasive. It saves operative and recovery times and is associated with low morbidity and mortality rates.

Keywords: Eeg = Electroencephalography; Etv = Endoscopic Third Ventriculostomy; Ipac = Intraparenchymal Arachnoid Cyst; Arachnoid Cyst; Congenital; Cystoventriculostomy; Endoscopy; Intraparenchymal

Dept. of Obstetrics and Gynecology

717. Gonadotropin-Releasing Hormone Agonist Versus HCG for Oocyte Triggering in Antagonist-Assisted Reproductive Technology

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Cochrane Database Syst Rev, 8: 1-59 (2014) IF: 5.939

Objectives: To evaluate the effectiveness and safety of GnRH agonists in comparison with HCG for triggering final oocyte maturation in IVF and ICSI for women undergoing COH in a GnRH antagonist protocol.

Search Methods: We searched databases including the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register of Controlled Trials, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsyCINFO, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and trial registers for published and unpublished articles (in any language) on randomised controlled trials (RCTs) of gonadotropin-releasing hormone agonists versus HCG for oocyte triggering in GnRH antagonist IVF/ICSI treatment cycles. The search is current to 8 September 2014.

Selection Criteria: RCTs that compared the clinical outcomes of GnRH agonist triggers versus HCG for final oocyte maturation triggering in women undergoing GnRH antagonist IVF/ICSI treatment cycles were included.

Data Collection and Analysis: Two or more review authors independently selected studies, extracted data and assessed study risk of bias. Treatment effects were summarised using a fixed-effect model, and subgroup analyses were conducted to explore potential sources of heterogeneity. Treatment effects were expressed as mean differences (MDs) for continuous outcomes and as odds ratios (ORs) for dichotomous outcomes, together with 95% confidence intervals (CIs). Primary outcomes were live birth and rate of ovarian hyperstimulation syndrome (OHSS) per women randomised. Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methods were used to assess the quality of the evidence for each comparison.

Main Results: We included 17 RCTs (n = 1847), of which 13 studies assessed fresh autologous cycles and four studies assessed donor-recipient cycles. In fresh autologous cycles, GnRH agonists were associated with a lower live birth rate than was seen with HCG (OR 0.47, 95% CI 0.31 to 0.70; five RCTs, 532 women, I(2) = 56%, moderate-quality evidence). This suggests that for a woman with a 31% chance of achieving live birth with the use of HCG, the chance of a live birth with the use of an GnRH agonist would be between 12% and 24%. In women undergoing fresh autologous cycles, GnRH agonists were associated with a lower incidence of mild, moderate or severe OHSS than was HCG (OR 0.15, 95% CI 0.05 to 0.47; eight RCTs, 989 women, P = 42%, moderate-quality evidence). This suggests that for a woman with a 3% risk of mild, moderate or severe OHSS with the use of HCG, the risk of OHSS with the use of a GnRH agonist would be between nil and 2%. In women undergoing fresh autologous cycles, GnRH agonists were associated with a lower ongoing pregnancy rate than was seen with HCG (OR 0.70, 95% CI 0.54 to 0.91; 11 studies, 1198 women, I(2) = 59%, low-quality evidence) and a higher early miscarriage rate (OR 1.74, 95% CI 1.10 to 2.75; 11 RCTs, 1198 women, P = 1%, moderate-quality evidence). However, the effect was dependent on the type of luteal phase support provided (with or without luteinising hormone (LH) activity); the higher rate of pregnancies in the HCG group applied only to the group that received luteal phase support without LH activity (OR 0.36, 95% CI 0.21 to 0.62; I(2) = 73%, five RCTs, 370 women). No evidence was found of a difference between groups in risk of multiple pregnancy (OR 3.00, 95% CI 0.30 to 30.47; two RCTs, 62 women, I(2) = 0%, low-quality evidence). In women with donor-recipient cycles, no evidence suggested a difference between groups in live birth rate (OR 0.92, 95% CI 0.53 to 1.61; one RCT, 212 women) or ongoing pregnancy rate (OR 0.88, 95% CI 0.58 to 1.32; three RCTs, 372 women, P = 0%). We found evidence of a lower incidence of OHSS in the GnRH agonist group than in the HCG group (OR 0.05, 95% CI 0.01 to 0.28; three RCTs, 374 women, P = 0%). The main limitation in the quality of the evidence was risk of bias associated with poor reporting of methods in the included studies.

Authors' Conclusions: Final oocyte maturation triggering with GnRH agonist instead of HCG in fresh autologous GnRH antagonist IVF/ICSI treatment cycles prevents OHSS to the detriment of the live birth rate. In donor-recipient cycles, use of GnRH agonists instead of HCG resulted in a lower incidence of OHSS, with no evidence of a difference in live birth rate. Evidence suggests that GnRH agonist as a final oocyte maturation trigger in fresh autologous cycles is associated with a lower live birth rate, a lower ongoing pregnancy rate (pregnancy beyond 12 weeks) and a higher rate of early miscarriage (less than 12 weeks). GnRH agonist as an oocyte maturation trigger could be useful for women who choose to avoid fresh transfers (for whatever reason), women who donate oocytes to recipients or women who wish to freeze their eggs for later use in the context of fertility preservation.

Keywords: Oocyte Trigger; Hcg; Ivf; Gnrh Antagonist.
Background: In women undergoing in vitro fertilisation (IVF) and intracytoplasmic sperm injection (ICSI), embryos transferred into the uterine cavity can be expelled due to many factors including uterine peristalsis and contractions, low site of deposition and negative pressure generated when removing the transfer catheter. Techniques to reduce the risk of embryo loss following embryo transfer (ET) have been described but are not standard in all centres conducting ET.

Objectives: To evaluate the efficacy of interventions used to prevent post-transfer embryo expulsion in women undergoing IVF and ICSI.

Search Methods: We searched the Menstrual Disorders and Subfertility Group Specialised Register of controlled trials to June 2014 and PubMed, MEDLINE, EMBASE, CENTRAL, PsycINFO, CINAHL, World Health Organization ICTRP, and trial registers from inception to June 2014, with no language restrictions. Additionally, we handsearched reference lists of relevant articles, and ESHRE and ASRM conference abstracts.

Selection Criteria: We included randomised controlled trials (RCTs) of interventions used to prevent post-transfer embryo expulsion in women undergoing IVF and ICSI. Two review authors independently screened titles and abstracts and reviewed the full-texts of all potentially eligible citations to determine whether they met our inclusion criteria. Disagreements were resolved by consensus.

Data Collection and Analysis: Two review authors independently extracted data and assessed the risk of bias of included trials using standardised, piloted data extraction forms. Data were extracted to allow intention-to-treat analyses. Disagreements were resolved by consensus. The overall quality of the evidence was rated using GRADE methods.

Main Results: We included four RCTs (n = 1392 women) which administered the following interventions: bed rest (two trials), fibrin sealant (one trial), and mechanical closure of the cervix (one trial).

Our primary outcome, live birth rate, was not reported in any of the included trials; nor were the data available from the corresponding authors. For the ongoing pregnancy rate, two trials comparing more bed rest with less bed rest showed no evidence of a difference between groups (odds ratio (OR) 0.88; 95% confidence interval (CI) 0.60 to 1.31, 542 women, I(2) = 0%, low quality evidence).

Secondary outcomes were sporadically reported with the exception of the clinical pregnancy rate, which was reported in all of the included trials. There was no evidence of a difference in clinical pregnancy rate between more bed rest and less bed rest (OR 0.88; 95% CI 0.60 to 1.31, 542 women, I(2) = 0%, low quality evidence) or between fibrin sealant and usual care (OR 0.98; 95% CI 0.54 to 1.78, 211 women, very low quality evidence). However, mechanical closure of the cervix was associated with a higher clinical pregnancy rate than usual care (OR 1.92; 95% CI 1.40 to 2.63, very low quality evidence).

The quality of the evidence was rated as low or very low for all outcomes. The main limitations were failure to report live births, imprecision and risk of bias. Overall, the risk of bias of the included trials was high.

The use of a proper method of randomisation and allocation concealment was fairly well reported, while only one trial clearly reported blinding. There was no evidence that any of the interventions had an effect on adverse event rates but data were too few to reach any conclusions.

Authors’ Conclusions: There is insufficient evidence to support any specific length of time for women to remain recumbent, if at all, following embryo transfer, nor is there sufficient evidence to recommend the use of fibrin sealants added to the embryo transfer fluid. There is very limited evidence to support the use of mechanical pressure to close the cervical canal following embryo transfer. Further well-designed and powered studies are required to determine the true effectiveness and safety of these interventions.

Keywords: ET; IVF; ICSI; Rest.

719. Prevalence of Coagulation Factor XIII and Plasminogen Activator Inhibitor-1 Gene Polymorphisms Among Egyptian Women Suffering from Unexplained Primary Recurrent Miscarriage

Iman Rifaat Elmahgoub, Reham Abdelalem Aafiya, Asmaa Ahmed Abdel Aala and Walid Sayed El-Sherbiny

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Recurrent miscarriage (RM) is an obstetric challenge. Polymorphisms of factor XIII (FXIII) and plasminogen activator inhibitor-1 (PAI-1) may cause an imbalance between coagulation and fibrinolysis that can end in RM. The aim of the work was to determine the prevalence of FXIII Val34Leu and PAI-1 4G/5G gene polymorphisms in Egyptian women presenting with unexplained primary first trimester RM. Genotyping of 120 unexplained primary first trimester RM patients and 130 healthy controls by polymerase chain reaction (PCR) amplification of target genes followed by the allele-specific restriction enzyme digestion (RFLP technique). Among the cases, 67.5% of individuals had wild-type FXIII; 21.7% were heterozygous and 10.8% were homozygous for the FXIII Val34Leu polymorphism. Among controls, the proportions were 89.2%, 8.5% and 2.3% respectively. In addition, comparison between the two groups regarding Leu and 4G allele frequencies showed statistically significant differences (P values = 0.0001 and 0.027 respectively). RM is more frequent in women with combined polymorphisms than in women with a single gene polymorphism (RR = 3.91; OR = 4.51; 95% CI = 1.79–11.38; P = 0.002). FXIII Val34Leu and PAI-1 4G/5G polymorphisms are prevalent in Egyptian women, with unexplained primary first trimester RM and combined polymorphisms statistically increasing the risk.

Keywords: Recurrent miscarriage; Polymorphism; Plasminogen activator inhibitor-1; Coagulation factor XIII.

720. A Prospective Randomized Clinical Trial Comparing Immediate Versus Delayed Removal of Urinary Catheter Following Elective Cesarean Section

Akmal El-Mazny, Mohamed El-Sharkawy and Amr Hassan


Objective: To compare immediate and 12h postoperative removal of urinary catheter after elective cesarean section.
Study Design: In a prospective clinical trial at a university teaching hospital, 300 eligible women admitted for primary or repeat elective cesarean section were randomized into two equal groups. In group A, the catheter was removed immediately after the procedure; whereas in group B, the catheter was removed 12h postoperatively.

Results: The incidence of postoperative significant bacteriuria (p=0.020), dysuria (p=0.030), burning on micturition (p=0.016), urinary frequency (p=0.031), and urgency (p=0.011) were significantly lower in group A compared with group B. The mean postoperative ambulation time (p<0.001), time till the first voiding (p<0.001), and length of hospital stay (p<0.001) were also significantly shorter in group A. There were no significant differences between the two groups in the incidence of urinary retention necessitating recatheterization (p=0.371).

Conclusion: Immediate removal of urinary catheter after elective cesarean section is associated with lower risk of urinary infection and earlier postoperative ambulation.

Keywords: Cesarean section, Urinary catheter, Urinary infection.

721. Does Flushing the Endometrial Cavity With Follicular Fluid After Oocyte Retrieval Affect Pregnancy Rates in Subfertile Women Undergoing Intracytoplasmic Sperm Injection? A Randomized Controlled Trial
Hashish NM, Badway HS, Abdelmoty HI, Mowafy A and Youssef MA

Objective: Follicular fluid of mature oocytes is rich in growth factors and cytokines that may exert paracrine and autocrine effects on implantation. The aim of this study was to investigate if flushing the endometrial cavity with follicular fluid after oocyte retrieval improved pregnancy rates in subfertile women undergoing intracytoplasmic sperm injection (ICSI).

Study Design: One hundred subfertile women undergoing ICSI between April 2012 and September 2012 at the centre for reproductive medicine, Cairo University, Egypt were enrolled in this open label, parallel randomized controlled study. Patients were randomized into two groups at the start of treatment using a computer-generated programme and sealed opaque envelopes: the follicular fluid group (n=50) and the control group (n=50).

Inclusion criteria were: age 20-38 years; basal follicle stimulating hormone <10mIU/ml; body mass index <35kg/m(2); and estradiol >1000pg/ml and <4000pg/ml on the day of human chorionic gonadotrophin administration. Exclusion criteria were: evidence of endometriosis; uterine myoma; hydropsalpinges; endocrinological disorders; history of implantation failure in previous in-vitro fertilization/ICSI cycles; and severe male factor infertility.

Results: Clinical pregnancy and implantation rates were higher in the follicular fluid group compared with the control group [354% (17/48) vs 319% (15/47); p=0718] and (18.6% vs 11.3%; p=0.153), respectively. However, the difference was not statistically significant.

Conclusion: Flushing the endometrial cavity with follicular fluid after oocyte retrieval neither improved nor adversely affected clinical pregnancy and implantation rates in subfertile women undergoing ICSI.

Keywords: Follicular fluid; ICSI; Implantation rate.

722. A Randomized Controlled Trial of Uterine Exteriorization Versus in Situ repair of the Uterine Incision During Cesarean Delivery
Waleed El-Khayat, Mohamed Elsharkawi and Amr Hassan

Objective: To compare extra-abdominal repair of the uterine incision at cesarean delivery with in situ repair.

Methods: The present study was a double-blind randomized controlled trial conducted at a university hospital in Egypt during 2012–2013, and includedwomenwith an indication for cesarean delivery. Extra-abdominal repair was used in group 1 (n=500) and in situ repair in group 2 (n=500). The primary outcome measure was the surgery duration.

Results: Surgery duration was significantly longer in group 1 than group 2 (49.9 ± 2.3 minutes vs 39.9 ± 1.8 minutes; P b 0.001). More patients in group 1 than in group 2 had postoperative moderate-to-severe pain (165 [33.0%] vs 115 [23.0%]; P = 0.001) and needed additional postoperative analgesia (100 [20.0%] vs 50 [10.0%]; P b 0.001). Moreover, mean time to bowel movement was longer in group 1 than in group 2 (17.0 ± 2.7 hours vs 14.0 ± 1.9 hours; P b 0.001).

Conclusion: In situ uterine closure is more advantageous than extra-abdominal repair in terms of surgery duration, postoperative pain and need for additional analgesia, and return of bowel movement.

Keywords: Cesarean delivery; Exteriorization; In situ repair; Uterine repair site.

723. A Review of the Contemporary Evidence on Rescue Cervical Cerclage
Hatem Abu Hashim, Hesham Al-Inany and Zaid Kilani

Background: Rescue cervical cerclage (RCC) is essentially a salvage procedure to prolong pregnancy in women with advanced cervical changes and prolapsed membranes in the second trimester. However, its effectiveness and safety remain controversial.

Objectives: To provide a comprehensive review of the contemporary evidence on RCC and evaluate which treatment modalities can be offered to pregnant women based on the best available evidence.

Search Strategy: A PubMed search of published studies on RCC and perinatal outcome was conducted using defined keywords.

Selection Criteria: Clinical studies were included with priority for level I evidence (randomized controlled trials [RCTs]) followed by other evidence levels.

Data Collection and Analysis: Abstracts of 141 articles were screened and 40 articles were selected.

Main Results: Evidence from retrospective and nonrandomized prospective trials shows a benefit of RCC. It may prolong pregnancy by an average of 4-5 weeks, with a 2-fold reduction in the chance of preterm birth before 34 weeks. A higher chance of failure is expected if cervical dilatation exceeds 4 cm or if membranes are bulging into the vagina.

Conclusions: The decision for an RCC should be individualized after comprehensive counseling by a senior obstetrician. Further research in the form of robust RCTs is recommended.
724. Reproductive Health and HIV Awareness Among Newly Married Egyptian Couples Without Formal Education
Salesh WF, Gamaleldin SF, Abdelmoty HI, Raslan AN, Fouda UM, Moheisen MN and Youssef MA

Objective: To assess awareness of several reproductive health and HIV issues and to determine the sources of reproductive health knowledge.

Methods: A cross-sectional survey of 150 randomly recruited, newly married couples without formal education attending gynecology or andrology outpatient clinics in Cairo, Egypt, was conducted from January 2012 to January 2013. Participants were interviewed separately and asked to respond to a semi-structured questionnaire on reproductive health and HIV awareness.

Results: Most participants had not received premarital counseling or undergone premarital testing. Awareness about HIV was relatively high: 117 (78.0%) women and 128 (85.3%) men had heard of HIV and had some awareness of the modes of HIV transmission. Only 24 (16.0%) women had ever used a condom compared with 36 (24.0%) men. Only two men out of the 150 couples questioned were aware of the free HIV hotline. Television and friends were the main sources of reproductive health knowledge.

Conclusion: Routine premarital counseling and testing by reproductive health, gynecology, and andrology specialists need to be enforced. Mass media is an essential source of knowledge about HIV and reproductive health. Premarital, reproductive health, and HIV education programs need to be improved.

Keywords: Awareness; Egypt; HIV; Newly married; Premarital counseling; Premarital testing; Reproductive health.

725. Helicobacter Pylori Seropositivity in Patients With Hyperemesis Gravidarum
Mona M. Shaban, Hisham O. Kandil and Arwa H. Elshafei

Background: Nausea and vomiting during pregnancy are the most common conditions affecting pregnancy, occurring in about 80% of all pregnancies and always disappearing on the 16th to 18th weeks of gestation. This may be mild and it does not affect the general condition of the patient (the condition is called emesis gravidarum), or it may be severe enough to affect the patient physically and psychologically, causing intractable vomiting, electrolyte imbalance, weight loss >5%, impairment of liver and kidney functions and dehydration. Helicobacter pylori is one of the most common bacterium affecting humans. It is a gram-negative helix-shaped microaerophilic bacterium transmitted by the oro-oral or feco-oral route. It is more prevalent in developing countries and affects young children. Acute infection manifests as acute gastritis and stomach pain, whereas chronic infection causes chronic gastritis and peptic ulcer, 2% of which may develop into stomach cancer. The authors tried to investigate the association between H pylori infection and hyperemesis gravidarum.

Methods: Fifty patients with hyperemesis gravidarum and 50 patients with normal pregnancy were included in the study. H pylori infection was determined using a 1-step H pylori test device (serum/plasma), which is a qualitative membrane-based immunoassay.

Results: Regarding maternal age, gestational age and socioeconomic status, there is no statistical difference between both groups. There is a marked statistical difference between both groups in terms of Helicobacter pylori seropositivity and frequency of vomiting.

Conclusions: There is a powerful correlation between H pylori and hyperemesis gravidarum.

Keywords: Hyperemesis gravidarum; Helicobacter pylori; Egyptian population.

726. Is Intracytoplasmic Sperm Injection (ICSI) Associated With Higher Incidence of Congenital Anomalies? A Single Center Prospective Controlled Study in Egypt
Yasmin Ahmed Bassiouney, Yomna Ali BayOumi, Hisham Mohamed Gouda and Ayman Ahmed Hassan

Objective: To compare the incidence of congenital anomalies by ultrasound in intracytoplasmic sperm injection (ICSI) pregnancies and in spontaneous pregnancies with correlation to the neonatal outcome.

Methods: This is a prospective comparative study carried out in Kasr Al Aini Hospital Cairo University from January 2010 to December 2012, comparing 739 pregnant women conceived through ICSI and 843 pregnant women conceived spontaneously as regard to incidence of congenital anomalies, multiple pregnancy, preterm labor, cesarean section and neonatal outcome.

Results: The number of anomalies diagnosed by antenatal ultrasound in ICSI group was 14 (1.62%) while in spontaneous group was 13 (1.51%). The number of anomalies detected by postnatal examination in ICSI group was 20 (2.31%) while in spontaneous group was 16 (1.86%) (Odds ratio [OR] 1.438; 95% confidence interval [CI] 0.739–2.796). ICSI group was associated with higher incidence of twins 12.7% (p<0.001), preterm labor 3.8% (p 0.022), preterm premature rupture of membranes 4.6% (p 0.001), cesarean section 74.1% (p<0.001) and neonatal deaths 10.4% (p<0.001).

Conclusion: ICSI was associated with higher incidence of multiple pregnancy and cesarean section, with no difference in the incidence of congenital anomalies compared to spontaneous conception.

Keywords: Assisted reproduction; Congenital malformations; multiple pregnancies; Neonatal outcome; Rupture of membranes spontaneous conception.

727. Comparative Study Between Different Biomarkers for Early Prediction of Gestational Diabetes Mellitus
Ahmed Mohamed Maged, Ghada Abdel Fattah Moety, Walaa Ahmed Mostafa and Dalia Ahmed Hamed
Objective: To study various biomarkers in prediction of gestational diabetes mellitus (GDM).

Patients and methods: Prospective observational study included 400 pregnant women. Maternal serum sex hormone binding globulin (SHBG), high-sensitive C-reactive protein (hs-CRP), uric acid, creatinine and albumin were measured before 15 weeks of gestation. Patients were followed-up for development of GDM.

Results: A total of 269 women were eligible for analysis. GDM complicated 27 (10.03%) of pregnancies. hs-CRP levels were significantly higher and SHBG levels were significantly lower among women who subsequently developed GDM compared with normoglycemic. Uric acid, albumin and creatinine levels were not significantly different between both groups. For prediction of GDM, hs-CRP at a cutoff value of 2.55 mg/l showed a sensitivity and a specificity of 89% and 55%, respectively. SHBG at a cutoff value of 211.5 nmol/l showed a sensitivity and a specificity of 85% and 37%, respectively. Low SHBG with high hs-CRP predicted GDM with a sensitivity and specificity of 74.07% and 75.62%, respectively with an overall accuracy of 75.46%.

Conclusion: hs-CRP and SHBG are important early predictors of GDM. Adding SHBG to hs-CRP improves specificity and serves good overall accuracy. Uric acid, creatinine and albumin have no role in GDM prediction.

Keywords: Albumin, C-Reactive Protein, Creatinine Gestational Diabetes Mellitus, Sex Hormonebinding Globulin, Uric Acid.

728. Fetal Middle Cerebral and Umbilical Artery Doppler After 40 Weeks Gestational Age
Ahmed M. Maged, Aly Abdelhafiez, Walaa Al Mostafa and Wael Elsherbiny

Objective: To determine the value of fetal Doppler indices named middle cerebral artery (MCA)-PI, umbilical artery (UA)-PI and MCA-PI/UA-PI ratio, and amniotic fluid volume assessment in pregnancies 280–294 d and their correlation with the mode of delivery and perinatal outcome.

Study design: Prospective observational study conducted on 100 whose gestational age (GA) from 40 to 42 weeks. MCA and UA Doppler and MCA-PI/UA-PI ratio, amniotic fluid volume assessment (AFV) were assessed. They were divided into two groups based on the presence or absence of adverse perinatal outcome.

Results: Women with adverse perinatal outcome showed lower MCA-PI (0.92 versus 1.29), MCA-PI/UA-PI ratio (1.04 versus 1.83), lower gestational age when assessed by ultrasound (37.82 versus 39.48 weeks), lower neonatal birth weight (2705 versus 3108 g), fetal biophysical profile (BPP) (4.55 versus 7.21) when compared to women with normal perinatal outcome. They also had higher cases with oligohydramnios (34 versus 5), and higher UA-PI (0.89 versus 0.72).

Conclusion: Women with adverse neonatal outcome had higher UA-PI and lower MCA-PI, MCA-PI/UA-PI ratio, GA (by US), AFV, BPP, estimated fetal weight, neonatal birth weight when compared to those with normal perinatal outcome. Women with adverse neonatal outcome had a higher rate of cesarean section mostly due to fetal distress and induced VB due to oligohydramnios compared to the normal outcome group.

Keywords: Amniotic Fluid Volume, Doppler Velocimetry Mode Of Delivery, Perinatal Outcome.

729. Measuring the Rate of Fetal Urine Production Using Three-Dimensional Ultrasound During Normal Pregnancy and Pregnancy-Associated Diabetes
Ahmed M. Maged, Abdelsameie Abdelmoneim, Wessam Said and Walaa A. I. Mostafa


Objective: To establish a nomogram of fetal urine production according to gestational age as a predictor for fetal well-being in normal and diabetic women.

Study design: Prospective observational study included 180 pregnant women classified into two groups: Group I (120 women) without any medical complications and Group II (60 women) with gestational diabetes mellitus (GDM). The fetal bladder is measured by the virtual organ computer-aided analysis VOCAL 3D ultrasound scanner.

Results: There was a significant positive correlation between gestational age and fetal urine production rate (UPR) (the mean UPR rate in normal pregnancy at 25, 30, 35, 40 weeks were 12.3, 14.38, 56.13 and 90.73 ml/h, respectively). There was no significant difference regarding UPR ml/h between women with normal pregnancy and those with controlled GDM (p>0.005). There was a statistically significant difference regarding UPR ml/h between women with normal pregnancy and those with uncontrolled GDM (p<0.001) and a statistically significant difference between women with controlled GDM and those with uncontrolled GDM (p<0.003).

Conclusion: Fetal UPR is considered to be more reliable as an assessment method for fetal well-being and shows significant increase in patients with uncontrolled gestational DM.

Keywords: 3D Ultrasound, Bladder Volume, Fetal Urineproduction, Gestational Diabetes Mellitus.

730. Assessment of Endometrial Receptivity Using Doppler Ultrasonography in Infertile Women Undergoing Intrauterine Insemination
Riad ON and Hak AA


Objective: The aim of this study was assessment of subendometrial blood flow with Doppler ultrasonography as an indicator of endometrial receptivity in stimulated cycles for intrauterine insemination (IUI).

Patients and Methods: This prospective study enrolled 90 women scheduled for IUI after ovarian stimulation randomly assigned to one of the three equal groups; group (C) received Clomiphene citrate, group (H) received HMG and group (CH) received Clomiphene citrate in addition to HMG. All participants had ultrasound folliculometry starting on day 9, followed by transvaginal Doppler study of the subendometrial blood flow and perifolllicular blood flow on the day of detecting at least one follicle418mm. Resistivity index (RI) and pulsatility index (PI) of subendometrial and perifolllicular flow were measured. Endometrial thickness was measured on day of hCG injection.

Results: Group (H) showed significantly higher frequency of subendometrial flow (80%) compared to the other two groups (p<0.005). In cases of positive subendometrial flow, the RI and PI were significantly lower in group (H) compared to the other two groups (p<0.0007 and 0.012, respectively). Endometrial
thickness was significantly lower in group (C) compared to group (H) \((p<0.001)\) and group (CH) \((p<0.001)\). Successful intrauterine implantation was documented in a total of 16 women (17.8%); the highest frequency was in group (H) (23.3%) and the lowest in group (C), however, the difference between the three groups was not significant \((p=0.372)\). Subendometrial indices and perifollicular RI were significantly lower in cases of successful implantation, while endometrium was significantly thicker in these cases \((p<0.001)\).

**Conclusion:** The presence of subendometrial flow is associated with successful IUI in women under stimulated cycles undergoing IUI. HMG seems a superior option for induction of ovulation regarding success of implantation.

**Keywords:** Endometrium, Ovulation Induction, Pregnancy, Uterus.

### 731. Role of Ultrasonographic Markers of Ovarian Reserve in Prediction of IVF and ICSI Outcome

**Mona Mohamed Shaban and Ghada Abdel Fattah Abdel Moety**

*Gynecol Endocrinol, 30(4): 290-293 (2014) IF: 1.136*

The aim of the study was to assess correlation of ultrasonographic markers of ovarian reserve and IVF/ICSI outcome. Two-hundred twelve IVF/ICSI patients were included. Upon pituitary suppression confirmation, antral follicle count (AFC), ovarian volume (OV), and ovarian stromal indices (vascularization index (VI), flow index (FI), and vascularization flow index (VFI)) were assessed by three-dimensional (3D) and power Doppler (PD) ultrasound and correlated with the number of mature oocytes retrieved. The number of mature oocytes retrieved correlated strongly with AFC \((r=0.832, p \leq 0.001)\) and OV \((r=0.835, p \leq 0.001)\), but weakly with VI \((r=0.166, p=0.016)\), FI \((r=0.151, p=0.028)\), and VFI \((r=0.14, p=0.041)\). AFC and OV correlate strongly with the number of mature oocytes retrieved in IVF/ICSI cycles, whereas 3D PD indices of the ovarian stromal vascularity have a weak correlation.

**Keywords:** Antral follicle count; IVF/ICSI Outcome; Ovarian stromal vascularity; Ovarian volume; Power doppler.

### 732. Body Mass Index and Labour Outcome in Egyptian Women

**M. M. Shaban, Y. A. Bassiouny, I. M. Elzhaby and A. A. Hassan**


We conducted a cross-sectional descriptive study to evaluate the impact of body mass index (BMI) on maternal medical disorders, progress of labour, mode of delivery and neonatal outcome in Cairo University hospital between September 2012 and March 2013. A total of 574 parturients were divided into two groups: group A with a BMI < 30 and group B with a BMI = 30. A statistically significant difference was found in favour of group B, regarding medical disorders, especially gestational hypertension and pre-eclampsia \((p < 0.001)\), caesarean deliveries \((p < 0.001)\) and neonatal birth weight \((p = 0.001)\). There was no difference regarding gestational age at delivery, progress of labour (cervical dilatation, cervical effacement, duration of first and second stage of labour) and neonatal outcome (Apgar score at 1 and 5 min and neonatal deaths). Our conclusion is that increased maternal BMI is associated with an increased incidence of medical disorders during pregnancy, caesarean section rate and fatal macrosomia.

**Keywords:** Body mass index; Labour outcome.

### 733. Angiotensin-Converting Enzyme Gene Polymorphisms and Hypertension in Occupational Noise Exposure in Egypt

**Nermin Zawilla, Dalia Shaker, Amaal Abdelaal and Wael Aref**


**Background:** The gene-environment interaction in the pathogenesis of hypertension has not been extensively studied in occupational noise.

**Objectives:** The aim of this study was to determine the relationship between noise and hypertension in Egyptian workers, the interaction of angiotensin-converting enzyme (ACE) gene polymorphisms as modifiers, and the possible relationship between noise hearing impairment and hypertension.

**Methods:** Study subjects were divided into two groups depending on noise exposure level. The control group \((n=161)\) was exposed to noise intensity \(<85\) dB and the exposed group \((n=217)\) was exposed to noise intensity \(\geq85\) dB. A polymerase chain reaction was used to differentiate the various genotypes of ACE insertion/deletion (I/D) and ACE G2350A.

**Results:** Noise significantly increased the likelihood of hypertension. Carriers of the genotypes AG, GG, and DD were more vulnerable to hypertension on noise exposure. No association between hypertension and hearing impairment or noise-induced hearing loss (NIHL) was found.

**Conclusion:** Our results support the association between ACE gene polymorphisms and occurrence of hypertension in noise-exposed workers.

**Keywords:** Ace I/D Gene, Ace G2350a Gene, Genetic Susceptibility, Gene Polymorphism Occupational Noise, Hypertension.

### 734. Liver Functions in Silica-Exposed Workers in Egypt: Possible Role of Matrix Remodeling and Immunological Factors

**Nermin Zawilla, Taha F and Ibrahim Y.**


**Background:** Brick manufacturing constitutes an important industrial sector in Egypt with considerable exposure to silica.

**Objectives:** We aimed for evaluating hepatic functions in silica-exposed workers in the clay brick industry, and the possible role of matrix remodeling and immunological factors.

**Methods:** A case–control study, 87 workers as exposed and 45 as control subjects. Questionnaire, clinical examination, and laboratory investigations: liver functions, matrix metalloproteinase-9, immunoglobulins G and E, and anti-liver kidney microsomal antibody.

**Results:** In the exposed workers, mean levels of liver functions, matrix metalloproteinase-9 (MMP-9), and IgG and IgE were significantly higher. In the silicotic subgroup the mean level of GGT was almost twice the level in the non-silicotic subjects. Logistic regression showed that abnormal GGT and ALT were associated with production workers.
Conclusions: Both trabeculectomy and deep sclerectomy induced considerable postoperative astigmatism. A longer follow-up period is recommended to study the different patterns of astigmatism in either procedure.

Keywords: Trabeculectomy. Deep Sclerectomy. Keratometry. Astigmatic Vector.

737. Dexamethasone Intravitreous Implant Versus Bevacizumab for Central Retinal Vein Occlusion-Related Macular Oedema: A Prospective Randomized Comparison

Gado A.S. and T. A. Macky

Clinical and Experimental Ophthalmology, 42 (7): 650-655 (2014) IF: 1.953

Background: To compare the efficiency of dexamethasone implants to bevacizumab injections in macular oedema secondary to central retinal vein occlusion.

Design: Randomized clinical trial at Cairo University Hospitals.

Participants: Sixty eyes of 60 newly diagnosed patients with macular oedema secondary to central retinal vein occlusion with best corrected visual acuity 0.3 logMAR (6/12) to counting fingers, no evidence of retinal ischaemia and/or neovascularization on fluorescein angiography and central subfield thickness ≥500 μm on ocular coherence tomography.

Methods: Patients were randomly assigned (30 eyes each group) to either intravitreal dexamethasone implant or bevacizumab injections repeated whenever needed. Best corrected visual acuity and ocular coherence tomography were done at baseline and monthly for 6 months.

Main Outcome Measures: Comparing best corrected visual acuity and central foveal subfield thickness between both groups during the 6-month period.

Results: There was no significant difference in best corrected visual acuity between the two groups during the 6 months (P-values > 0.05). The bevacizumab group had a statistically significant thinner central subfield thickness at 1 month (P-value 0.006) and no statistically significant difference for the rest of the 6 months (P-values > 0.05). There was a statistically significant higher intraocular pressure for dexamethasone implant group (compared with bevacizumab) at 3-6 months (P-values < 0.05), respectively.

Conclusion: Both drugs provided effective best corrected visual acuity improvements and central subfield thickness reductions that showed no statistically significant difference between the two groups.

Keywords: Central Retinal Vein Occlusion; Dexamethasone Implant (Ozurdex); Intravitreal Bevacizumab (Avastin); Macular Oedema.
738. Orbital Epidermoid Cysts: A Diagnosis to Consider

Rania A. Ahmed and Rasha M. Eltanamly

**Background:** Orbital epidermoid forms rare pathological entity that is separate from dermoid cysts. They have variable clinical and radiological presentations and they should be considered in the differential diagnosis of orbital cystic lesions. This work describes the various clinical and radiological presentations of 17 cases of epidermoid cysts and the surgical outcome. Method. A prospective interventional study was conducted on 17 patients diagnosed with epidermoid cysts. Patients’ symptoms and signs were recorded; CT scan was done for all patients. All lesions were removed through anterior orbitotomy and histopathological diagnosis confirmed.

**Results:** Mean age of patients was 16.3 years ± 10.54. Main complaints were lid swelling, masses, ocular dissimilarity, chronic pain, and ocular protrusion. Clinical signs varied from lid swelling and masses in all cases to proptosis, globe displacement, limitation of ocular motility, and scars. Radiological findings ranged from homogenous hypodense masses (58.8%) to homogenous radiolucent (17.6%) and heterogenous masses (23.5%). No recurrences following surgeries were reported throughout the follow-up (mean 18.8 months ± 0.72).

**Conclusion:** Deep orbital epidermoid cysts are a separate entity that can behave like deep orbital epidermoid; however, they usually present at a relatively older age. They can be associated with increased orbital volume but not necessarily related to bony sutures.

**Keywords:** Epidermoid Cyst; Orbit; Proptosis; CT Imaging.

739. Changes in Corneal Sensation Following 20 and 23G Vitrectomy in Diabetic and Nondiabetic Patients

MM Mahgoub and TA Macky
Eye, 28: 1286-1291 (2014) IF: 1.897

Purpose To evaluate the changes in corneal sensation (CS) following two different port sizes vitrectomy in diabetic and nondiabetic patients. Patients and Methods Patients prepared for pars plana vitrectomy were randomly assigned to four groups: diabetics to either 20G or 23G and non-diabetics to either 20G or 23G vitrectomy systems. CS was measured using the Cochet–Bonnet aesthesiometer at baseline preoperatively and at 1 day, 1 week, and 1 month postoperative. Results A total of 40 eyes of 40 patients were included in this study; 20 patients (20 eyes) in each of the 20-G and 23-G groups. The mean age was 55.51±10 years and male/female ratio was 2:3. There were no significant difference between CS at baseline, and at 1 day, 1 week, and 1 month between both the 20-G and 23-G groups. There were significant drops in CSs at 1 day and 1 week for both groups (20G and 23 G) with incomplete recovery for the 20-G group and complete recovery for the 23-G group. Comparing the two diabetic subgroups (20G and 23G) and two non-diabetic subgroups (20G and 23G), there were no significant differences in CS between subgroups. Diabetics’ eyes had lower CSs throughout the study period in the 20-G and 23-G groups, which was significant at day 1 and week 1 postoperatively. Conclusion The vitrectomy procedure showed reduction in CS in the postoperative period with minimal nonsignificant difference between 20G and 23G systems. However, diabetics’ eyes showed compromised CS preoperatively and a further significant reduction for 1 month postoperatively compared with nondiabetics.

**Keywords:** Vitrectomy; Corneal sensation; Diabetic patients.

740. Intermittent Exotropia: Relation Between Age and Surgical Outcome: A Change-Point Analysis

A Awadein, RM Eltanamly and M Elshazly
Eye, 28: 587-593 (2014) IF: 1.897

Purpose To study the relationship between age and response to surgery in patients with intermittent exotropia and to identify change points in response to surgery. Methods A retrospective analysis was conducted on 311 patients with intermittent exotropia who had bilateral lateral rectus recession using standard tables with minimum follow-up of 6 months. Data were analyzed using the change-point analysis software to identify cutoff points. A prospective pilot study was then performed on 171 consecutive patients with intermittent exotropia with the same clinical characteristics, in whom amount of recession was modified according to the identified cutoff points. In angles with two change points, 1-mm recession was reduced from patients younger than the lower change point and 1.5-mm recession was added to those older than the upper change point. In angles with one change point, 1.5-mm recession was added to those older than the change point. Satisfactory alignment was defined as esophoria/tropia <5D to exophoria/tropia >5D.

**Results:** There was a negative correlation (P<0.01) between response to surgery and age at surgery for all angles. In younger patients (<7 years) in whom surgical dose was reduced, there was no significant change in success rate (77%), compared with those who had surgery using standard tables (75%). In older patients (412 years) in whom surgical dose was increased, there was a statistically significant increase in success rate (80% vs 41%).

**Conclusions:** Modifying the surgical dose according to age can improve the success in patients with intermittent exotropia.

**Keywords:** Intermittent exotropia; Surgery; Recession.

Dept. of Orthopaedic

741. Low-Intensity Pulsed Ultrasound Shortens the Treatment Time in Tibial Distraction Osteogenesis

Salem KH and Schmelz A.
International Orthopaedics, 38: 1477-1482 (2014) IF: 2.019

**Purpose:** Low-intensity pulsed ultrasound (LIPUS) has been used successfully to accelerate healing of fresh fractures and non-unions. It also improved callus maturation with distraction osteogenesis in animal trials. However, only few clinical studies are available to support its widespread use for the latter indication in humans.

**Methods:** Twenty-one patients undergoing callus distraction for posttraumatic tibial defects were randomized into two groups: the trial group (12 men; mean age 32 years) which received 20 minutes LIPUS daily during treatment and the control group (six men and three women; mean age 29 years) without LIPUS treatment. The Ilizarov ring fixator was used in all cases. Results were examined clinically and radiologically, analysing callus maturation with a computer-assisted measurement.

**Results:** Patients in the LIPUS group needed a mean of 33 days to consolidate every 1 cm of new bone in comparison to 45 days in
the control group. The healing index was therefore shortened by 12 days/cm in the LIPUS group. This means that callus maturation was 27 % faster in the LIPUS group. The fixator time was shortened by 95 days in the LIPUS group. The overall daily increase in radiographic callus density was 33 % more in the LIPUS group than in the control group.

**Conclusions:** LIPUS treatment is an effective non-invasive adjuvant method to enhance callus maturation in distraction osteogenesis. With the help of this treatment, the healing time and the duration of external fixation can be reliably shortened.

**Keywords:** Low-Intensity Pulsed Ultrasound; Ilizarov; Callus Distraction; Bone Defects.

### 742. Management of Neglected Bennett Fracture in Manual Laborers by Tension Fixation

Mohammad M, El Shafie S, Menorca RM and Elfar JC


**Purpose:** To report the results of open reduction and internal fixation (ORIF) of Bennett fractures in young, active patients using a K-wire and wire loop construct to achieve anatomical reduction and to allow return to manual labor.

**Methods:** In this prospective series, we treated 10 male manual laborers (mean age, 30 y; range, 20–44 y) with Bennett fractures diagnosed after a minimum of 12 weeks (mean, 16 wk; range, 12–18 wk). ORIF using 2 K-wires with a wire loop and a neutralizing transarticular K-wire was performed with direct articular visualization. Patients were evaluated for range of motion, grip strength, and pinch strength, and a visual analog scale score rated pain before surgery and 12 months later.

**Results:** The mean follow-up was 16 months (range, 12–36 mo). The average visual analog scale improved from 6 to 2, mean palmar abduction improved from 15° to 40°, mean radial abduction increased from 22° to 39°, average pinch strength improved from 9.9 kg to 15.5 kg, and average grip strength increased from 34 kg to 49 kg. Complications included transient irritation of the radial sensory nerve or lateral cutaneous nerve of the forearm in 3 patients, pin track granuloma formation in 2 patients, and marginal osteophyte formation in 2 patients. Union was achieved in all 10 patients, and 9 patients returned to their previous manual labor occupation.

**Conclusions:** Our results suggest that neglected Bennett fractures can be effectively managed by ORIF using K-wires and a wire loop without compromising strength or motion. This technique reliably restored the anatomy and provided adequate thumb motion and strength to allow a return to manual labor. Type of study/level of evidence Therapeutic IV.

**Keywords:** Internal Fixation; K-Wires; Manual Laborers; Neglected Bennett; Wire Loops.

### 743. The Effect of Praziquantel and Carica Papaya Seeds on Hymenolepis Nana Infection in Mice Using Scanning Electron Microscope

Maha Mohamed Abou El-Magd Basyoni

*Parasitology Research, 113: 2827-2836 (2014) IF: 2.327*

Hymenolepis nana (H. nana) is the most common tapeworm infection worldwide. It is more prevalent in warm climates where sanitation is poor, particularly among children. The effect and mechanism of action of praziquantel (PZQ), given at a dose of 25-mg/kg BW, and Carica papaya dried seed crude aqueous extract (CAE), given at a dose of 1.2-g/kg BW, were assessed on H. nana worms in experimentally infected mice. Tegumental changes were studied using the scanning electron microscope (SEM) and different parasitological parameters were observed. Each group of infected mice was divided into two subgroups. The first subgroup received either treatment before the 4th day after infection to investigate their effects on the cysticercoid stage. The other subgroup received treatments after the development of the adult stage, confirmed by eggs detection in stool. Both PZQ and C. papaya dried seed CAE resulted in a significant reduction of worm burden, total egg output and viable egg count. Marked tegumental changes were evident in adult worms treated with either treatment including shrinkage of the scolex and neck region with rostellar edema and complete loss of its hooks. However, all previous effects were exerted more rapidly in the case of PZQ treatment. They both significantly reduced cysticercoid stage size. Nevertheless, C. papaya outstand PZQ in having a deforming effect on adults arising from treated cysticercoids. It was concluded that C. papaya has significant anti-cestodial properties that enable its seed extract to be a very effective alternative to PZQ against H. nana.

**Keywords:** Hymenolepis Nana; Praziquantel; C. Papaya; Scanning Electron Microscope Introduction.

### 744. Molecular Copro-prevalence of Cryptosporidium in Egyptian Children and Evaluation of Three Diagnostic Methods

Mona M Fathy, Noha M Abdelrazek, Fayza A Hassan and Ayman A El-Badry

*Indian Pediatrics, 51: 1144-1147 (2014) IF: 1.014*

**Objective:** To determine molecular prevalence of Cryptosporidium in a cohort of Egyptian children and compare three diagnostic tests.

**Methods:** Stool samples from children with diarrhea and from apparently healthy children were examined for Cryptosporidium using microscopy, enzyme linked immunosorbant assay (ELISA) and polymerase chain reaction (PCR). Results: PCR detected Cryptosporidium in 22.4% of children. Acid–fast stain and ELISA showed false negativity but 100% specificity with PCR as gold standard.

**Conclusion:** Cryptosporidium is a common cause of diarrhea in children in Egypt.

**Keywords:** Diarrhea, Etiology, Elisa, Nested Pcr.

### 745. Lymphatic Obstruction: A Novel Etiologic Factor in the Formation of Antrochoanal Polyps

Mostafa HS, Fawzy TO, Jabri WR and Ayad E.


**Objectives:** Antrochoanal polyps (ACPs) originate from the inner wall of the maxillary sinus and either pass through the natural sinus ostia or cause pressure-induced destruction of the medial sinus wall. Eventually, they extend into the choanae and nasopharynx. Most authors who have studied the microstructure of ACPs, including the component stromal cells and surface
epithelium, have not examined the transitional area between the sinus mucosa and the pedicle of the polyp. No explanation has been given for the absence of a cystic intrasinus portion of the polyp, in many cases refuting the therapy (most accepted) that polyps are caused by a mucous gland with a blocked acinus. We noted during endoscopic removal of the ACPs that the antral part of the polyp was cystic in only 5% of patients, and polypoid in 95%. The cystic intrasinus portion of the polyp is a cornerstone of the pathophysiology of ACPs, whether caused by inflammation, cicatrization, or allergy. This finding prompted us to examine the transitional area between the sinus mucosa and the pedicle of the polyp to verify the possibility that lymphatic obstruction—whether primary (areas of higher tissue pressure) or secondary (cicatrization or inflammation)—could be an etiologic factor in the formation of ACPs.

**Methods:** The study material consisted of 25 ACPs and 25 chronic maxillary sinusitis mucosal biopsy specimens (control group). The detection of lymphatic vessels was based on the identification of lymph vessel endothelial hyaluronic acid receptor 1 (LYVE-1) in the endothelial cells of the lymphatic capillaries. This was the first lymph-specific hyaluronic acid receptor to be characterized, and is a uniquely powerful marker for lymph vessels, differentiating them from (blood) capillaries.

**Results:** The density of the lymphatic vessels was marked in 22 of the 25 ACP specimens, i.e., 88% of the ACP cases, compared with 16% of the control group.

**Conclusions:** This study resulted in two main findings. The first was the absence of intramaxillary cysts in the ACPs in 23 cases (92%). The second was the markedly high density of lymphatic vessels in the transitional area between the sinus mucosa and the pedicle of the ACPs, in comparison with the density in the control group. These two findings refute the “blocked acinus theory” and indicate that lymphatic obstruction, whether primary or secondary to chronic sinus infection, might play a leading role in the formation and further growth of ACPs.

**Keywords:** Acinous Mucous Gland, Antrochoanal Polyp, Endoscopic Sinus Surgery, Functional Endoscopic Sinus Surgery, Killian Polyp, Lymphatic Capillary, Lyve-1, Maxillary Sinus, Maxillary Sinusitis Mucosal Biopsy, Nasal Polyp.

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**Dept. of Pediatrics**

746. Exome Sequencing Links Corticospinal Motor Neuron Disease to Common Neurodegenerative Disorders


Hereditary spastic paraplegias (HSPs) are neurodegenerative motor neuron diseases characterized by progressive age-dependent loss of corticospinal motor tract function. Although the genetic basis is partly understood, only a fraction of cases can receive a genetic diagnosis, and a global view of HSP is lacking. By using whole-exome sequencing in combination with network analysis, we identified 18 previously unknown putative HSP genes and validated nearly all of these genes functionally or genetically. The pathways highlighted by these mutations link HSP to cellular transport, nucleotide metabolism, and synapse and axon development. Network analysis revealed a host of further candidate genes, of which three were mutated in our cohort. Our analysis links HSP to other neurodegenerative disorders and can facilitate gene discovery and mechanistic understanding of disease.

747. BCG Vaccination in Patients With Severe Combined Immunodeficiency: Complications, Risks, and Vaccination Policies


*The Journal of Allergy and Clinical Immunology,* 133: 1134-1141 (2014) IF: 11.248

**Background:** Severe combined immunodeficiency (SCID) is a syndrome characterized by profound T-cell deficiency. BCG vaccine is contraindicated in patients with SCID. Because most countries encourage BCG vaccination at birth, a high percentage of patients with SCID are vaccinated before their immune defect is detected.

**Objectives:** We sought to describe the complications and risks associated with BCG vaccination in patients with SCID.

**Methods:** An extensive standardized questionnaire evaluating complications, therapeutics, and outcomes regarding BCG vaccination in patients given a diagnosis of SCID was widely distributed. Summary statistics and association analysis was performed.

**Results:** Data on 349 BCG-vaccinated patients with SCID from 28 centers in 17 countries were analyzed. Fifty-one percent of the patients had BCG-associated complications, 34% disseminated and 17% localized (a 33,000- and 400-fold increase, respectively, over the general population).

Patients receiving early vaccination (=1 month) showed an increased prevalence of complications (P = .006) and death caused by BCG-associated complications (P < .0001). The odds of experiencing complications among patients with T-cell numbers of 250/µL or less at diagnosis was 2.1 times higher (95% CI: 1.4-3.4 times higher; P = .001) than among those with T-cell numbers of greater than 250/µL. BCG-associated complications were reported in 2 of 78 patients who received antimycobacterial therapy while asymptomatic, and no deaths caused by BCG-associated complications occurred in this group. In contrast, 46 BCG-associated deaths were reported among 160 patients treated with antimycobacterial therapy for a symptomatic BCG infection (P < .0001).

**Conclusions:** BCG vaccine has a very high rate of complications in patients with SCID, which increase morbidity and mortality rates. Until safer and more efficient antituberculosis vaccines
become available, delay in BCG vaccination should be considered
to protect highly vulnerable populations from preventable
complications.

**Keywords:** Primary immunodeficiency; Severe combined
immunodeficiency; Vaccine; BCG; Mycobacteria; Newborn
screening.

**748. Clinical Picture and Treatment of 2212 Patients
With Common Variable Immunodeficiency**

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RN, MSc, Javier De Gracia, Torsten Witte, Reinhold E. Schmidt,
Jiri Litzman, Eva Hlavackova,Vojtech Thon, Michael Borte,
Stephan Borte, Dinakantha Kumararatne, Conleth Feighery,
Hilary Longhurst, Matthew Helbert, Anna Szafalarska, Anna
Sediva, Bernd H. Belohradsky, Alison Jones, Ulrich Baumann,
Isabelle Meyts, Necil Kutukculer, Per W agstrom, Nermoen
Mouftah Galal, Joachim Roessler, Evangelia Farmaki, Natalia
Zinovieva, Peter Ciznar, Efimia Papadopoulou-Alataki, Kirsten
Bienemann, Sirje Velbi, Zoya Panahloo and Bodo Grimbacher

The *Journal of Allergy and Clinical Immunology*, 134: 116-126
(2014) IF: 11.248

**Background:** Common variable immunodeficiency (CVID) is an
antibody deficiency with an equal sex distribution and a high
variability in clinical presentation. The main features include
respiratory tract infections and their associated complications,
tenteropathy, autoimmunity, and lymphoproliferative disorders.

**Objective:** This study analyzes the clinical presentation,
association between clinical features, and differences and effects of
immunoglobulin treatment in Europe.

**Methods:** Data on 2212 patients with CVID from 28 medical
centers contributing to the European Society for
Immunodeficiencies Database were analyzed retrospectively.

**Results:** Early disease onset (<10 years) was very frequent in our
cohort (33.7%), especially in male subjects (39.8%). Male
subjects with early-onset CVID were more prone to pneumonia
and less prone to other complications suggesting a distinct disease
entity. The diagnostic delay of CVID ranges between 4 and 5
years in many countries and is particularly high in subjects with
early-onset CVID. Enteropathy, autoimmunity, granulomas, and
splenomegaly formed a set of interrelated features, whereas
bronchiectasis was not associated with any other clinical feature.
Patient survival in this cohort was associated with age at onset
and age at diagnosis only. There were different treatment
strategies in Europe, with considerable differences in
immunoglobulin dosing, ranging from 130 up to 750 mg/kg/mo.
Patients with very low trough levels of less than 4 g/L had poor
clinical outcomes, whereas higher trough levels were associated
with a reduced frequency of serious bacterial infections.

**Conclusion:** Patients with CVID are being managed differently
throughout Europe, affecting various outcome measures.
Clinically, CVID is a truly variable antibody deficiency syndrome.

**Keywords:** Common variable immunodeficiency; Autoimmunity;
Enteropathy; Granulomas; Immunoglobulin replacement;
Lymphadenopathy; Patient self-reported outcomes; Primary
antibody deficiency; Quality of Life; Treatment.

**749. A 1-Year Randomized Controlled Trial of
Deferasirox Vs Deferoxamine for Myocardial Iron Removal in
β-Thalassemia Major (CORDELIA)**

Pennell DJ, Porter JB, Piga A, Lai Y, El-Beshlawy A, Belhoul
KM, Elalfy M, Yesilipek A, Kiling Y, Lawniczek T, Habr D,
Weisskopf M, Zhang Y and Aydinok Y

Blood, 123, 10: 1447-1454 (2014) IF: 9.775

Randomized comparison data on the efficacy and safety of
deferasirox for myocardial iron removal in transfusion dependent
patients are lacking. CORDELIA was a prospective, randomized
comparison of deferasirox (target dose 40 mg/kg per day) vs
subcutaneous deferroxamine (50-60 mg/kg per day for 4-5
weeks/month) for myocardial iron removal in 197 β-thalassemia
major patients with myocardial siderosis (T2* 6-20 milliseconds)
and no signs of cardiac dysfunction (mean age, 19.8 years).
Primary objective was to demonstrate noninferiority of
deferasirox for myocardial iron removal, assessed by changes
in myocardial T2* after 1 year using a per-protocol analysis.
Geometric mean (Gmean) myocardial T2* improved with
deferasirox from 11.2 milliseconds at baseline to 12.6
milliseconds at 1 year (Gmeans ratio, 1.12) and with
deferoxamine (11.6milliseconds to 12.3 milliseconds;Gmeans
ratio, 1.07). The between-arm Gmeans ratio was 1.056 (95%
confidence interval [CI], 0.998,1.133). The lower 95% CI
boundary was greater than the prespecified margin of 0.9,
establishing noninferiority of deferasirox vs deferoxamine (P5
0.057 for superiority of deferasirox).

Left ventricular ejection fraction remained stable in both arms.
Frequency of drug-related adverse events was comparable
tweendeferasirox (35.4%) and deferoxamine (30.8%).
CORDELIA demonstrated the noninferiority of deferasirox
compared with deferoxamine for myocardial iron removal. This
trial is registered at www.clinicaltrials.

**Keywords:** Deferasirox, Deferoxamine; B-thalassemia major,
Cordelia.

**750. Mutations in 12 Known Dominant Disease-
Causing Genes Clarify Many Congenital Anomalies of The Kidney and Urinary Tract**

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Saisawat, Asaf Vivante, Alina C. Hilger, Heiko M. Reutter,
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Velibor Tasic and Friedhelm Hildebrandt


Congenital anomalies of the kidney and urinary tract (CAKUT)
account for approximately half of children with chronic kidney
disease. CAKUT can be caused by monogenic mutations;
however, data are lacking on their frequency. Genetic diagnosis
has been hampered by genetic heterogeneity and lack of
genotype-phenotype correlation. To determine the percentage of
cases with CAKUT that can be explained by mutations in known
CAKUT genes, we analyzed the coding exons of the 17 known
dominant CAKUT-causing genes in a cohort of 749 individuals
from 650 families with CAKUT. The most common phenotypes
in this CAKUT cohort were vesicoureteral reflux in 288 patients,
renal hypoplasia in 120 patients, and unilateral renal agenesis
in 90 patients. We identified 37 different heterozygous mutations
(33 novel) in 12 of the 17 known genes in 47 patients from 41 of
the 650 families (6.3%). These mutations include (number of
families): BMP7 (1), CDC5L (1), CHD1L (5), EYA1 (3), GATA3 (2), HNF1B (6), PAX2 (5), RET (3), ROBO2 (4), SALL1 (9), SIX2 (1), and SIX5 (1). Furthermore, several mutations previously reported to be disease-causing are most likely benign variants. Thus, in a large cohort over 6% of families with isolated CAKUT are caused by a mutation in 12 of 17 dominant CAKUT genes. Our report represents one of the most in-depth diagnostic studies of monogenic causes of isolated CAKUT in children.

Keywords: Renal Agenesis, Renal Development, Genetic Renal Disease.

751. The Influence of Physiological Matrix Conditions on Permanent Culture of Induced Pluripotent Stem Cell-Derived Cardiomyocytes

Wael Ahmed Attia Taha Abdel Wahab

Biomaterials., 35:7374-7385 (2014) IF: 8.312

Cardiomyocytes (CMs) from induced pluripotent stem (iPS) cells mark an important achievement in the development of in vitro pharmacological, toxicological and developmental assays and in the establishment of protocols for cardiac cell replacement therapy. Using CMs generated from murine embryonic stem cells and iPS cells we found increased cell-matrix interaction and more matured embryoid body (EB) structures in iPS cell-derived EBs. However, neither suspension-culture in form of purified cardiac clusters nor adherence-culture on traditional cell culture plastic allowed for extended culture of CMs. CMs grown for five weeks on polystyrene exhibit signs of massive mechanical stress as indicated by a-smooth muscle actin expression and loss of sarcomere integrity. Hydrogels from polyacrylamide allow adapting of the matrix stiffness to that of cardiac tissue. We were able to eliminate the bottleneck of low cell adhesion using 2,5-Dioxopyrrolidin-1-yl-6-acylamidoxanenolate as a crosslinker to immobilize matrix proteins on the gels surface. Finally we present an easy method to generate polyacrylamide gels with a physiological Young's modulus of 55 kPa and defined surface ligand, facilitating the culture of murine and human iPS-CMs, removing excess mechanical stresses and reducing the risk of tissue culture artifacts exerted by stiff substrates.

Keywords: Cardiomyocyte; Cell Adhesion; Cell Culture; Cell Viability; Cross-Linking; Hydrogel.

752. Serum Ferritin Level And Morbidity Risk in Transfusion-Independent Patients With B-Thalassemia Intermedia: the Orient Study

Khaled M. Musallam, Maria Domenica Cappellini, Shahina Daur, Mehran Karimi, Amal El-Beshlawy, Giovanna Graziadei, Matthew Magestro, Jerome Wulff, Guilhem Pietri and Ali T. Taher


Similar to other forms of non-transfusion-dependent thalassemia, the diagnosis of β-thalassemia intermedia is associated with a state of iron overload. This occurs in the absence of regular transfusion therapy and is primarily attributed to increased intestinal iron absorption signaled by ineffective erythropoiesis and low serum hepcidin levels. Although iron accumulation in transfusion-independent β-thalassemia intermedia patients is slower than in regularly-transfused β-thalassemia major, recent evidence highlights that a considerable proportion of patients ultimately reach clinically significant levels that can cause serious morbidities after the age of ten years. Accordingly, current management guidelines recommend initiating iron chelation therapy in β-thalassemia intermedia patients over ten years of age and in whom liver iron concentration has reached 5 mg Fe/g dry weight (dw) or over. This threshold was primarily selected in the light of its established association with morbidity in β-thalassemia intermedia patients, as well as recent evidence on the efficacy and safety of iron chelation therapy in non-transfusion-dependent thalassemia (including β-thalassemia intermedia) patients for whom treatment was started at 5 mg Fe/g dw or over (THALASSA trial). A liver iron concentration of 3 mg Fe/g dw was also used and this was the recommended threshold at which to interrupt iron chelation therapy and avoid overchelation. When liver iron concentration measurement is unavailable, serum ferritin levels of 800 and 300 ng/mL can be used as an alternative to the 5 and 3 mg Fe/g dw liver iron concentration values, respectively, as established in the THALASSA trial through correlation analysis between both iron overload indices.

Keywords: Serum Ferritin; Transfusion-Independent; β-Thalassemia Intermedia.

753. PRRT2 Mutations: Exploring the Phenotypic Boundaries


Background: Mutations in the proline-rich transmembrane protein 2 (PRRT2) gene have been identified in patients with benign (familial) infantile convulsions (B(F)IC), infantile convulsions with choreoathetosis (ICCA) and paroxysmal dyskinesias (PDs). However it remains unknown whether PRRT2 mutations are causal in other epilepsy syndromes. After we discovered a PRRT2 mutation in a large family with ICCA containing one individual with febrile seizures (FS) and one individual with West syndrome, we analysed PRRT2 in a heterogeneous cohort of patients with different types of infantile epilepsy.

Methods: We screened a cohort of 460 patients with B(F)IC or ICCA, fever related seizures or infantile epilepticencephalopathies. All patients were tested for point mutations using direct sequencing.

Results: We identified heterozygous mutations in 16 individuals: 10 familial and 6 sporadic cases. All patients were diagnosed with B(F)IC, ICCA or PD. We were not able to detect mutations in any of the other epilepsy syndromes. Several mutation carriers had learning disabilities and/or impaired fine motor skills later in life.

Conclusions: PRRT2 mutations do not seem to be involved in the aetiology of FS or infantile epilepticencephalopathies. Therefore B(F)IC, ICCA and PD remain the core phenotypes associated with PRRT2 mutations. The presence of learning disabilities or additional neuropsychiatric problems in several mutation carriers calls for additional clinical studies addressing this developmental aspect in more detail.

Keywords: Clinical Neurology; Epilepsy; Genetics; Neurogenetics.
Background and Objectives: In steroid-resistant nephrotic syndrome (SRNS), >21 single-gene causes are known. However, mutation analysis of all known SRNS genes is time and cost intensive. This report describes a new high-throughput method of mutation analysis using a PCR-based microfluidic technology that allows rapid simultaneous mutation analysis of 21 single-gene causes of SRNS in a large number of individuals.

Design, Setting, Participants and Measurements: This study screened individuals with SRNS; samples were submitted for mutation analysis from international sources between 1996 and 2012. For proof of principle, a pilot cohort of 48 individuals who harbored known mutations in known SRNS genes was evaluated. After improvements to the method, 48 individuals with an unknown cause of SRNS were then examined in a subsequent diagnostic study. The analysis included 16 recessive SRNS genes and 5 dominant SRNS genes. A 10-fold primer multiplexing was applied, allowing PCR-based amplification of 474 amplicons in 21 genes for 48 DNA samples simultaneously. Forty-eight individuals were indexed in a barcode PCR, and high-throughput sequencing was performed. All disease-causing variants were confirmed via Sanger sequencing.

Results: The pilot study identified the genetic cause of disease in 42 of 48 (87.5%) of the affected individuals. The diagnostic study detected the genetic cause of disease in 16 of 48 (33%) of the affected individuals with a previously unknown cause of SRNS. Seven novel disease-causing mutations in PLCE1 (n=5), NPHS1 (n=1), and LAMB2 (n=1) were identified in <3 weeks. Use of this method could reduce costs to 1/29th of the cost of Sanger sequencing.

Conclusions: In adult patients with Ei syndrome, bosentan therapy improves ventricular and atrial functions resulting in enhancement of physical exercise and reduction in the NT-proBNP level, while the pulmonary vascular resistance does not change substantially.

Keywords: Pulmonary arterial hypertension; Echocardiography myocardial contraction remodeling.
Conclusion: We identified two novel NR5A1 mutations showing impaired function in 23 Egyptian XY DSD patients with hypospadias (8.5%). This is the first study searching for NR5A1 mutations in oriental patients from the Middle East and Arab region with XY DSD and no adrenal insufficiency, revealing a frequency similar to that in European patients (6.5-15%). We recommend screening for NR5A1 in patients with hypospadias and gonadal dysgenesis. Yearly follow-ups of gonadal function and early cryoconservation of sperms should be performed in XY DSD patients with NR5A1 mutations given the risk of future fertility problems due to early gonadal failure.

Keywords: Steroidogenic factor-1; 46 Xy disorder of sex development.

757. A Double-Blind, Placebo-Controlled Phase II Study of the Efficacy and Safety of 2,2-Dimethylbutyrate (HQK-1001), an Oral Fetal Globin Inducer, in Sickle Cell Disease
American Journal of Hematology, 89 (7): 709-713 (2014) IF: 3.477

This placebo-controlled phase II study evaluated the pharmacodynamics, efficacy and safety of 2,2-dimethylbutyrate (HQK-1001), a fetal globin gene-inducing short-chain fatty acid derivative, administered orally at 15 mg/kg twice daily for 48 weeks in 76 subjects with sickle cell disease (SCD). The median age was 26 years (range: 12–55 years) and 37 subjects (49%) were treated previously with hydroxyurea.

Sixty subjects (79%) had Hb SS and 16 (21%) had S/b0 thalassemia. The study was terminated after a planned interim analysis showed no significant increase in fetal hemoglobin (Hb F) and a trend for more pain crises in the HQK-1001 group. For 54 subjects with Week 24 data, the mean absolute increase in Hb F was 0.9% (95% confidence interval (CI): 0.1–1.6%) with HQK-1001 and 0.2% (95% CI: 0.07–1.1%) with placebo.

Absolute increases in Hb F greater than 3% were noted in 9 of 38 subjects (24%) administered HQK-1001 and 1 of 38 subjects (3%) administered placebo. The mean changes in hemoglobin at Week 24 were comparable between the two groups. The mean annualized rate of pain crises was 3.5 with HQK-1001 and 1.7 with placebo. The most common adverse events in the HQK-1001 group, usually graded as mild or moderate, consisted of nausea, headache, vomiting, abdominal pain, and fatigue. Additional studies of HQK-1001 at this dose and schedule are not recommended in SCD. Intermittent HQK-1001 administration, rather than a daily regimen, may be better tolerated and more effective, as shown previously with arginine butyrate, and warrants further evaluation.

Keywords: 2,2-Dimethylbutyrate, Globin Inducer, Sickle Cell Disease.

758. Multicenter Validation of Spin-Density Projection-Assisted R2-MRI for the Noninvasive Measurement of Liver Iron Concentration
Magnetic Resonance In Medicine, 71: 2215-2223 (2014) IF: 3.398

Purpose: Magnetic resonance imaging (MRI)-based techniques for assessing liver iron concentration (LIC) have been limited by single scanner calibration against biopsy. Here, the calibration of spin-density projection-assisted (SDPA) R2-MRI (FerriScanVR) in iron-overloaded b-thalassemia patients treated with the iron chelator, deferasirox, for 12 months is validated.

Methods: SDPA R2-MRI measurements and percutaneous needle liver biopsy samples were obtained from a subgroup of patients (n/6233) from the ESCALATOR trial. Five different makes and models of scanner were used in the study.

Results: LIC, derived from mean of MRI- and biopsy-derived values, ranged from 0.7 to 50.1 mg Fe/g dry weight. Mean fractional differences between SDPA R2-MRI and biopsy-measured LIC were not significantly different from zero. They were also not significantly different from zero when categorized for each of the Ishak stages of fibrosis and grades of necroinflammation, for subjects aged 3 to <8 versus ≥8 years, or for each scanner model. Upper and lower 95% limits of agreement between SDPA R2-MRI and biopsy LIC measurements were 74% and 71%.

Conclusion: The calibration curve appears independent of scanner type, patient age, stage of liver fibrosis, grade of necroinflammation, and use of deferasirox chelation therapy, confirming the clinical usefulness of SDPA R2-MRI for monitoring iron overload.

Keywords: Deferasirox; Iron Overload; B-Thalassemia; Escalator; Biopsy.

759. Evidence for Self-Maintaining Pluripotent Murine Stem Cells in Embryoid Bodies

Pluripotent stem cells have great potential for regenerative medicine; however, their clinical use is associated with a risk of tumor formation. We utilized pluripotent cells expressing green fluorescent protein and puromycin resistance under control of the Oct4 promoter to study the persistence of potential pluripotent cells under embryoid body (EB) culture conditions, which are commonly used to obtain organotypic cells. We found that i.) OCT4-expressing cells dramatically decrease during the first week of differentiation, ii.) the number of OCT4-expressing cells recovers from day 7 on, iii.) the OCT4-expressing cells are similar to embryonic stem cells grown in the presence of leukemia inhibitory factor LIF but express several markers associated with germ cell formation, such as DAZL and STRA-8 and iv.) the persistence of potentially pluripotent cells is independent of supportive cells in EBs. Finally, OCT4-expressing cells, isolated from EBs after 2-month of culture, were further maintained under feeder-free conditions in absence of LIF and continued to express OCT4 in 95% of the population for at least 36 days. These findings point to an alternative state of stable OCT4 expression. In the frame of the landscape model of differentiation two attractors of pluripotency might be defined based on their different characteristics.

Keywords: OCT4; Pluripotency; Self-Renewal; Stemcells; Embryoid Bodies; Landscapemodel.
760. CD4+ CD25+ Cells in Type 1 Diabetic Patients With Other Autoimmune Manifestations

Dalia S. Abd Elaziz, Mona H. Hafez, Nermeen M. Galal, Safa S. Meshaal and Aisha M. El Marsafy


The existence of multiple autoimmune disorders in diabetes may indicate underlying primary defects of immune regulation. The study aims at estimation of defects of CD4+ CD25+ high cells among diabetic children with multiple autoimmune manifestations, and identification of disease characteristics in those children. Twenty-two cases with type 1 diabetes associated with other autoimmune diseases were recruited from the Diabetic Endocrine and Metabolic Pediatric Unit (DEMPU), Cairo University along with twenty-one normal subjects matched for age and sex as a control group. Their anthropometric measurements, diabetic profiles and glycemic control were recorded. Laboratory investigations included complete blood picture, glycosylated hemoglobin, antithyroid antibodies, celiac antibody panel and inflammatory bowel disease markers when indicated. Flow cytometric analysis of T-cell subpopulation was performed using anti-CD3, anti-CD4, anti-CD8, anti-CD25 monoclonal antibodies. Three cases revealed a proportion of CD4+ CD25+high below 0.1% and one case had zero counts. However, this observation did not mount to a significant statistical difference between the case and control groups neither in percentage nor absolute numbers. Significant statistical differences were observed between the case and the control groups regarding their height, weight centiles, as well as hemoglobin percentage, white cell counts and the absolute lymphocytic counts. We concluded that, derangements of CD4+ CD25+ high cells may exist among diabetic children with multiple autoimmune manifestations indicating defects of immune controllers.

**Keywords:** CD4+ CD25+ Cells.

761. Profile of Cystic Fibrosis in A Single Referral Center in Egypt

Mona M. El-Falaki, Walaa A. Shahin, Noussa R. El-Basha, Aliaa A. Ali, Dina A. Mehaney and Mona M. El-Attar

*Journal of Advanced Research, 5: 563-568 (2014) IF: 3*

It was generally believed that Cystic fibrosis (CF) is rare among Arabs; however, the few studies available from Egypt and other Arabic countries suggested the presence of many undiagnosed patients. The aim of the present study was to determine the frequency of CF patients out of the referred cases in a single referral hospital in Egypt. A total of 100 patients clinically suspected of having CF were recruited from the CF clinic of the Allergy and Pulmonology Unit, Children’s Hospital, Cairo University, Egypt, throughout a 2 year period. Sweat chloride testing was done for all patients using the Wescor macrodust system for collection of sweat. Quantitative analysis for chloride was then done by the thiocyanate colorimetric method. Patients positive for sweat chloride (>60 mmol/L) were tested for the ΔF508 mutation using primer specific PCR for cystic fibrosis transmembrane conductance regulator (CFTR) gene. Thirty-six patients (36%) had a positive sweat chloride test. The main clinical presentations in patients were chronic cough in 32 (88.9%), failure to thrive in 27 (75%), steatorrhea in 24 (66.7%), and hepatobiliary involvement in 5 (13.9%). Positive consanguinity was reported in 50% of CF patients. Thirty-two patients were screened for ΔF508 mutation. Positive ΔF508 mutation was detected in 22 (68.8%) patients, 8 (25%) were homozygous, 14 (43.8%) were heterozygous, and 10 (31.3%) tested were negative. CF was diagnosed in more than third of patients suspected of having the disease on clinical grounds. This high frequency of CF among referred patients indicates that a high index of suspicion and an increasing availability of diagnostic tests lead to the identification of a higher number of affected individuals.

**Keywords:** CF; Children; Sweat Chloride; ΔF508 Mutation; Egypt.

762. MEFV Mutations in Egyptian Children With Systemic-Onset Juvenile Idiopathic Arthritis

Hala M. Lotfy, Manal E. Kandil, Marianne Samir Makboul Issac, Samia Salah, Nagwa Abdalbah Ismail and Mohamed A. Abdel Mawla


**Background and Objectives:** Systemic-onset juvenile idiopathic arthritis (SoJIA) is a chronic auto-inflammatory disease of childhood, with a complex genetic trait, which is characterized by arthritis associated with systemic manifestations. Familial Mediterranean fever (FMF) is another auto-inflammatory disorder that is monogenic. There are speculations as to whether Mediterranean fever (MEFV) mutations are among the genetic determinants of SoJIA. Our aim was to explore the frequency and clinical significance of MEFV mutations in Egyptian SoJIA patients. A group of healthy children were assigned to the control group in an attempt to estimate the carrier rate of MEFV mutations in Egypt.

**Methods:** Eighty-four children were recruited in this study; 54 children, age (mean ± standard deviation; 8.31 ± 2.85 years), diagnosed as having SoJIA with no typical symptoms of FMF; 30 healthy age- and gender-matched children served as the control group. All recruited children were screened for 12 common MEFV mutations using a reverse hybridization assay of biotinylated PCR products.

**Results:** SoJIA patients had a significantly higher frequency of MEFV mutations (66.7 %) than in the healthy control population (16.7 %). V726A was the leading mutation in SoJIA patients, with an allelic frequency of 15.74 %, followed by E148Q, with an allelic frequency of 7.4 %. Children who were carriers of MEFV mutations had an 18 times higher risk of developing SoJIA than wild-type carriers [odds ratio 18.0 (95 % CI 5-69), P < 0.01].

**Conclusion:** These findings suggest that MEFV mutations may be responsible for auto-inflammatory diseases other than FMF, and patients with SoJIA, especially those with a positive family history of FMF or SoJIA, should be screened for MEFV mutations in countries where FMF is frequent.

**Keywords:** Systemic-Onset Juvenile Idiopathic Arthritis.

763. Applicability and Efficacy of A Model for Prevention of Perinatal Transmission of Hepatitis B Virus Infection: Singlecenter Study in Egypt

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It is generally believed that Cystic fibrosis (CF) is rare among Arabs; however, the few studies available from Egypt and other Arabic countries suggested the presence of many undiagnosed patients. The aim of the present study was to determine the frequency of CF patients out of the referred cases in a single referral hospital in Egypt. A total of 100 patients clinically suspected of having CF were recruited from the CF clinic of the Allergy and Pulmonology Unit, Children’s Hospital, Cairo University, Egypt, throughout a 2 year period. Sweat chloride testing was done for all patients using the Wescor macrodust system for collection of sweat. Quantitative analysis for chloride was then done by the thiocyanate colorimetric method. Patients positive for sweat chloride (≥60 mmol/L) were tested for the ΔF508 mutation using primer specific PCR for cystic fibrosis transmembrane conductance regulator (CFTR) gene. Thirty-six patients (36%) had a positive sweat chloride test. The main clinical presentations in patients were chronic cough in 32 (88.9%), failure to thrive in 27 (75%), steatorrhea in 24 (66.7%), and hepatobiliary involvement in 5 (13.9%). Positive consanguinity was reported in 50% of CF patients. Thirty-two patients were screened for ΔF508 mutation. Positive ΔF508 mutation was detected in 22 (68.8%) patients, 8 (25%) were homozygous, 14 (43.8%) were heterozygous, and 10 (31.3%) tested were negative. CF was diagnosed in more than third of patients suspected of having the disease on clinical grounds. This high frequency of CF among referred patients indicates that a high index of suspicion and an increasing availability of diagnostic tests lead to the identification of a higher number of affected individuals.

**Keywords:** CF; Children; Sweat Chloride; ΔF508 Mutation; Egypt.
Aim: To identify possible maternal risk factors for hepatitis B virus (HBV) acquisition and assess the efficacy of immunoprophylaxis given to infants born to hepatitis B virus surface antigen (HBsAg) positive mothers.

Methods: Screening of 2000 pregnant females was carried out using rapid test and confirmed by enzyme immunoassay. A questionnaire consisting of 20 questions about the possible risk factors for acquisition of HBV infection was filled for every pregnant HBsAg positive female in addition to at least 2 pregnant HBsAg negative females for each positive case. Infants of HBsAg positive women were offered passive and active immunoprophylaxis within the 1st 48 h after birth, in addition to 2nd and 3rd doses of HBV vaccine after 1 and 6 mo respectively. Infants were tested for HBsAg and hepatitis B surface antibodies (HBsAb) at six months of age.

Results: HBsAg was confirmed positive in 1.2% of tested pregnant women. Risk factors significantly associated with HBV positivity were; history of injections (OR= 5.65), history of seeking medical advice in a clinic (OR= 7.02), history of hospitalization (OR = 6.82); history of surgery (OR = 4) and family history of hepatitis (OR = 3.89) (P < 0.05). Dropout rate was 28% for HBsAg women whose rapid test was not confirmed and could not be reached to provide immunoprophylaxis for their newborns. Immunoprophylaxis failure was detected in only one newborn (3.7%) who tested positive for HBsAg at 6 mo of age; and vaccine failure (seronegative to HBsAb after 4 doses of the vaccine) was detected in another one (3.7%). The success rate of the immunoprophylaxis regimen was 92.6%.

Conclusion: This pilot study shows that a successful national program for prevention of perinatal transmission of HBV needs to be preceded by an awareness campaign to avoid a high dropout rate.

Keywords: Egypt; Hepatitis B Virus; Hepatitis B Virus surface Antigen Positive Mothers; Immunoprophylaxis; Perinatal Transmission.

764. Safety and Efficacy of Hansenula -Derived Pegylated-Interferon Alpha-2A and Ribavirin Combining in Chronic Hepatitis C Egyptian Children


Aim: To investigate the safety and efficacy of a Hansenula-derived PEGylated (polyethylene glycol) interferon (IFN)-alpha-2a (Reiferon Retard) plus ribavirin customized regimen in treatment-naive and previously treated (non-responders and relapsers) Egyptian children with chronic hepatitis C infection.

Methods: Forty-six children with chronic hepatitis C virus (HCV) infection were selected from three tertiary pediatric hematology centers. Clinical and laboratory evaluations were undertaken. Quantitative polymerase chain reaction (PCR) for HCV-RNA was performed before starting treatment, and again at 4, 12, 24, 48, 72 wk during treatment and 6 mo after treatment cessation. All patients were assigned to receive a weekly subcutaneous injection of PEG-IFN-alpha-2a plus daily oral ribavirin for 12 wk. Thirty-four patients were treatment-naive and 12 had a previous treatment trial. Patients were then divided according to PCR results into two groups. Group I included patients who continued treatment on a weekly basis (7-d schedule), while group II included patients who continued treatment on a 5-d schedule. Patients from either group who were PCR-negative at week 48, but had at least one PCR-positive test during therapy, were assigned to have an extended treatment course up to 72 wk. The occurrence of adverse effects was assessed during treatment and follow up. The study was registered at www.ClinicalTrials.gov (NCT02027493).

Results: Only 11 out of 46 (23.9%) patients showed a sustained virological response (SVR), two patients were responders at the end of treatment; however, they were lost to follow up at 6 mo post treatment. Breakthrough was seen in 18 (39.1%) patients, one patient (2.17%) showed relapse and 14 (30.4%) were non-responders. Male gender, short duration of infection, low viral load, mild activity, and mild fibrosis were the factors related to a better response. On the other hand, patients with high viral load and absence of fibrosis failed to respond to treatment. Before treatment, liver transaminases were elevated. After commencing treatment, they were normalized in all patients at week 4 and were maintained normal in responders till the end of treatment, while they increased again significantly in non-responders (P = 0.007 and 0.003 at week 24 and 72 respectively). The 5-d schedule did not affect the response rate (1/17 had SVR). Treatment duration (whether 48 wk or extended course to 72 wk) gave similar response rates (9/36 vs 2/8 respectively; P = 0.49). Type of previous treatment (short acting IFN vs PEG-IFN) did not affect the response to retreatment. On the other hand, SVR was significantly higher in previous relapsers than in previous non-responders (P = 0.039). Only mild reversible adverse effects were observed and children tolerated the treatment well.

Conclusion: Reiferon Retard plus ribavirin combined therapy was safe. Our customized regimen did not influence SVR rates. Further trials on larger numbers of patients are warranted.

Keywords: Children; Chronic Hepatitis C; Hansenula: Polymorpha; Pegylated Interferon; Response Rate; Ribavirin; Treatment.

765. Continuation of Deferiprone Therapy in Patients With Mild Neutropenia May Not Lead to A More Severe Drop in Neutrophil Count

El-Beshlawy AM, El-Alfy MS, Sari TT, Chan LL and Tricta F.


Approximately 6% of patients with thalassemia receiving deferiprone develop neutropenia. Present practice is to monitor absolute neutrophil count (ANC) weekly and to interrupt treatment at the first sign of neutropenia, lest continuation lead to progressive neutrophil reduction. In a 6-month study evaluating the safety and efficacy of a liquid form of deferiprone in 100 children, ANC was initially checked weekly for all patients. For individuals experiencing mild neutropenia, deferiprone was continued but monitoring was increased to daily until resolution. Therapy was to be suspended only if the episode was prolonged or if it worsened. Four patients experienced single episodes of mild neutropenia, and two others each experienced two episodes. All eight episodes resolved within 4–7 d despite continued therapy. (One patient later developed agranulocytosis and had treatment terminated.) This study showed that not all cases of mild neutropenia during deferiprone therapy develop into...
Agranulocytosis, and suggests that many may not be caused by deferiprone. Transient declines in ANC to levels defined as neutropenic are common even in healthy individuals, particularly children; and it could be that the frequent monitoring of ANC mandated during deferiprone therapy may reveal cases of transient neutropenia that would otherwise have gone undetected and resolved on their own without clinical consequences. In patients with thalassemia, several factors increase the probability of a transient fall in ANC. These findings raise the question of whether deferiprone should be routinely stopped in cases of mild neutropenia, provided that such patients have their ANC monitored more frequently during the neutropenic episode.

**Keywords:** Agranulocytosis; Deferiprone; Neutropenia; Thalassemia.

### 766. Low Prevalence of Cardiac Siderosis in Heavily Iron Loaded Egyptian Thalassemia Major Patients


Myocardial siderosis in thalassemia major remains the leading cause of death in developing countries. Once heart failure develops, the outlook is usually poor with precipitous deterioration and death. Cardiovascular magnetic resonance (CMR) can measure cardiac iron deposition directly using the magnetic relaxation time T2*. This allows earlier diagnosis and treatment and helps to reduce mortality from this cardiac affection. This study aims to determine the prevalence of cardiac siderosis in Egyptian patients who are heavily iron loaded and its relation to liver iron concentration, serum ferritin, and left ventricular ejection fraction. Eighty-nine β-thalassemia patients receiving chelation therapy (mean age of 20.8 ± 6.4 years) were recruited in this study. Tissue iron levels were determined by CMR with cardiac T2* and liver R2*. The mean ± standard deviation (range) of cardiac T2* was 28.5 ± 11.7 ms (4.3 to 53.8 ms), the left ventricular ejection fraction (LVEF) was 67.7 ± 4.7 % (55 to 78 %), and the liver iron concentration (LIC) was 26.1 ± 13.4 mg Fe/g dry weight (dw) (1.5 to 56 mg Fe/g dw). The mean serum ferritin was 4,510 ± 2,847 ng/ml (533 to 22,360 ng/ml), and in 83.2 %, the serum ferritin was >2,500 ng/ml. The prevalence of myocardial siderosis (T2* of <20 ms) was 24.7 % (mean age 20.9 ± 7.5 years), with mean T2* of 12.7 ± 4.4 ms, mean LVEF of 68.6 ± 5.8 %, mean LIC of 30.9 ± 13 mg Fe/g dw, and median serum ferritin of 4,996 ng/ml. There was no correlation between T2* and age, LVEF, LIC, and serum ferritin (P = 0.65, P = 0.085, P = 0.99, and P = 0.63, respectively). Severe cardiac siderosis (T2* of <10 ms) was present in 7.9 %, with a mean age of 18.4 ± 4.4 years. Although these patients had a mean T2* of 7.8 ± 1.7 ms, the LVEF was 65.1 ± 6.2 %, and only one patient had heart failure (T2* of 4.3 ms and LVEF of 55 %). LIC and serum ferritin results were 29.8 ± 17.0 mg/g and 7,200 ± 6,950 ng/ml, respectively. In this group of severe cardiac siderosis, T2* was also not correlated to age (P = 0.5), LVEF (P = 0.14), LIC (P = 0.97), or serum ferritin (P = 0.82). There was a low prevalence of myocardial siderosis in the Egyptian thalassemia patients in spite of very high serum ferritin and high LIC. T2* is the best test that can identify at-risk patients who can be managed with optimization of their chelation therapy. The possibility of a genetic component for the resistance to cardiac iron loading in our population should be considered.

**Keywords:** Thalassemia; Cardiac Siderosis; Cardiac Magnetic Resonance; Egypt; Liver Iron Concentration.

### 767. Response to Hydroxy carbamide in Pediatric β-Thalassemia Intermedia: 8 Years’ Follow-Up in Egypt

El-Beshlawy A, El-Ghamrawy M, EL-Ela MA, Said F, Adolf S, Abdel-Razeq AR, Magdy RI and Abdel-Salam A.

*Annals of Hematology, 93: 2045-2050 (2014) IF: 2.396*

Hydroxy carbamide (hydroxyurea or HU) has been shown to increase fetal hemoglobin (HbF) in patients with β-thalassemia intermedia (TI). The reported effects of HU in increasing the total hemoglobin (Hb) have been inconsistent. Studies of long-term therapy with HU in pediatric TI are rather uncommon. A retrospective observational study was carried out to evaluate the clinical responses to HU in Egyptian patients with β-TI. One hundred patients; children (n = 82, mean age 9.9 ± 4.1 years) and adults (n = 18) were studied for the mean Hb, HbF %, median serum ferritin, transfusion history, and splenic size before and after HU therapy (mean dose 20.0 ± 4.2 mg/kg/day, range 10-29 mg/kg/day) over a follow-up period 4 to 96 months (mean 35.4 ± 19.2 months). Molecular studies were also done for group of patients (n = 42). The overall response rate to HU was 79 %; 46 % were minor responders (with a reduction in transfusion rate by 50 % or more and/or an increase in their total hemoglobin level by 1-2 g/dl) and 33 % major responders (becoming transfusion-free and/or having an increase in total hemoglobin level by >2 g/dl). Mean hemoglobin increased among responders from 6.9 ± 0.9 g/dl to 8.3 ± 1.4 g/dl (p < 0.001). A significant rise in mean HbF (27.0 vs. 42.5 %; p < 0.011) and a decrease in median serum ferritin (800 vs. 644 ng/ml; p < 0.001) were also observed among responders (n = 45). Transfusions stopped in 44 % of pretreatment frequently transfused responders (n = 11/25). Splenic size decreased in 37 % of patients (n = 30/81). The predominant β-thalassemia mutation was 1-6 (T > C) in 32/42 (76 %) of studied patients; 28/32 were responders. Bivariate analysis showed no predictors of response as regards sex, pediatric or adult age, splenic status, or genotype. Hydroxy carbamide is a good therapeutic modality in the management of pediatric as in adult TI patients. It can minimize the need for blood transfusion, concomitant iron overload, and blood-borne viral transmission especially in developing countries like Egypt.

**Keywords:** Hydroxy carbamide; Hydroxyurea; Thalassemia Intermedia (TI); Children; Egypt.

### 768. The 6-Min Walk Test: an Independent Correlate of Elevated Tric ispud Regurgitant Jet Velocity in Children and Young Adult Sickle Cell Patients

Hala Agha, Mona El Tagui, Mona El Ghamrawy and Marwa Abdel Hady

*Ann Hematol, 93: 1131-1138 (2014) IF: 2.396*

Elevation of echocardiography-determined tricuspid regurgitant jet velocity (TRV) predicts high systolic pulmonary artery pressure. The present study tested the hypotheses that elevated tricuspid regurgitant jet velocity is associated with both hemolysis and hypoxia and abnormal 6-min walk test (6MWT) results. This study aims to correlate elevated TRV with different clinical laboratory findings and 6MWT and to find the independent
predictors of increased TRV. A prospective study of 80 patients aged 5–25 years old with sickle cell disease (SCD) under basal conditions and 40 matched controls was conducted. Hemolytic analysis was assessed by the levels of lactate dehydrogenase, serum bilirubin, and reticulocyte count. Oxygen saturation determination using pulse oximeter and 6MWT were done. The overall prevalence of elevated TRV (≥2.5 m/s) was 28.75 %. Associated risk factors were older age (r=0.28, p=0.01), longer duration of disease (r=0.25, p=0.025), higher reticulocytic count (r=0.344, p=0.002), lower O2 saturation (r=-0.574, p=0.0001), and shorter walked distance in 6MWT (r=-0.75, p=0.0001). By multivariate logistic analysis, only the distance walked during 6MWT was the independent correlate of elevated TRV (odds ratio=0.85; 95 % CI=0.74 to 0.98 p=0.033).

The study provides evidence for independent association of TRV with abnormal 6MWT results. The 6-min walk test can be used as noninvasive adjuvant tool for functional capacity assessment of SCD patients with elevated TRV.

**Keywords**: Sickle cell disease; Pulmonary hypertension; Hemolysis; Oxygen saturation; Tricuspid regurgitant jet velocity; 6-Min walk test.

**769. Selective Screening for Inborn Errors of Metabolism by Tandem Mass 2 Spectrometry in Egyptian Children: A 5 Year Report**


**Clinical Biochemistry, 47(9): 823-828 (2014) IF: 2.229**

**Objective**: In order to enhance awareness and promote registry for inborn errors of metabolism (IEMs) in Egypt, we aimed to evaluate the prevalence and main clinical findings of IEMs detectable by tandem mass spectrometry (MS/MS) among high risk pediatric patients presenting to our tertiary care facility at Cairo University Children's Hospital over a period of 5 years and to compare the disease burden in Egypt in the absence of a national screening program for inherited metabolic disorders with other populations.

**Methods**: During this period 3380 Egyptian children were suspected of having IEMs based on clinical/laboratory presentation and were analyzed by MS/MS. Confirmatory testing was performed according to flagged analyte by MS/MS using a different sample type such as plasma or urine or by a different technique such as GC/MS.

**Results**: A relatively high number of patients (203/3380 (6%)) were confirmed with 17 different types of IEMs. Averages for age at diagnosis for different disorders ranged from 2.5 months to 6.6 years with general developmental delay and irreversible neurological damage being the most common presenting features (75.9% and 65.5%, respectively). Amino acid disorders (127/203 (62.6%)), mainly phenylketonuria (100/203 (49.3%)), were the most encountered, followed by organic acidemias (69/203 (34%)), while fatty acid oxidation defects (7/203 (3.4%)) were relatively rare. 88% of patients were born to consanguineous parents.

**Conclusions**: The development of a nationwide screening program for IEMs is mandatory for early detection of these potentially treatable disorders, prompt and properly timed therapeutic intervention and prevention of the devastating neurological outcomes.

**Keywords**: Children; Inborn errors; Metabolic disorders; Selective screening; Tandem mass spectrometry.

**770. Nesfatin-1 in Childhood and Adolescent Obesity and Its Association With Food Intake, Body Composition and Insulin Resistance.**

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**Regulatory Peptides, 188: 21-24 (2014) IF: 2.014**

Nesfatin-1 is an anorexigenic peptide that controls feeding behavior and glucose homeostasis. However, there is little data that exists regarding nesfatin-1 secretion in obese children and young adolescents. The aim of this study is to investigate serum nesfatin-1 in childhood and adolescent obesity and to study potential correlations with food intake, anthropometric indices, body composition and insulin resistance. Forty obese children and adolescents and 40 healthy control subjects were studied. Anthropometric measurements were assessed, dietary food intake was evaluated based on 3-days food record and body composition indices were evaluated using bioelectrical impedance analysis. Lipid profile, fasting blood sugar, fasting insulin and HOMA-IR were measured. Fasting serum nesfatin-1 was quantitatively assayed by ELISA. Serum nesfatin-1 was significantly higher in obese group (2.49±1.96 ng/ml) than in control group (0.70±0.81 ng/ml), P<0.001. Positive correlations with serum insulin (P<0.001), HOMA-IR (P<0.000), BMI-SDS (P<0.04), body fat % (P<0.000), fat mass (P<0.000), fat free mass (P<0.03), CHO % (P<0.000), and saturated fat % (P<0.01) were found. While significant negative correlation with protein % (P<0.000) was observed. In conclusion, our results denote that nesfatin-1 might have an important role in regulation of food intake and pathogenesis of insulin resistance in obese children and young adolescents.

**Keywords**: Body composition; Food intake; Insulin resistance; Nesfatin; Obesity.

**771. Diagnosis of Gastrointestinal Basidiobolomycosis: A Mini-Review**

Mortada Hassan Fakhri El-Shabrawi

**Mycoses, 57: 138-143 (2014) IF: 1.805**

Basidiobolus ranarum (Entomophthoromycotina) very rarely affects the gastrointestinal (GI) tract. To date, reported paediatric GI basidiobolomycosis cases are 27 worldwide; 19 from Saudi Arabia and 8 from other parts of the world. Often these cases present a diagnostic dilemma, are prone to misdiagnosis and lack of disease confirmation by proper molecular methodologies. The fungal mass removed by surgery is usually sent for conciliar histopathology, isolation by fungal cultures and final molecular testing for basidiobolomycosis. The incidence of basidiobolomycoses, their predisposing factors and the molecular diagnosis of the fungus causing the disease in combination with a phylogenetic framework are reviewed.

**Keywords**: 18S Rrna; Gastrointestinal basidiobolomycosis; Identification; Molecular typing; Splendore–hoeplii Phenomenon.

**772. Entomophthoromycosis: A Challenging Emerging Disease**

Mortada H. F. El-Shabrawi, Heba Arnaout, Lamiaa Madkour and Naglaa Mohamed Kamal

**Mycoses, 57: 132-137 (2014) IF: 1.805**

Entomophthora ramosa is a basidiobolomycetous fungus which can cause a systemic condition, entomophthoromycosis, in children and newborns. The disease is often fatal, and without prompt diagnosis and adequate therapy outcome is poor.
Entomophthoromycosis is a rare fungal infection that may affect immunocompetent hosts; predominantly in tropical and subtropical regions. Recently, the importance of this emerging mycosis has increased and the scope of its manifestations has been expanded. These manifestations; however, may masquerade as other clinical entities. Prompt diagnosis of this infection requires a high index of suspicion. Although histopathological examination and cultures are the gold standard diagnostic tools; molecular diagnosis is now available and started to play an important role. The cornerstone treatment is prolonged anti-fungal therapy along with surgical debridement. More awareness of this mycosis is warranted for definitive diagnosis and implementation of early proper therapeutic strategies.

**Keywords:** Entomophthoromycosis, Basidiobolomycosis, Condidiobolomycosis, Zygomycosis, Emerging Disease, Fungal Infection.

### 773. Urinary 6-Sulphatoxymelatonin Levels and Sleep Disorders in Children With Migraine

Maha K. Abou-Khada, Nirmeen A. Kishk, Olfat G. Shaker and Amr Hassan


We conducted the present study to assess melatonin secretion in a sample of children with migraine, to describe their sleep patterns and problems, and to examine the impact of sleep problems on migraine disability. The parents of 18 children with migraine completed the Children's Sleep Habits Questionnaire and Pediatric Migraine Disability Assessment Score in Arabic. The parents of 18 healthy controls also completed the Children's Sleep Habits Questionnaire. Urinary 6-sulphatoxymelatonin levels were determined with the enzyme-linked immunosorbent assay method. There was no significant difference in urinary 6-sulphatoxymelatonin between the migraine and control groups (Z = -0.127, P = .889). There were no significant differences between groups in Children's Sleep Habits Questionnaire subscales or total scores. There were significant correlations between bedtime resistance, parasomnias subscales, and migraine disability. Our findings indicate that nocturnal production of melatonin is not reduced in children with migraine, and sleep disturbances impact the degree of migraine disability.

**Keywords:** 6-Sulphatoxymelatonin; Migraine; Sleep.

### 774. MEFV Gene Mutations in Egyptian Children With Henoch-Schonlein Purpura

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*Pediatric Rheumatology, 18 (5): 549-557 (2014) IF: 1.622*

**Background:** Due to an increased frequency of vasculitis in FMF patients, many investigators have studied MEFV mutations in patients with HSP. The aim of the study is to investigate the frequency and clinical significance of MEFV mutations in Egyptian children with Henoch-Schonlein purpura (HSP). Investigating MEFV mutations in controls may help in estimating the prevalence of MEFV mutation carrier rate in Egyptian children.

**Methods:** The study enrolled 90 individuals, sixty children with Henoch-Scheinlein purpura (HSP), together with 30 sex-and age-matched apparently healthy controls. The entire study group was screened for 12 common MEFV mutations using a reverse hybridization assay of biotinylated PCR products.

**Results:** Patients with HSP had a significantly higher frequency of MEFV mutations (61.7%), when compared to the apparently healthy control population (36.7%). V726A was the most frequent mutation with an allelic frequency of 10.8%. Ninety-one percent of patients with MEFV mutations were heterozygous for one mutation, while 8.1% had a compound heterozygous MEFV gene mutations. The mutation V726A, followed by E148Q, were the leading mutations, present in 16.6% and in 13.3% of controls.

**Conclusions:** MEFV mutations may be related to HSP susceptibility in children. The mutations were not associated with any clinical and laboratory manifestations. Screening for MEFV mutations in larger number of HSP children may be beneficial to evaluate any possible relationship between certain types of MEFV mutations and HSP, and compare the HSP MEFV mutations to the types of MEFV mutations associated with FMF.

**Keywords:** Familial Mediterranean Fever; Henoch-Schonlein Purpura (Hsp); Mefv; Mutations.

### 775. Altered Right Ventricular Function in the Long-Term Follow-Up Evaluation of Patients After Delayed Aortic Reimplantation of the Anomalous Left Coronary Artery from the Pulmonary Artery

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*Pediatric Cardiology, 35: 530-535 (2014) IF: 1.55*

This study aimed to evaluate regional and global ventricular functions in the long term after aortic reimplantation of the anomalous left coronary artery from the pulmonary artery (ALCAPA) and to assess whether the time of surgical repair influences ventricular performance.

The study examined 20 patients with a median age of 15 years (range 3–37 years) who had a corrected ALCAPA and 20 age-matched control subjects using echocardiography and tissue Doppler imaging (TDI). The median follow-up period after corrective surgery was 6 years (range 2.6–15 years). Seven patients underwent surgery before the age of 3 years (early-surgery group), whereas 13 patients had surgery after that age (late-surgery group).

The TDI-derived myocardial strain of the interventricular septum (IVS), lateral wall of the left ventricle (LV), and lateral wall of the right ventricle (RV) in the basal and mid regions were examined, and a mean was calculated. The pulsed Doppler-derived Tei index was used to assess global left ventricular function.

No significant differences were found between the early-surgery group and the control group regarding the regional myocardial strain or the Tei index. Compared with the early-surgery group, the late-surgery group had a significantly higher Tei index (mean 0.37; range 0.31–0.42 vs. mean 0.52; range 0.39–0.69; p = 0.005), a lower strain percentage of the lateral wall of the LV (mean 29; range 17–30 vs. mean 9; range 7–23), IVS (mean 23; range 21–31 vs. mean 19; range 13–25). The age at operation correlated significantly with the Tei index (r = 0.84, p < 0.001) and inversely with the mean strain of the lateral wall of the LV (r = -0.53, p = 0.028), IVS (r = -0.68, p = 0.003), and lateralwall of the RV (r = -0.68, p = 0.003).
At the midterm follow-up evaluation after corrective surgery of ALCAPA, not only the left but also the right ventricular function seemed to be affected in patients with delayed diagnosis and late surgical repair but preserved among the younger patients with early diagnosis and corrective surgery.

Keywords: Aortic Reimplantation; Ventricular Function; anomalous left coronary artery from the pulmonary artery; ALCAPA; Tissue Doppler Imaging (TDI).

776. Pulmonary Functions Before and After Pediatric Cardiac Surgery

Agha H, El Heimady F, El Falaky M and Sobih A.

Pediatric Cardiology, 35: 542-549 (2014) IF: 1.55

This study aimed to assess pulmonary functions before and after cardiac surgery in infants with congenital heart diseases and pulmonary over flow and to clarify which echocardiographic parameter correlates best with lung mechanics. Between 2008 and 2009, 30 infants with left-to-right shunt congenital acyanotic heart diseases who had indications for reparative surgery of these lesions were assessed by echocardiography and infant pulmonary function tests before the operation and 6 months afterward. Tests using baby body plethysmography were performed to assess the following infant pulmonary functions: tidal volume, respiratory rate, respiratory system compliance (Cr s) and respiratory system resistance, functional residual capacity (FRC), and airway resistance. The mean age of the patients was 10.47 ± 3.38 months, and their mean weight was 6.81 ± 1.67 kg. Ventricular septal defect and combined lesions were the predominant cardiac diseases (26.7%). Comparison of the infant pulmonary function tests showed a highly significant improvement in all the parameters between the preoperative and 6-month postoperative visits (p<0.0001). Systolic pulmonary artery pressure had a statistically significant negative correlation with Cr s (r = -0.493, p = 0.006) and a positive correlation with FRC (r = 0.450, p = 0.013). The findings showed that Cr s had a statistically significant negative correlation with the pulmonary artery size (r = -0.398, p = 0.029) and the left atrium size (r = -0.395, p = 0.031), whereas the pulmonary artery size had a statistically positive correlation with effective resistance (r = 0.416, p = 0.022) and specific effective resistance (r = 0.604, p = 0.0001). Surgical correction of left-to-right shunt congenital heart diseases had a positive impact on lung compliance, airway resistance, and FRC. Noninvasive echocardiographic parameters assessing pulmonary vascular engorgement and pulmonary artery pressure were closely related to these infant pulmonary function test indexes.

Keywords: Congenital Heart Diseases; Left-To-Right Shunt; Pulmonary Function Tests; Systolic Pulmonary Artery Pressure.

777. Clinical, Neuroimaging, and Genetic Characteristics of Megalencephalic Leukoencephalopathy With Subcortical Cysts in Egyptian Patients

Mahmoud IG, Mahmoud M, Refaat M, Girgis M, Waked N, El Badawy A, Selim L, Hassan S and Abdel Aleem AK


Background: Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a rare and genetically heterogeneous cerebral white matter disease. Clinically, it is characterized by macrocephaly, developmental delay, and seizures. We explore the clinical spectrum, neuroimaging characteristics, and gene involvement in the first patients with megalencephalic leukoencephalopathy with subcortical cysts described from Egypt.

Patients: Six patients were enrolled from three unrelated families. Patient inclusion criteria were macrocephaly, developmental delay, normal urinary organic acids, and brain imaging of diffuse cerebral white matter involvement. Direct sequencing of the MLC1 gene in patients’ families and GliaCAM in one questionable case was performed using BigDye Terminator cycle sequencing.

Results: Clinical heterogeneity, both intra- and interfamilial, was clearly evident. Developmental delays ranged from globally severe or moderate to mild delay in achieving walking or speech. Head circumference above the ninety-seventh percentile was a constant feature. Neuroimaging featured variability in white matter involvement and subcortical cysts. However, findings of posterior fossa changes and brain stem atrophy were frequently (66.6%) identified in these Egyptian patients. Discrepancy between severe brain involvement and normal mental functions was evident, particularly in patients from the third family. MLC1 mutations were confirmed in all patients. Deletion/insertion mutation in exon 11 (c.908-918delinsGCA, p.Val303 Gly fsX96) was recurrent in two families, whereas a missense mutation in exon 10 (c.880 C > T, p.Pro294Ser) was identified in the third family.

Conclusions: This report extends our knowledge of the clinical and neuroimaging features of megalencephalic leukoencephalopathy with subcortical cysts. It confirms the apparent lack of selective disadvantage of MLC1 mutations on gamete conception and transmission as supported by the presence of multiple affected siblings in Egyptian families.

Keywords: GliaCAM gene; MLC1 gene; Van der Knaap disease; developmental delay; macrocephaly; megalencephalic leukodystrophy; subcortical cysts.

778. Neutrophil CD64 as a Diagnostic Marker of Sepsis in Neonates

Sanaa Elawady, Shahira K. Botros, Ashraf E. Sorour, Eman Abdel Ghany, Gamal Elbatran and Raghdaa Ali


Background: Sepsis in neonates hospitalized in the neonatal intensive care unit is a global problem and is a significant contributor to morbidity and mortality. Neutrophil surface CD64, the high-affinity Fc receptor, is quantitatively up-regulated during infection and sepsis.

Objective: Our goal in this prospective study was to measure the neutrophil CD64 in blood as an adjunct to our previously validated hematologic scoring system for detecting neonatal sepsis.

Methods: A prospective study enrolled newborns with documented sepsis (n = 25), clinical sepsis (n = 25), and control newborns (n = 25). C-reactive protein, neutrophil CD64, complete blood counts, and blood cultures were taken. Neutrophil CD64 was analyzed by flow cytometry.

Results: CD64 was significantly elevated in the groups with documented and clinical sepsis (P G 0.001). CD64 had a sensitivity of 96%, a specificity of 100%, a positive predictive value of 96.2%, and a negative predictive value of 100% with a cutoff value of 45.8% and 46.0% in the confirmed and the clinical sepsis groups, respectively.
Conclusions: CD64 expression on neutrophils increases significantly in neonates with sepsis and can be considered a useful diagnostic marker for early diagnosis of neonatal infection as a single determination compared with other inflammatory markers.

Keywords: Neutrophil; CD64; Neonatal sepsis.

779. Soluble Adhesion Molecules as Markers of Native Arteriovenous Fistula Thrombosis in Children on Uremia
Fadel FI, Elshamaa MF, Nabhan MM, Essam RG, Kantoush N, El Sonbaty MM, Raafat M and Abd-El Haleem DA

Vascular access represents a lifeline for children undergoing hemodialysis. A failure of vascular access among patients receiving regular hemodialysis is associated with increased morbidity, mortality and costs. We assessed the possibility of using soluble adhesion molecules as reliable predictors of vascular access failure in children on hemodialysis. Moreover, we evaluated whether there is an association among the different studied adhesion molecules in hemodialysis patients with thrombosed and non-thrombosed arteriovenous fistula fistulas (AVFs). This study included 55 hemodialysis children, 36 with good access and 19 with access failure, and 20 healthy volunteers. Forty-four patients had native AVFs and 11 patients had tunneled permanent catheter (11 with thrombosed and 33 with non-thrombosed AVFs). Serum-soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), soluble E-selectin (sE-selectin) and soluble P-selectin (sP-selectin) were measured using ELISA technique. A significant increase was found in the levels of sVCAM-1, sICAM-1, sE-selectin and sP-selectin versus controls and all hemodialysis patients, hemodialysis patients with good access and hemodialysis patients with access failure (P=0.001 for sVCAM-1 and sICAM-1 and P=0.0001 for sE-selectin and sP-selectin). A significant increase was found in the levels of sVCAM-1, sE-selectin and sP-selectin in both chronic hemodialysis patients with thrombosed and non-thrombosed native AVFs versus controls (P=0.0001 for all parameters). There was significant difference between both chronic hemodialysis patients with thrombosed and non-thrombosed native AVFs as regard to sVCAM-1 (54.6±30.82 versus 25.69±27.96ng/ml, P=0.04). Both sICAM-1 and sP-selectin were positively correlated with the erythropoietin (EPO) dose in hemodialysis children (r=0.31, P=0.04 and r=0.32, P=0.04, respectively). A significant positive association was found between E-selectin and sP-selectin in hemodialysis patients with thrombosed AVFs (r=0.83, P=0.04). There was a significant correlation between sVCAM-1 and EPO dose in thrombosed AVF group (r=0.84, P=0.01). The assessment of serum sVCAM-1 might be useful for the identification of the chronic hemodialysis patients at an increased risk for native AVFs thrombosis. The role of EPO in vascular access failure should be taken into consideration. The clinical relevance of these observations warrants further investigations.

Keywords: Adhesion Molecules; Hemodialysis; Native Arteriovenous Fistula.

780. Glutathione S Transferase Theta1 and Mu1 Gene Polymorphisms and Phenotypic Expression of Asthma in Egyptian Children: A Case–Control Study
Nihal El Rifai, Nadia Moustafa, Nelly Degheidy and Manal Wilson

Background: Asthma is the result of a complex interaction between environmental factors and genetic variants that confer susceptibility. The glutathione S-transferases (GSTT1 and GSTM1) are phase II enzymes thought to protect the airways from oxidative stress. Few and contradictory data are available on the association between asthma development and GSTT1 and GSTM1 polymorphisms in different ethnic groups. The current study aimed to investigate whether these polymorphisms are associated with asthma development in the Egyptian population.

Methods: The cross-sectional study was performed on 94 asthmatic children 6 -12 yrs and 90 matched healthy controls. Candidates were subjected to clinical evaluation and measurement of absolute blood eosinophilic count, total serum IgE, and GSTT1 and GSTM1 genotype by multiplex PCR technique.

Results: The results for GSTT1 null genotype were 87.2% and 97.2% for asthmatic children and controls respectively and showed to be significantly more in controls (P =0.007, OR:0.683, CI: 0.034 -0.715). The results for GSTM1 null genotype were 50% and 61.1% for asthmatic children and controls respectively and showed to be nonsignificant (p =0.130, OR: 1.000, CI: 0.54-1.86). Also, no association was detected between GSTT1 and GSTM1 polymorphisms and atopic conditions or asthma severity.

Conclusion: The significant detection of GSTT1 null genotype more in controls than in asthmatics with no association with other atopic manifestations or asthma severity and the lack of association detected between GSTM1 polymorphism in relation to asthma, atopy or asthma severity confirm the uncertain role of those genes in the development of asthma.

Keywords: Asthma; Children; Egyptian; Glutathione S-Transferase; Polymorphism.

781. Outcome of Acute Kidney Injury in Pediatric Patients Admitted To theIntensive Care Unit

Background: Acute kidney injury (AKI) is common in the pediatric intensive care unit (PICU). We aimed to describe the etiology, clinical features, and outcome of AKI in pediatric patients and to determine the predictors for initiation of renal replacement and mortality.

Methods: A retrospective chart review was performed of the medical records for all patients who were admitted to the PICU at King Abdulaziz University Hospital between January 1 and December 31, 2011. The pediatric-modified RIFLE criteria were used to classify AKI.

Results: We included 102 children with AKI, aged 4 – 60 months. Oliguria (61.5%, p < 0.0001) and hypervolemic signs (38.5%, p = 0.03) were more common among patients with RIFLE class failure. They also had the highest mortality (53.9%, p = 0.01). Oliguric patients were ~ 23 times more likely than their...
non-oliguric counterparts, to be initiated on renal replacement therapy (RRT) \((RR = 23.38, 95\% CI: 3.07 – 178.16)\). Diuretic infusion was also a strong predictor for RRT initiation \((RR = 10.00, 95\% CI: 2.77 – 36.12)\). Hypervolemic patients were twice more likely to die during hospitalization in both unadjusted and adjusted models \((RR = 2.06, 95\% CI: 1.09 – 3.90, and aRR = 2.45, 95\% CI: 1.09 – 5.51, respectively)\). Mechanical ventilation and RRT initiation were associated with higher likelihood of death \((aRR = 13.23, 95\% CI: 1.90 – 92.04, and aRR = 2.20, 95\% CI: 1.18 – 4.12, respectively)\).

Patients with RIFLE class Failure were about thrice more likely than patients with RIFLE class Risk to die in both the unadjusted \((RR = 2.76, 95\% CI: 1.35 – 5.65)\), and adjusted models \((aRR = 2.88, 95\% CI: 1.38 – 6.04)\). Children with AKI had longer PICU stay \((0.0003)\) and higher mortality \((< 0.0001)\) than the non-AKI group.

**Conclusion:** Severe AKI predicted high mortality in critically ill children.

**Keywords:** Acute Kidney Injury – Intensive Care Unit – Pediatric Rife.

### 782. Vitamin D Deficiency in Egyptian Mothers and Their Neonates and Possible Related Factors

El Rifai NM, Abdel Moety GA, Gafar HM and Hamed DA


**Objective:** To correlate vitamin D level in Egyptian mothers with that of their newborns, and examine risk factors related to maternal vitamin D deficiency.

**Methods:** A cross-sectional study was carried out at the university teaching hospital in Cairo, Egypt. Serum 25(OH)D levels were measured by enzyme-linked immunosorbent assay in 135 pregnant women at 37 weeks’ gestation immediately before delivery and in cord blood of their newborns.

**Results:** The levels of serum 25(OH)D were 32.6 ± 21.4 ng/ml in mothers and 16.7 ± 10 ng/ml in their newborns. Maternal vitamin D level was strongly correlated with that of the newborns \((r = 0.7, p < 0.0001)\). Maternal vitamin D deficiency/insufficiency and neonatal vitamin D deficiency/insufficiency were encountered in 40%, 28.9% and 60%, 32.6% respectively. Maternal vitamin D levels showed significant correlations with maternal body mass index \((r = 0.201, p < 0.021)\), gestational age at delivery \((r = 0.315, p < 0.0001)\), fish consumption \((r = 0.185, p = 0.032)\), educational level \((r = 0.29, p = 0.001)\), and skin exposure \((r = 0.247, p = 0.004)\).

**Conclusion:** Maternal vitamin D levels strongly correlate with neonatal levels. Maternal vitamin D deficiency is a real problem in Egypt; this is generally related to high BMI, low fish consumption, low educational level, and limited skin exposure.

**Keywords:** Mothers; Neonates; Vitamin D.

### 783. Role of Online Hemodiafiltration in Improvement of Inflammatory Status in Pediatric Patients With End-Stage Renal Disease

Morad AA, Bazarra HM, Abdel Aziz RE, Abdel Halim DA, Shoman MG and Saleh ME.

*Iranian Journal of Kidney Diseases, 8: 481-485 (2014) IF: 0.979*

**Introduction:** Patients with end-stage renal disease are known to suffer from chronic inflammation as the result of an ongoing subacute cytokine induction, which may contribute considerably to dialysis-related long-term morbidity and mortality. In order to assess the inflammatory risk associated with online hemodiafiltration compared to conventional hemodialysis, we compared the cytokine induction profile of pediatric patients during treatment with each these modalities of dialysis.

**Materials and Methods:** Thirty pediatric patients on regular hemodialysis for at least 6 months were shifted to online hemodiafiltration. We collected serum samples before and 6 months after initiation of online hemodiafiltration. The target pro-inflammatory cytokines selected were interleukin-6, tumor necrosis factor-α, and high-sensitivity C-reactive protein.

**Results:** High-sensitivity C-reactive protein decreased significantly on hemodiafiltration. The mean C-reactive protein level after 6 months was 3.41 μg/mL in the online hemodiafiltration as compared to 7.98 μg/mL in the hemodialysis group \((P = .01)\). Plasma interleukin-6 and tumor necrosis factor-α also decreased significantly on hemodiafiltration and the values were 100.44 pg/mL versus 168.40 pg/mL \((P = .002)\) and 11.45 pg/mL versus 15.70 pg/mL \((P = .008)\), respectively, for the hemodiafiltration and hemodialysis groups.

**Conclusions:** Online hemodiafiltration is associated with dampened pro-inflammatory cytokine profile compared to conventional hemodialysis in children with end-stage renal disease.

**Keywords:** End-Stage Renal.

### 784. Acute Hemolytic Anemia as An Initial Presentation of Wilson Disease in Children

El Raziky MS, Ali A, El Shahawy A and Hamdy MM.

*J Pediatr Hematol Oncol, 36.3: 173-178 (2014) IF: 0.956*

**Background:** Wilson disease (WD) is an inherited disorder of copper metabolism. Hemolytic anemia in WD occurs in up to 17% of patients at some point during their illness.

**Aim:** To screen for WD among children presenting with hemolytic anemia.

**Methodology:** Twenty cases (mean age, 8.8 ± 3.9 y) with Coombs-negative hemolytic anemia, attending the hematology clinic of children hospital, Cairo University, were screened for WD by serum ceruloplasmin level, 24 hours urinary copper before and after D-penicillamine challenge test, and slit-lamp examination for detecting Kayser-Fleischer rings.

**Results:** No case had low ceruloplasmin, whereas bilateral Kayser-Fleischer rings was detected in 5% of our cases. Urinary copper was elevated in 5% before and in 40% after D-penicillamine challenge test. According to the scoring system used, 1 case had definite WD and 7 cases were likely to have WD. These 8 (40%) cases were referred to as group B. Group B had a significantly lower hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, and reticulocyte counts \((P=0.04, 0.001, 0.04, 0.04, \text{ respectively})\) and a significantly higher urinary copper after penicillamine \((P=0.000)\) when compared with group A (unlikely WD).

**Conclusion:** WD is not uncommon in children with hemolytic anemia after exclusion of other common causes.

**Keywords:** Wilson Disease; Hemolytic Anemia; Screening.
785. Oxidant-Antioxidant Status in Egyptian Children With Sickle Cell Anemia: A Single Center Based Study
El-Ghanrawy MK, Hanna WM, Abdel-Salam A, El-Sonbaty MM, Youness ER and Adel A
Jornal De Pediatria, 90(3): 286-292  (2014) IF: 0.935

Objective: the present study was conducted to investigate the oxidant-antioxidant status in Egyptian children with sickle cell anemia.

Methods: the serum levels of total antioxidant capacity (TAO), paraoxonase (PON), vitamin E, nitrite, and malondialdehyde (MDA) were measured in 40 steady state children with homozygous sickle cell anemia (24 males and 16 females) and 20 apparently healthy age- and gender-matched controls.

Results: mean serum TAO, PON, vitamin E, and nitrite levels were significantly lower in the group with sickle cell anemia, whereas mean serum MDA was significantly higher in these children compared to controls. No significant differences in mean levels of TAO, PON, nitrite, vitamin E, and MDA were found in sickle cell anemia patients receiving hydroxyurea when compared with those not receiving hydroxyurea. A significant negative correlation between serum nitrite and the occurrence of vaso-occlusive crises (VOC) was observed (r=-0.3, p=0.04). PON level was found to be positively correlated with patients' weight and BMI (r=0.4, p=0.01; r=0.7, p=0.001, respectively), but not with frequency of VOC. The area under the curve of serum nitrite in predicting occurrence of VOC was 0.782, versus 0.701 for PON, and 0.650 for TAO (p=0.006). Serum MDA was not correlated with nitrite, PON, TAO, or vitamin E levels. No significant correlations were detected between serum nitrite and hemoglobin or antioxidant enzymes.

Conclusion: children with sickle cell anemia have chronic oxidative stress that may result in increased VOC, and decreased serum nitrite may be associated with increases in VOC frequency. A novel finding in this study is the decrease in PON level in these patients, which is an interesting subject for further research.

Keywords: Anemia Falciforme; Antioxidantes; Antioxidants; Children; Crianças; Malondialdeído; Malondialdeido; Nitrite; Nitrito; Paraoxonase; Sickle Cell Anemia.

786. Hypertrophic Cardiomyopathy: Prognostic Factors and Survival Analysis in 128 Egyptian Patients
El-Saiedi SA, Seliem ZS and Esmail RI
Cardiology In The Young, 24: 702-708  (2014) IF: 0.857

Background: Hypertrophic cardiomyopathy is an important cause of disability and death in patients of all ages. Egyptian children may differ from Western and Asian patients in the pattern of hypertrophy distribution, clinical manifestations, and risk factors.

Objectives: The aim of our study was to report the clinical characteristics and outcomes of Egyptian children with hypertrophic cardiomyopathy studied over a 7-year duration and to determine whether the reported adult risk factors for sudden cardiac death are predictive of the outcome in these affected children.

Study Design and Methods: This retrospective study included 128 hypertrophic cardiomyopathy children. The data included personal history, family history, physical examination, baseline laboratory measurements, electrocardiogram, and Holter and echocardiographic results. Logistic regression analysis was used for the detection of risk factors of death.

Results: Fifty-one out of 128 patients died during the period of the study. Of the 51 deaths, 36 (70.5%) occurred in patients presenting before 1 year of age. Only eight patients had surgical intervention. Extreme left ventricular hypertrophy, that is, interventricular septal wall thickness or posterior wall thickness Z-score >6, sinus tachycardia, and supraventricular tachycardia were found to be independent risk factors for prediction of death in patients with hypertrophic cardiomyopathy.

Conclusions: At our Egyptian tertiary care centre, hypertrophic cardiomyopathy has a relatively worse prognosis when compared with reports from Western and Asian series. Infants have a worse outcome than children presenting after the age of 1 year. A poorer prognosis in childhood hypertrophic cardiomyopathy is predicted by an extreme left ventricular hypertrophy, the presence of sinus tachycardia, and supraventricular tachycardia.

Keywords: Hypertrophic Cardiomyopathy; Echocardiography; Children.

787. Influence of Iron Regulating Genes Mutations on Iron Status in Egyptian Patients With Sickle Cell Disease
Hala A. Abdel Rahman, Heba H. Abou-Elew, Reem M. El-Shorbagy, Rania Fawzy and Ilham Youssry
Annals of Clinical and Laboratory Science, 44(3): 304-309 (2014) IF: 0.839

Background: Mutations of HAMP gene encoding the major iron regulator peptide hepcidin and HFE gene encoding hemochromatosis protein have been implicated in iron overload. The aim of this work was first to analyze the frequency of G71D mutation of HAMP gene and H63D mutation of HFE gene in sickle cell disease (SCD) patients and secondly to study the relative contributions of these genetic variations on iron status.

Methods: This study was performed on a total of 92 Egyptian subjects: 47 SCD patients and 45 age- and sex- matched healthy controls. Genotyping of G71D of HAMP and of H63D of HFE variants was performed by polymerase chain reaction-restriction fragment length polymorphism analysis. Estimation of iron overload was based on steady-state serum ferritin and transferrin saturation.

Results: Genotyping of HAMP-G71D and HFE-H63D variants in SCD patients revealed that 61.7% showed a wild type genetic profile in both genes, 14.9% had a variation in HAMP and H63D variants were performed by polymerase chain reaction-restriction fragment length polymorphism analysis. Estimation of iron overload was based on steady-state serum ferritin and transferrin saturation.

Conclusions: Genotyping of HAMP-G71D and HFE-H63D variants in SCD patients revealed that 61.7% showed a wild type genetic profile in both genes, 14.9% had a variation in HAMP and H63D variants were performed by polymerase chain reaction-restriction fragment length polymorphism analysis. Estimation of iron overload was based on steady-state serum ferritin and transferrin saturation.

Keywords: HAMP; HFE; Sickle cell Disease; Iron overload.
788. Clinical and Ultrasonographical Characterization of Childhood Cystic Kidney Diseases in Egypt
Marwa Mohamed Ibrahim Nabhan
Renal Failure, 36: 694-700 (2014) IF: 0.775

Background: Renal cystic disorders (RCD) constitute an important and leading cause of end-stage renal disease (ESRD) in children. It can be acquired or inherited; isolated or associated with extrarenal manifestations. The precise diagnosis represents a difficult clinical challenge.

Methods: The aim of this study was to define the pattern of clinical phenotypes of children with renal cystic diseases in Pediatric Nephrology Center, Cairo University. We have studied the clinical phenotypes of 105 children with RCD [45 (43%) of them had extrarenal manifestations].

Results: The most common disorders were the presumably inherited renal cystic diseases (65.7%) mainly nephronophthisis and related ciliopathies (36.2%), as well as polycystic kidney diseases (29.5%). Moreover, multicystic dysplastic kidneys accounted for 18% of study cases. Interestingly, eight syndromic cases are described, yet unclassified as none had been previously reported in the literature.

Conclusion: RCD in this study had an expanded and complex spectrum and were largely due to presumably inherited/genetic disorders (65.7%). Moreover, we propose a modified algorithm for clinical and diagnostic approach to patients with RCD.

Keywords: Multicystic Dysplastic Kidneys; Nephronophthisis, Polycystic Kidney; Disease; Renal Ciliopathies; Ultrasonography.

789. Treatment of Hepatitis B and C in Children
El-Shabrawi M and Hassanin F.
Minerva Pediatr, 66: 473-489 (2014) IF: 0.723

Chronic viral hepatitis B and C infections are highly prevalent and create a substantial burden to healthcare systems globally. These two chronic infections are the cause of significant global morbidity and mortality with approximately 1 million annual deaths attributable to them and their sequelae. Children are vulnerable to both infections. The availability of new drugs and new therapeutic strategies are increasing the complexity and individuals’ management of children with viral hepatitis. Therefore, it is extremely important to educate and advise pediatricians concerning the new lines of treatment. More than 350 million persons worldwide are infected with HBV. Although its incidence has dramatically declined since the implementation of universal immunization programs in many countries, scores of children are still being infected each year. Despite its benign course, chronic hepatitis B (CHB) during childhood and adolescence, 3.5% and 0.01-0.03% of chronic carriers develop cirrhosis or hepatocellular carcinoma (HCC), respectively, before adulthood. Treatment of CHB in childhood has been hampered by the long delay in licensing new drugs for pediatric use. Safe and effective antiviral therapies are available in adults, but few are labeled for use in children, and an accurate selection of whom to treat and the identification of the right timing for treatment are needed to optimize response and reduce the risk of antiviral resistance. Although several guidelines on the management of adult patients with CHB have been published by major international societies, the clinical approach to infected children is still evolving, and is mostly based on the expert opinions.

790. Pediatric Air Gun Shot Injury
Naglaa M Kamal
Saudi Medical Journal, 12: 1507-1509 (2014) IF: 0.554

Air guns (AGs) use air or another compressed gas to propel a projectile. Different injuries may occur in children due to their body structure, which is less-resistant with thin soft tissue coverage that can be easily penetrated by an AG shot. We present 3 cases of pediatric AG shot injury. The first-case had right lumbar deep tissue penetration of AG pallet without internal damage, the second-case had a complex course of pellet into the perineum, and the third-case was shot in the left shoulder. All cases were accidentally shot. The shooters were all children, and relatives of the victims. All patients were generally stable on arrival. Two cases were operated, and one received conservative coverage that can be easily penetrated by an AG pallet. We present 3 cases of pediatric AG shot injury. The first-case had right lumbar deep tissue penetration of AG pallet without internal damage, the second-case had a complex course of pellet into the perineum, and the third-case was shot in the left shoulder. All cases were accidentally shot. The shooters were all children, and relatives of the victims. All patients were generally stable on arrival. Two cases were operated, and one received conservative management. On follow up, no complications were noted. At first sight, AGs and air rifles may appear relatively harmless, but they are potentially lethal and children should not be allowed to play with them.

Keywords: Pediatric; Air Gun Shot; Injury.

791. Toe Tourniquet Syndrome
Naglaa M Kamal, Ubaid U. Khan, Shazia J. Mirza and Talal A. Al-Malki
Saudi Medical Journal, 35: 865-867 (2014) IF: 0.554

Toe tourniquet syndrome refers to external, mechanical, circumferential constriction of the toes. We report a series of 4 infants with toe tourniquet syndrome from Saudi Arabia who presented during wintertime with very similar symptoms (approximately 48 hours of inconsolable crying and irritability), similar involved region (toes), and similar constricting agent (hairs). Immediate removal of the hair fibers was carried out in all patients, fortunately followed by fast healing with no signs of...
tissue necrosis. The prompt diagnosis and treatment of the condition were vital in attaining the good outcome and preventing ischemic complications.

Keywords: Toe Tourniquet Syndrome; Saudi; Pediatrics.

792. the Role of Intensive Phototherapy in Decreasing the Need for Exchange Transfusion in Neonatal Jaundice

Amira Abdel Fattah Edris, Eman Abdel Ghany Abdel Ghany, Abdel Rahman Ahmed Abdel Razek and Amany Mosad Zahran

J. of Pakistan Medical Association, 64: 5-8 (2014) IF: 0.403

Objectives: To assess the effectiveness of intensive phototherapy in reducing the need for exchange transfusion and the duration of phototherapy.

Methods: The prospective study with historical controls was conducted at Cairo University Paediatric Hospital, from February to July 2012 in 183 subjects aged by 3 months, and comprised 360 newborns with indirect hyperbilirubinaemia. The 183 subjects were treated with Bilisphere 360 (Bilisphere group) compared with 177 who had been treated with conventional phototherapy (control group). Both groups were subjected to complete clinical evaluation and laboratory investigations.

Results: Bilisphere 360 decreased the need for exchange transfusion in 19 (10.4%) neonates of the Bilisphere group versus 130 (73.4%) of the control group (p<0.001); decreased the level of serum bilirubin as exchange transfusion (6.7 mg/dl [24.9%] in the subjects vs. 6.9 mg/dl [22.7%] in the controls); shortened the duration of phototherapy (2.7 days in the subjects, vs. 4.2 days in the controls; p<0.001).

Conclusion: The use of Bilisphere 360 in the treatment of indirect pathological hyperbilirubinaemia is as effective as exchange transfusion in lowering Total Serum Bilirubin when its level is within 2-3 mg/dl (34-51 umol/l) of the exchange level. Bilisphere 360 is effective in reducing needs for exchange transfusion and duration of phototherapy.

Keywords: Intensive Phototherapy, Exchange Transfusion, Neonatal Jaundice.

794. Mutation of Congenital Chloride Loosing Diarrhea in Saudi Children

Abdulla A. Alharthi, Naglaa M. Kamal, Samer E. Ismail, Gaber M. G. Shhab, Hamdi M. Youssef and Youssri M. Hussein

Wolfenstien, 21: 234-242 (2014) IF: 0.294

Congenital Chloride Diarrhea (CLD) is a watery diarrhea with metabolic alkalosis and excess chloride in feces. It is an autosomal recessive inherited disease caused by mutations in SLC26A3 gene with higher incidence in Arab countries. Due to Arab consanguineous marriages, only one founder mutation (Gly187Ter) was reported in exon5. We sequenced exon5 to study the molecular background in 27 CLD children from Taif, Saudi Arabia. Interestingly, the mutation (NG_008046.1:g.17175G>T, s904491498) was consistent in all children. These results will support developing CLD early detection kits and specific treatments. Adding it to the Saudi pre-marital check-up program would greatly decrease CLD burden. We are looking forward to include screening for the reported founder mutation in the Saudi pre-marital check-up program hoping to decrease the burden of this inherited lifelong disease and with the challenge of developing specific treatment.

Keywords: Chloride Diarrhea (CLD); Congenital Chloride Loosing Diarrhea (CCD), SNP, Founder Mutation.

795. Ocular Manifestations in Egyptian Children and Young Adults With Sickle Cell Disease

Mona Kamal El-Ghamrawy, Hanan F. El Behairy, Amal El Menshawy, Seham A. Awad, Ahmed Ismail and Mohamed Salah Gabal

Indian Journal of Hematology and Blood Transfusion, 30(4): 275-280 (2014) IF: 0.234

In sickle cell disease (SCD), ocular lesions result from stasis and occlusion of small eye vessels by sickled erythrocytes. Vaso-occlusive disease of the retina can be responsible for nonproliferative (NPR) and proliferative retinopathy (PR). Patients are often asymptomatic until serious complications arise as, vitreous hemorrhage and retinal detachment. This work aimed to study the frequency and pattern of ocular manifestations in Egyptian children and young adults with SCD. In this cross-sectional study, 40 steady state patients (80 eyes) aged 2-28 years (30 children and 10 young adults) with established diagnosis of SCD (26 with homozygous SS and 14 with Sβ thalassemia) underwent complete ophthalmic examination with dilated fundoscopy. Fluorescein angiography was performed for patients.
=12 years old. The overall frequency of retinal lesions was 47.5% (46.2 and 50% of SS and Sβ patients respectively). PR and NPR were evident in 32.5 and 27.5% of all enrolled patients respectively (five patients having both). Peripheral retinal occlusion was a frequent ocular finding in both groups; the youngest patient showing PR was 15 years old. Older age, longer disease duration and splenectomy were significantly more prevalent among patients with PR. Despite lack of visual symptoms, children and young adults are at risk of PR. Frequency of retinal lesions was comparable in SS and Sβ patients. Periodic ophthalmologic examination starting at the age of 12 years is recommended for timely-identification of retinal lesions thus minimizing the risk of sight threatening retinopathy.

**Keywords:** Children; Ocular; Retinopathy; Sickle Cell Disease.

### 796. Nutritional Biomarkers in Children and Adolescents With Beta-Thalassemia-Major: an Egyptian Center Experience

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**Background and Aim:** Trace elements and vitamins play a vital role in human body to perform its function properly. Thalassemic patients are at risk of micronutrient deficiency. This study estimated levels of vitamins A, C, E, B12, folic acid, total homocysteine (tHcy), and methylmalonic acid (MMA) along with trace elements, zinc, copper, and selenium in Beta-thalassemia-major patients.

**Methods:** This study included 108 patients with Beta-thalassemia-major and 60 age and sex matched healthy children. Serum levels of vitamin A, E, C, tHcy, and MMA were estimated by high pressure liquid chromatography while serum levels of folic acid and B12 were estimated by thin layer chromatography. Serum zinc, copper, and selenium were determined by atomic absorption spectrometry.

**Results:** There was a significant decrease of vitamins A, C, E, and B12 and trace elements zinc, copper, and selenium in thalassemic patients as compared to controls. tHcy and MMA were significantly elevated in patients. No significant correlations were found between the serum levels of the studied vitamins and trace elements as regards age, frequency of transfusion, duration of transfusion, and serum ferritin.

**Conclusion:** The level of various nutritional biomarkers (vitamins A, C, E, and B12 and trace elements zinc, copper, selenium) was reduced in chronically transfused Egyptian thalassemic patient. These patients should have periodic nutritional evaluation and supplementation. Multicenter studies are highly recommended.

**Keywords:** Nutritional Biomarkers; Children; Adolescents; Beta-Thalassemia-Major; Egyptian.

### 797. Rheumatic Heart Disease in Africa: the Mosi-O-Tunya Call to Action

Sahar Mohamed Shaker Abd El-fattah Sheta


Rheumatic heart disease is a neglected post-infectious chronic disease of children and young adults that continues to main and kill millions of people needlessly. Sub-Saharan Africa is the hotspot of the world, with a prevalence of 5.7 per 1000 in children aged 5–14 years in 2005. This information galvanised the Pan African Society of Cardiology (PASCAR), together with the WHO Regional Office for Africa (WHO-AFRO), the World Heart Federation, and the South African National Department of Health to convene the first All-Africa Workshop on rheumatic fever and rheumatic heart disease on Oct 15–16, 2005, near Drakensberg in South Africa.

**Keywords:** Rheumatic heart disease; Rheumatic fever.

### Dept. of Physiology

#### 798. Effect of Ghrelin on Chronic Liver Injury and Fibrogenesis in Male Rats: Possible Role of Nitric Oxide

Kabil NN, Seddiek HA, Yassin NA and Gamal-Eldin MM

*Peptides, 52: 90-97 (2014) IF: 2.614*

Recent studies have revealed that ghrelin may be an antioxidant and anti-inflammatory agent in many organs, however its role in chronic liver injury (CLI) remains unclear. The role of nitric oxide (NO) in CLI is controversial as evidence suggests that NO is either a primary mediator of liver cell injury or exhibits a protective effect against injurious stimuli. Recent evidence demonstrated that the therapeutic potential for ghrelin was through eNOS activation and increase in NO production. However, its role on NO production in the liver has not been previously investigated. The aim of this study was to investigate the role of ghrelin in treatment of CLI, and whether this action is mediated through NO. Forty male rats were divided into four groups; Group I: Control; Group II: chronic liver injury (CLI); Group III: CLI+Ghrelin; and Group IV: CLI+Ghrelin+NAME. Liver enzymes and tumor necrosis factor alpha (TNF-α), were measured to assess hepatocellular injury. Liver tissue collagen content, malondialdehyde (MDA), gene expression of Bax, Bcl-2, and eNOS were assessed to determine the mechanism of ghrelin action. Results showed that ghrelin decreased serum liver enzymes and TNF-α levels. Ghrelin also reduced liver tissue collagen, MDA, and Bax gene expression, and increased Bcl-2 and eNOS gene expression. The effects on TNF-α, collagen, Bax, and eNOS were partially reversed in Group IV, suggesting that ghrelin's action could be through modulation of NO levels. Therefore, ghrelin's hepatoprotective effect is partially mediated by NO release.

**Keywords:** Liver Injury Fibrosis Thioacetamide Ghrelin Nitric Oxide.

### 799. Cognitive Effects of Acute Restraint Stress in Male Albino Rats and the Impact of Pretreatment With Quetiapine Versus Ghrelin

Amin SN, Gamal SM, Esmail RS, Aziz TM and Rashed LA

*J Integr Neurosci, 13: 669-692 (2014) IF: 1.121*

Stress is any condition that seriously affects the balance of the organism physiologically and psychologically. Stress activates the hypothalamic-pituitary-adrenal (HPA) releasing glucocorticoid hormones that produce generalized effects on different body systems including the nervous system. This study aimed to investigate the effect of acute restraint stress (ARS) on cognitive performance by measuring spatial working memory in Y-maze, behavior (anxiety and exploratory behavior) in open field test, expression of synaptophysin and glial fibrillary acidic protein.
(GFAP) in the hippocampus by immunohistochemistry, dopaminergic receptors (D2) in the basal ganglia by gene expression and comparing the effect of ghrelin and quetiapine on the previous parameters. 36 adult male albino rats constituted the animal model of this work and have been divided into six groups: control group, control group exposed to ARS, quetiapine group, quetiapine group exposed to ARS, ghrelin group and ghrelin group exposed to ARS. We demonstrated more neuroprotective effect for quetiapine compared to ghrelin on stress response, anxiety behavior and working spatial memory impairment due to ARS.

Keywords: Acute Stress; D2 Dopaminergic Receptors; GFAP; Basal Ganglia; Hippocampus; Synaptophysin.

Dept. of Public Health

800. Genetic Polymorphisms in Nqo1 and Sod2: Interactions With Smoking, Schistosoma Infection, and Bladder Cancer Risk in Egypt

David Goerlitz, Sania Amr, Chiranjeev Dash, Doa’a A. Saleh, Mai El-Daly, Mohamed Abd El-Hamid, Sherif El-Kafrawy, Tamer Hifiawy, Sameera Ezzat, Mohamed A. Abd El-Aziz, Hussein Khaled, Yun-Ling Zheng, Nabil Mikhail and Christopher A. Loffredo

Urologic Oncology Seminars and Original Investigations, 9 (2014) IF: 3.363

Background: Bladder cancer is the most prevalent form of cancer in men among Egyptians, for whom tobacco smoke exposure and Schistosoma haematobium (SH) infection are the major risk factors. We hypothesized that functional polymorphisms in NAD(P)H: quinone oxidoreductase 1 (NQO1) and superoxidedismutase2 (SOD2), modulators of the effect of free active oxidative species, can influence an individual's susceptibility to these carcinogenic exposures and hence the risk of bladder cancer.

Methods: We assessed the effects of potential interactions between functional polymorphisms in the NQO1 and SOD2 genes and exposure to smoking and SH infection on bladder cancer risk among 902 cases and 804 population-based controls in Egypt. We used unconditional logistic regression to estimate the odds ratios (OR) and confidence intervals (CI) 95%.

Results: Water pipe and cigarette smoking were more strongly associated with cancer risk among individuals with the TT genotype for SOD2 (OR [CI95%] ¼ 4.41 [1.86–10.42]) as compared with those with the CC genotype (OR[CI95%] ¼ 2.60 [0.97–6.74]). Conversely, the risk associated with SH infection was higher among the latter (OR[CI95%] ¼ 3.59 [2.21–5.84]) than among the former (OR[CI95%] ¼ 1.86 [1.33–2.60]). Polymorphisms in NQO1 genotype showed a similar pattern, but to a much lesser extent. The highest odds for having bladder cancer following SH infection were observed among individuals with the CC genotypes for both NQO1 and SOD2 (OR [CI95%] ¼ 4.41 [2.32–8.38]).

Conclusion: Our findings suggest that genetic polymorphisms in NQO1 and SOD2 play important roles in the etiology of bladder cancer by modulating the effects of known contributing factors such as smoking and SH infection.

Keywords: Nqo1; Sod2; Bladdercancer; Epidemiology; Smoking; Schistosomiasis.

801. Multiple Pregnancies, Hepatitis C, and Risk for Hepatocellular Carcinoma in Egyptian Women

Sania Amr, Emily A Iarocci, Ghada R Nasr, Doa’a Saleh, Jan Biancato, Kirti Shetty and Christopher A Loffredo

Bmc Cancer, 29: 893-897 (2014) IF: 3.319

Background: The reasons for the worldwide sex disparity in the incidence of hepatocellular carcinoma (HCC) remain elusive. We investigated the role of multiple pregnancies on the associations between viral hepatitis C (HCV) infection and HCC risk among Egyptian women.

Methods: We used data collected from blood specimens and questionnaires administered to female HCC cases and controls in Cairo, Egypt, from 1999 through 2009. HCV infection was defined as being sero-positive for either anti-HCV antibodies or HCV-RNA. Using logistic regression models we calculated odds ratios (OR) and 95% confidence intervals (CI) to estimate the associations between being HCV positive and HCC risk, and how it is modified by the number of pregnancies, after adjustment for other factors, including hepatitis B status.

Results: Among 132 confirmed female cases and 669 controls, the risk of HCV-related HCC increased with the number of pregnancies. Women infected with HCV had higher risk for HCC if they had more than five pregnancies, as compared to those who had five or fewer pregnancies (adjusted OR (95% CI): 2.33 (1.29-4.22)). The association of HCV infection with HCC risk was significantly greater among the former (21.42 (10.43-44.00)) than among the latter (6.57 (3.04-14.25)).

Conclusion: Having multiple pregnancies increases the risk of HCV-related HCC among Egyptian women, raising questions about the roles of estrogens and other pregnancy-related hormones in modulating HCV infection and its progression to HCC.

Keywords: Hepatocellular Carcinoma; Hepatitis C; Epidemiology; Pregnancy; Women’S Health.

802. Knowledge Translation in Africa for 21St Century Integrative Biology: the “Know-Do Gap” in Family Planning With Contraceptive Use Among Somali Women

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Omics A Journal of Integrative Biology, 18: 696-704 (2014) IF: 2.73

An emerging dimension of 21st century integrative biology is knowledge translation in global health. The maternal mortality rate in Somalia is amongst the highest in the world. We set out to study the “know-do” gap in family planning measures in Somalia, with a view to inform future interventions for knowledge integration between theory and practice. We interviewed 360 Somali females of reproductive age and compared university-educated females to women with less or no education, using structured interviews, with a validated questionnaire. The mean age of marriage was 18 years, with 4.5 pregnancies per marriage. The mean for the desired family size was 9.3 and 10.5 children for the university-educated group and the less-educated group, respectively. Importantly, nearly 90% of the university-educated group knew about family planning, compared to 45.6% of the less-educated group. All of the less-educated group indicated that they would never use contraceptives, as compared to 43.5% of the
university-educated group. Prevalence of contraceptive use among ever-married women was 4.3%. In the less-educated group, 80.6% indicated that they would not recommend contraceptives to other women as compared to 66.0% of the university-educated group. There is a huge gap between knowledge and practice regarding family planning in Somalia. The attendant reasons for this gap, such as level of education, expressed personal religious beliefs and others, are examined here. For primary health care to gain traction in Africa, we need to address the existing “know-do” gaps that are endemic and adversely impacting on global health. This is the first independent research study examining the knowledge gaps for family planning in Somalia in the last 20 years, with a view to understanding knowledge integration in a global world. The results shall guide policy makers, donors, and implementers to develop a sound family planning policy and program to improve maternal and child health in 21st century primary healthcare.

Keywords: Family Planning Somalia Knowledge Translation Africa.


Scholarship knows no geographical boundaries. This science diplomacy and biotechnology journalism article introduces an original concept and policy petition to innovate the global translational science, a Science Peace Corps. Service at the new Corps could entail volunteer work for a minimum of 6 weeks, and up to a maximum of 2 years, for translational research in any region of the world to build capacity manifestly for development and peace, instead of the narrow bench-to-bedside model of life science translation. Topics for translational research are envisioned to include all fields of life sciences and medicine, as long as they are linked to potential or concrete endpoints in development, foreign policy, conflict management, post-crisis capacity building, and/or peace scholarship domains. As a new instrument in the global science and technology governance toolbox, a Science Peace Corps could work effectively, for example, towards elucidating the emerging concept of “one health”—encompassing human, environmental, plant, microbial, ecosystem, and planet health—thus serving as an innovative crosscutting pillar of 21st century integrative biology. An interdisciplinary program of this caliber for development would link 21st century life sciences to foreign policy and peace, in ways that can benefit many nations despite their ideological differences. We note that a Science Peace Corps is timely. The Intergovernmental Panel on Climate Change (IPCC) of the United Nations released the Fifth Assessment Report on March 31, 2014. Worrisomely, the report underscores that no person or nation will remain untouched by the climate change, highlighting the shared pressing life sciences challenges for global society. To this end, we recall that President John F. Kennedy advocated for volunteer work that has enduring, transgenerational, and global impacts. This culminated in establishment of the Peace Corps in 1961. Earlier, President Abraham Lincoln aptly observed, “nearly all men can stand adversity, but if you want to test a man’s character, give him power.” We therefore petition President Barack Obama, other world leaders, and international development agencies in positions of power around the globe, to consider deploying a Science Peace Corps to cultivate the essential (and presently missing) ties among life sciences, foreign policy, development, and peace agendas. A Science Peace Corps requires support by a credible and independent intergovernmental organization or development agency for funding, and arbitration in the course of volunteer work when the global versus local (glocal) value-based priorities and human rights intersect in synergy or conflict. In all, Science Peace Corps is an invitation to a new pathway for competence in 21st century science that is locally productive and globally competitive. It can open up scientific institutions to broader considerations and broader inputs, and thus cultivate vital translational science in a world sorely in need of solidarity and sustainable responses to the challenges of 21st century science and society.

804. Knowledge and Perceptions of Hepatitis C Infection and Pesticides Use in Two Rural Villages in Egypt

Doa’a A Saleh, Sania Amr, Irene A Jillson, Judy Huei-yu Wang, Walaa A Khairy and Christopher A Loffredo.

Background: Hepatocellular carcinoma (HCC), one of the most fatal types of malignancy, is increasing worldwide, and particularly in Egypt where there is a confluence of its contributing factors, including high prevalence of hepatitis C virus (HCV) infection, widespread use of pesticides, and diets that are contaminated by aflatoxin B1 (AFB1) in rural areas. We investigated knowledge, attitudes, and prevention practices related to HCV infection and pesticides use in rural Egypt, where over half of the population resides and agriculture is the predominant occupation.

Methods: From two rural villages we recruited 67 residents aged 18–80 years, who completed a 40-item survey that included questions about demographics, knowledge of and protective measures relevant to pesticides use in the home and in agriculture, awareness and perceptions of HCV infection and its treatment and prevention.

Results: Among the 67 study participants, gender distribution was equal, the mean age was 47.2, and one third never attended school. More than 50% reported using pesticides at home, but fewer reported having some knowledge about its health effects. Twelve participants were agricultural workers, and 11 of them applied pesticides in the field and knew about their toxicity; however only one person was correctly using the appropriate protective equipment. Among all the participants, 52 did not know what causes HCV infection, and 42 of those who knew it was a virus mentioned incorrect modes of transmission; and 30 did not know the disease manifestations.

Conclusion: In rural Egypt, there is a significant lack of knowledge of HCV infection and its transmission mode and limited use of protective measures against pesticides despite familiarity with these chemicals.
805. Agricultural Workers and Urinary Bladder Cancer Risk in Egypt

Sania Amr, Rebecca Dawson, Doa’a A. Saleh, Laurence S. Magder, Nabiel N. Mikhail, Diane Marie St. George, Katherine Squibb, Hussein Khaled and Christopher A. Loftredo

Archives of Environmental and Occupational Health, 69(1): 3-10 (2014) IF: 0.617

The authors examined the associations between farming and the risk for squamous cell (SCC) or urothelial cell (UC) carcinoma of the urinary bladder among Egyptians. The authors used data from a multicenter case-control study (1,525 male and 315 female cases, and 2,069 male and 547 female age- and residence-matched, population-based controls) to calculate adjusted odds ratios (AORs) and 95% confidence intervals (CIs). Men in farming and who never smoked had increased risk for either SCC or UC (AOR [95% CI]: 4.65 [2.59-8.36] and 6.22 [3.82-10.15], respectively). If they ever smoked, their risks were 2.27 (1.75–2.95) and 1.93 (1.58–2.35), respectively. Women in farmer households were at increased risk for SCC (1.40 [0.93–2.09]) and UC (1.25 (0.82–1.89)), although not statistically significant. Occupational and environmental exposures to farming increased the risk for bladder cancer among Egyptians.

Keywords: Agricultural Workers; Bladder Cancer; Egypt; Epidemiology; Tobacco Smoke Exposure.

Dept. of Rheumatology

806. Prevalence of Comorbidities in Rheumatoid Arthritis and Evaluation of Their Monitoring: Results of An International, Cross-Sectional Study (COMORA)


Background: PATIENTS with rheumatoid arthritis (RA) are at increased risk of developing comorbid conditions.

Objectives: To evaluate the prevalence of comorbidities and compare their management in RA patients from different countries worldwide.

Methods: Study Design: international, cross-sectional.

Patients: consecutive RA patients.

Data Collected: demographics, disease characteristics (activity, severity, treatment), comorbidities (cardiovascular, infections, cancer, gastrointestinal, pulmonary, osteoporosis and psychiatric disorders).

Results: Of 4586 patients recruited in 17 participating countries, 3920 were analysed (age, 56±13 years; disease duration, 10±9 years (mean±SD); female gender, 82%; DAS28 (Disease Activity Score using 28 joints)-erythrocyte sedimentation rate, 3.7±1.6 (mean±SD); Health Assessment Questionnaire, 1.0±0.7 (mean±SD); past or current methotrexate use, 89%; past or current use of biological agents, 39%. The most frequently associated diseases (past or current) were: depression, 15%; asthma, 6.6%; cardiovascular events (myocardial infarction, stroke), 6%; solid malignancies (excluding basal cell carcinoma), 4.5%; chronic obstructive pulmonary disease, 3.5%. High intercountry variability was observed for both the prevalence of comorbidities and the proportion of subjects complying with recommendations for preventing and managing comorbidities. The systematic evaluation of comorbidities in this study detected abnormalities in vital signs, such as elevated blood pressure in 11.2%, and identified conditions that manifest as laboratory test abnormalities, such as hyperglycaemia in 3.3% and hyperlipidaemia in 8.3%.

Conclusions: Among RA patients, there is a high prevalence of comorbidities and their risk factors. In this multinational sample, variability among countries was wide, not only in prevalence but also in compliance with recommendations for preventing and managing these comorbidities. Systematic measurement of vital signs and laboratory testing detects otherwise unrecognised comorbid conditions.

Keywords: Objectives To Evaluate The Prevalence Of Comorbidities.

807. Polymorphisms of Interleukin 6 and Interleukin 10 in Egyptian People With Behçet’s Disease

Talaat RM, Ashour ME, Bassyouni IH and Raouf AA

Immunobiology, 219(8): 573-582 (2014) IF: 3.18

Cytokines play critical roles in the pathogenesis of Behçet’s disease (BD). They mediated many of the effectors and regulatory functions of immune and inflammatory responses. Many studies have linked Interleukin-6 (IL-6) and Interleukin-10 (IL-10) pathologically to BD. Thus, this study aimed to investigate the associations between IL-6 and IL-10 promoter single-nucleotide polymorphisms (SNPs) and the susceptibility to BD and their implication on plasma levels. We genotyped IL-6 -174 G/C (rs1800795) using Mutagenically Separated Polymerase Chain Reaction PCR (MS-PCR) and IL-10 -1082 G/A (rs1800896) and -819 C/T (rs1800871) using Sequence Specific Primer PCR (SSP-PCR) in 87 Egyptian patients and 97 controls. The plasma levels of IL-6 and IL-10 were measured using Enzyme-linked Immunosorbent Assay (ELISA). Significant increase in the frequency of -1082 GG genotype (P<0.05, OR=2.25, 95%CI=1.03-4.91) and significant decrease in the frequency of -1082 GA genotype (P<0.05, OR=0.53, 95%CI=0.29-0.96) was demonstrated in BD patients compare to controls. Patients with genital ulcer had significantly lower frequency of -1082 GG (P<0.05, OR 0.2, 95%CI=0.04-0.99) and G allele (P<0.05, OR=0.28, 95%CI=0.08-0.93), while patients with ocular manifestations had significantly higher frequency of -1082 G allele (P<0.01, OR=2.28, 95%CI=1.19-4.36). BD patients had significantly higher level of IL-6 (P<0.001) and significantly lower level of IL-10 (P<0.001) compared to controls. The changes in the level of cytokines were independent of any genotype of IL-6 or any genotype/haplotype of IL-10. Patients with active disease state had significantly higher level of IL-6 compared to patients in remission (P<0.05). In conclusion, our preliminary study indicates that the polymorphism at IL-10 -1082 G/A may play a role in BD susceptibility. The significant increase in IL-6 level and the significant decrease in IL-10 level in BD patients were independent of any particular genotype in IL-6 or any particular genotype/haplotype in IL-10.
Keywords: Behçet’s Disease; Cytokines; II-10; II-6; Polymorphism; Snp.

808. Autoantibodies Against Complement C1q in Patients With Behcet’s Disease: Association With Vascular Involvement

Bassyouni IH, Gamal S, Talaat RM and Siam I


The aim of our study was to determine the prevalence of anti-C1q antibodies and their possible association with clinical presentation in Behçet’s disease (BD) patients with special emphasis for patients with vascular involvement. Plasma anti-C1q Abs levels were measured using an enzyme-linked immunosorbent assay in 51 BD patients and 25 age- and gender-matched healthy controls.

We found elevated concentrations of anti-C1q more frequently in patients with BD (18 %) than in healthy controls (8 %). The highest prevalence was found in patients with vascular BD (42 %) which was significantly higher than patients without vascular BD and healthy controls (p = 0.025). Furthermore, patients with vascular BD had the highest mean anti-C1q levels when compared to BD patients without vascular involvement or healthy control subjects (p = 0.015).

In conclusion, we found an increased prevalence of anti-C1q autoantibodies in BD patients with vascular involvement. Further large scale longitudinal studies are required to assess and clarify the significance and the pathogenic role of anti-C1q antibodies in BD and other autoimmune diseases in which vasculitis is a component.

Keywords: Anti-C1q antibodies; Behcet’s disease; Complement; Vascular disease.

809. Subclinical Reduced G6PD Activity in Rheumatoid Arthritis and Sjögren’s Syndrome Patients: Relation To Clinical Characteristics, Disease Activity and Metabolic Syndrome.

Gheita TA, Kenawy SA, El Sisi RW, Gheita HA and Khalil H.

Modern Rheumatology, 24: 612-617 (2014) IF: 2.206

Objective: Glucose-6-phosphate dehydrogenase (G6PD) is an important site of metabolic control in the pentose phosphate pathway. The purpose of this study was to investigate the enzyme activity of G6PD in Rheumatoid Arthritis (RA) and Sjögren’s Syndrome (SS) patients not known to be deficient in this enzyme. It was also within the scope of the aim to find the relation of G6PD to the presence of metabolic syndrome (MetS) in these patients.

Methods: Erythrocyte G6PD activity was evaluated in 40 RA patients, 30 SS patients and in 30 age- and sex-matched control. The clinical characteristics, disease activity score (DAS28), SS disease activity (SSDAI) and damage (SSDDI) indices and presence of MetS of the included patients were analyzed in relation to the enzyme level.

Results: The G6PD activity in RA patients (7.72 ± 3.57 U/g Hb) was significantly reduced compared to that in the SS patients (11.55 ± 3.14 U/g Hb) and control (13.23 ± 3.34 U/g Hb) especially those with MetS (4.61 ± 1.84 U/g Hb) (p < 0.001). There was a significant negative correlation of the G6PD activity with the disease duration and DAS28 (p < 0.001).

Conclusion: The results of this study, suggest that G6PD not only does not protect against MetS in RA, but may even be considered a risk factor for the development of this disorder. The identification of regulatory tools for G6PD activity may prove promising for treating the associated metabolic disorders and chronic inflammation in RA.

Keywords: G6pd; Rheumatoid Arthritis; Sjogrens Syndrome; Metabolic syndrome.

810. Detection of asymptomatic cranial neuropathies in patients with Systemic Lupus Erythematosus and their relation to antibosomal P antibody levels and disease activity

Gaber W, Ezzat Y, El Fayoumy NM, Helmy H and Mohey AM

Clin Rheumatol, 33: 1459-1466 (2014) IF: 1.774

The objectives of this study are to assess the risk of asymptomatic cranial neuropathy among patients with systemic lupus erythematosus (SLE) and find any association with disease activity and antibosomal P antibodies.

This study is a case-control study including 60 female patients and 30 healthy female controls. Disease activity was measured with the SLE disease activity index (SLEDAI). All patients were evaluated using evoked potentials, blink reflex, and levels of antibosomal P antibodies. Patients with abnormal electrophysiological parameters had significantly higher levels of antibosomal P antibodies (P=0.034) and secondary antiphospholipid syndrome (P=0.044). Antibosomal P antibodies.

Keywords: Antibosomal P Antibodies; Auditory Brain Reflex; Evoked Blink Reflex; Systemic Lupus Erythematosus.

811. Involvement of IL-23 in Enteropathic Arthritis Patients With Inflammatory Bowel Disease: Preliminary Results

Gheita TA, El Gazzar II, El-Fishawy HS, Aboul-Ezz MA and Kenawy SA.

Clinical Rheumatology, 33: 713-717 (2014) IF: 1.774

The role of interleukin (IL)-23 in the pathogenesis of inflammatory bowel disease (IBD) remains unclear. The aim of this work was to study the serum level of IL-23 in IBD with and without arthritis and determine its relation to the subsets and clinical features of the disease. Thirty-seven patients with IBD including 11 with arthritis were included in the study with a mean age of 30.86±4.66 years. Twenty healthy subjects served as control. Seronegative spondyloarthropathy was present in 11 (29.73 %) of the IBD patients; Crohn’s disease (CD) was present in 23 and 14 had ulcerative colitis (UC). Serum level of IL-23 was measured in all patients and control by ELISA. IL-23 was significantly higher in IBD patients (46.24±27.19 pg/ml) compared to control (24.1±2.31 pg/ml) (P=0.0001) being higher in CD patients (52.57±32.78 pg/ml) compared to those with UC (35.80±6.41 pg/ml) (P=0.026). Furthermore, it was significantly higher in those with peripheral and/or axial arthritis (67.73±40.85 pg/ml) compared to patients without (37.15±10.37 pg/ml) (P=0.03). There was a tendency to a higher level in males
The aim of this work was to clarify the effect of leflunomide (LEF) on the eye dryness in patients with secondary Sjögren's syndrome associated with rheumatoid arthritis (RA-SsS) and in patients with rheumatoid arthritis (RA). Seventy-five female patients, 45 with RA-SsS (group A) and 30 with RA (group B), taking methotrexate at a dose of 20 mg/week for more than 6 months were enrolled in this study. They all had a loading dose of leflunomide then were maintained at a dose of 20 mg/day in addition to methotrexate for another 3 months. The modified disease activity score (DAS28) was calculated and modified Schirmer's-I test was performed. Assessment of disease parameters was done to all patients before and after 3 months of taking LEF. The mean modified Schirmer's-I test showed a significant decrease after 3 months of taking LEF in group A (3 Å± 1.6 before versus 1.9 Å± 1.6 after 3 months, P < 0.001), while this difference was non-significant in group B (21.3 Å± 10 versus 19.9 Å± 11). One patient (group A) developed peripheral ulcerative keratitis (PUK) with exacerbation of disease activity (DAS28 = 6.9) that improved by taking corticosteroids. Three patients (group A) had aggravation of punctate keratoconjunctivitis sicca with punctate erosions without PUK. The condition improved dramatically by stopping LEF and using topical lubricants. We report in this study a significant deterioration of the eye dryness in patients with sSS-RA after 3 months of receiving LEF inspite of the significant improvement of their DAS28. This finding was not clearly detected in RA patients. Close monitoring of eye dryness changes by special tests in patients using LEF is recommended, especially in cases with sSS-RA having very low baseline values.

Keywords: Eye Dryness; Leflunomide; Peripheral Ulcerative Keratitis; Punctate Keratoconjunctivitis Sicca; Rheumatoid Arthritis; Secondary Sjögren’s Syndrome.

813. Therapeutic Potential of Hydroxychloroquine On Serum B-Cell Activating Factor Belonging To theTumor Necrosis Factor Family (BAFF) in Rheumatoid Arthritis Patients

Amina A. Mahdy, Hala A. Raafat, Hussein S. El-Fishawy and Tamer A. Gheita

Bulletin of Faculty of Pharmacy, Cairo University, 52: 37-43 (2014)

Objective: To assess the serum B-cell activating factor belonging to the tumor necrosis factor family (BAFF) level in rheumatoid arthritis (RA) patients in view of different treatment regimens received and evaluate its relation with disease activity.

Patients and methods: Ninety female RA patients were included. Sixty were on disease modifying anti-rheumatic drugs (DMARDs); 34 on hydroxychloroquine (HCQ) plus metotrexate (MTX), 26 on leflunomide (LFN) plus MTX and 30 newly diagnosed cases not yet on any treatment. Thirty age and gender matched healthy subjects served as controls. Full history taking, clinical examination and relevant laboratory investigations were performed. Disease activity score, in 28 joints (DAS-28), was calculated.

Results: Serum BAFF level was significantly higher in patients (1.82 ± 0.91 ng/ml) compared to control (0.71 ± 0.33 ng/ml; p < 0.001). There was a significantly lower BAFF and disease activity in patients receiving DMARDs (1.55 ± 0.73 ng/ml and 3.08 ± 0.73) compared to new cases (2.36 ± 1.02 ng/ml and 3.46 ± 0.82) (p < 0.001 and p = 0.036, respectively). Those receiving HCQ + MTX had a lower BAFF level (1.29 ± 0.51 ng/ml) compared to those receiving LFN + MTX (1.94 ± 0.85 ng/ml; p = 0.002). The BAFF level significantly correlated with the presence of anti-CCP antibodies, DAS28 and MTX dose in all RA patients (r = 0.24, p = 0.02; r = 0.504, p < 0.001, 0.511, p = 0.001, respectively). Only DAS28 and MTX dose would highly influence the BAFF level (p = 0.015 and p = 0.001, respectively).

Conclusion: Elevated level of BAFF in RA has been confirmed with a notable relation to disease activity making it a promising marker. The beneficial effect of hydroxychloroquine in dampening BAFF level throws light on the importance of considering it in combination among the newly developed biologics that also target B-cells.

Keywords: Serum Baff; Ra; Das28; Hydroxychloroquine; Methotrexate; Leflunomide.

Dept. of Urology Dept

814. Slow VS Rapid Delivery Rate Shock Wave Lithotripsy for Pediatric Renal Urolithiasis: A Prospective Randomized Study

Salem HK, Fathy H, Elfayoumy H, Aly H, Ghonium A, Mohsen MA and Hegazy Ael R


Purpose: We compared slow vs fast shock wave frequency rates in disintegration of pediatric renal stones less than 20 mm.

Materials and Methods: Our study included 60 children with solitary 10 to 20 mm radiopaque renal stones treated with shock wave lithotripsy. Patients were prospectively randomized into 2 groups, ie those undergoing lithotripsy at a rate of 80 shock waves per minute (group 1, 30 patients) and those undergoing lithotripsy at a rate of 120 shock waves per minute (group 2, 30 patients). The 2 groups were compared in terms of treatment success, anesthesia time, secondary procedures and efficiency quotient.

Results: Stone clearance rate was significantly higher in group 1 (90%) than in group 2 (73.3%, p = 0.025). A total of 18 patients in group 1 (60%) were rendered stone-free after 1 session, 8 required 2 sessions and 1 needed 3 sessions, while shock wave lithotripsy failed in 3 patients. By comparison, 8 patients (26.6%) in group 2 were rendered stone-free after 1 session, 10 (33.3%) required 2 sessions and 4 (13.3%) needed 3 sessions to become stone-free. Mean general anesthesia time was significantly longer in group 1 (p = 0.041). Postoperatively 2 patients in group 1 and 4 in group 2 suffered low grade fever (Clavien grade II). Significantly more secondary procedures (percutaneous nephrolithotomy, repeat shock wave lithotripsy) were required in
group 2 (p = 0.005). The predominant stone analysis was calcium oxalate dihydrate in both groups. Efficiency quotient was 0.5869 and 0.3437 for group 1 and group 2, respectively (p = 0.0247).

Conclusions: In children with renal stones slow delivery rates of shock wave lithotripsy have better results regarding stone clearance than fast delivery rates.

Keywords: High-Energy Shock Waves; Kidney Calculi; Lithotripsy; Pediatrics; Urolithiasis.


Elsheemy MS, Maher A, Mursi K, Shouman AM, Shoukry AI, Morsi HA and Meshref A.


Objectives: To evaluate the impact of age, stone size, location, radiolucency, extraction of stone fragments, size of ureteroscope and presence and degree of hydronephrosis on the efficacy and safety of holmium:YAG (Ho:YAG) laser lithotripsy in the ureteroscopic treatment of ureteral stones in children.

Methods: Between October 2011 and May 2013, a total of 104 patients were managed using semirigid Ho:YAG ureterolithotripsy. Patient age, stone size and site, radiolucency, use of extraction devices, degree of hydronephrosis and size of ureteroscope were compared for operative time, success and complications.

Results: In all, 128 URS were done with a mean age of 4.7 years. The mean stones size was 11 mm. Success rate was 81.25 %. Causes of failure were 12.5 % access failure, 1.5 % extravasation and 4.7 % stone migration. Overall complications were 23.4 %. Failure of dilatation and extravasation were detected only in children <2 years old. Extravasation was significantly higher in smaller ureters and cases with stone size >15 mm. Stone migration was significantly higher in upper ureteric stones.

Conclusions: Failure and complications rates in Ho:YAG ureterolithotripsy were significantly affected by younger age (<2 years), upper ureteric stones and smaller ureters but were not related to stone radiolucency or degree of hydronephrosis. Larger stones (>15 mm) were associated with increased complications. After multivariate analysis, the age of the patients remained significant predictor for failure of dilatation and stone migration, while size of the ureter was the only significant predicting factor for failure.

Keywords: Holmium Laser Intracorporeal Lithotripsy Stones Endourology Children.

816. Circulating miRNAs 21 and 221 as Biomarkers for Early Diagnosis of Prostate Cancer

Sameh Kotb, Ashraf Mosharafa, Mona Essawi, Heba Hassan, Alaa Meshref and Ahmed Morsy

Tumor Biology, 35: 12613-12617 (2014) IF: 2.84

To compare the expression of two promising circulating microribonucleic acids (miRNAs 21 and 221) in patients with prostate cancer to subjects without cancer and to evaluate their potential role as specific noninvasive molecular biomarkers for prostate cancer diagnosis, circulating miRNAs 21 and 221 expression profiles were analyzed in 20 men aged 50–75 years, presenting with lower urinary tract symptoms (LUTSs) and undergoing transrectal ultrasound (TRUS)-guided prostate biopsy based on either elevated serum prostatespecific antigen (PSA) (>4.0 ng/ml) or suspicious digital rectal examination (DRE). The performance of miRNAs 21 and 221 in differentiating prostate cancer from nonmalignant cases was evaluated and compared to DRE and elevated PSA. miRNA 21 was overexpressed in 90 % of group A vs. 10 % of group B, while miRNA 221 was overexpressed in 80 % of group A vs. 20 % of group B (p=0.001). MiRNA 21 overexpression had the highest performance as a diagnostic test with a sensitivity of 90 % and a specificity 90 % (p=0.02). No correlations were noted between Gleason score of prostate cancer cases and relative quantity (RQ) 21 (r=0.355, p=0.292) or RQ 221 (r=0.044, p=0.892). Our study showed that serum miRNAs 21 and 221 expression profiling tests may be used as specific noninvasive molecular biomarkers for prostate cancer diagnosis due to their higher sensitivity and specificity with a high negative predictive value leading to a decrease in the biopsies taken for patients with elevated serum PSA values.

Keywords: Mirnas . Prostate Neoplasms . Diagnosis .

817. Effect of Multiple Access Tracts During Percutaneous Nephrolithotomy on Renal Function: Evaluation of Risk Factors for Renal Function Deterioration

Amr S. Fayad, Mohamed G. Elsheikh, Ashraf Mosharafa, Ragheb El-Sergany, Mohammed A. Abdel-Rassoul, Ahmed Elshenofy, Hisham Ghamrawy, Ahmed Abd El Bary and Tarek Fayad

Journal of Endourology, 28: 775-779 (2014) IF: 2.095

Purpose: To assess the impact of multiple access tracts during percutaneous nephrolithotomy (PCNL) on shortand midterm renal function, and to determine risk factors predicting renal function deterioration and/or recoverability. Patients and Methods: Patients undergoing PCNL with multiple punctures were prospectively enrolled. Preoperative evaluation included dimercaptosuccinic acid and diethylenetriaminopentaacetic acid renography. Patients were classified according to baseline renal function into patients with normal (<1.4mg/dL) serum creatinine (group A) and patients with elevated (≥1.4mg/dL) serum creatinine (group B). Patients were followed with serial serum creatinine evaluations and a repeated renography at 12 months. Factors evaluated for possible impact on renal function changes included preoperative renal function, number of accesstracts, hypertension, and diabetes mellitus.

Results: There were 102 patients 21 to 65 (mean 39.9) years who completed the study. Fifty patients (group A) had normal preoperative serum creatinine levels and glomerular filtration rate (GFR), which showed no statistically significant change 12 months after PCNL. Fifty-two patients had baseline renal impairment (group B), and they experienced statistically significant worsening of the serum creatinine level and GFR at 12 months postoperatively (P<0.001). Ten (19.23%) patients in group B had a significant deterioration of GFR more than 25%. Independent risk factors for this poor outcome were elevated serum PSA values.

Conclusion: PCNL with multiple tracts carries a risk of adversely affecting renal function. Preoperative baseline renal impairment, diabetes, and hypertension are risk factors for significant renal function deterioration after the procedure.

Keywords: Percutaneous nephrolithotomy; Multiple tracts; Renal function.
818. Management of Obstructive Calcular Anuria With Acute Renal Failure in Children Less Than 4 Years in Age: A Protocol for Initial Urinary Drainage in Relation To Planned Definitive Stone Management

ElSheemy MS, Shoukry AI, Shouman AM, ElShenoufy A, Aboulela W, Daw K, Hussein AA and Morsi HA

J. of Pediatric Urology, 10 (6): 1126-1132 (2014) IF: 1.413

Objectives: To describe and evaluate our protocol for management of children≤4 years old with obstructive calculi anuria (OCA) and acute renal failure (ARF) to improve selection of initial urinary drainage (ID) method and to facilitate subsequent definitive stone management (DSM) as studies discussing this special group of patients are still few. Patients and Methods: Patients with a contraindication to any method of ID were excluded. Decision (percutaneous nephrostomy (PCN) or double J (JJ) stent) was based on degree of hydronephrosis and planned DSM. We used 4.8-5Fr JJ or 6-8Fr PCN under general anesthesia and fluoroscopic guidance. According to our protocol, JJ is inserted for hydronephrosis≤ grade 1. When the hydronephrosis is >grade 1, patients with radiolucent stones were treated by JJ whatever the site of the stone. When the stones were radiopaque, PCN was reserved for stones in a solitary functioning kidney and bilateral ureteric stones prepared for subsequent bilateral ureterolithotomy (or stone prepared for ureterolithotomy in a solitary kidney). After normalization of renal functions, DSM was staged attacking only one side before discharge. Both sides were cleared at the same session in cases with bilateral ureterolithotomy. Renal or ureteric stones suitable for SWL in a solitary kidney were treated with percutaneous nephrolithotripsy (PNL) or ureteroscopy. This was followed also in patients with bilateral stones suitable for SWL by clearing one side using ureteroscopy or PNL before discharge. Open surgery (OS) was reserved for cases with failed ureteroscopy or PNL, for ureteric stones>2.5 cm in size or very large volume complex renal stones. Stone free rate (SFR) was evaluated by CT. Our protocol was evaluated as regard recovery of renal functions, complications, and number of interventions to clear stones. Results: This study included 62 boys and 22 girls presented with anuria for 1-4 days. JJ and PCN were inserted in 105 and 30 ureterorenal units (URU), respectively. Creatinine returns normal within 72 h. JJ insertion formed a part of DSM in 78/159 (49%) URU (stones prepared for extracorporeal shockwave lithotripsy or oral chemolytic dissolution therapy). PCN was the ideal tract for subsequent PNL in 11/159 (6.9%) URU. Accordingly, ID participated by 55.97% in DSM. Both operative and imaging times were slightly longer with PCN than JJ. There was no statistically significant difference in the insertion success or mean period to return to normal chemistry. Complications of both methods were mild and without any significant difference. Endourologic procedures constituted the majority of our interventions. Open surgical and endoscopic interventions for clearance of stones (including ID, treatment conversion and 2ry procedures) were done once for 25 patients, twice for 43 patients while it needed three times for 16 patients. Total number of interventions was 149 procedures. SFR was 94%. Conclusion: Our protocol ensures adequate ID with minimal complications when using our selection criteria in children≤4 years in age with OCA and ARF. It also minimizes number of subsequent procedures to clear stones. Complications and success in insertion and drainage were equivalent in PCN and JJ groups.

Keywords: Anuria; Children; Nephrostomy; Stents; Urinary Calculi.

819. Surgical Complications and Graft Function Following Live-Donor Extraperitoneal Renal Transplantation in Children 20 Kt Or Less

ElSheemy MS, Shouman AM, Shoukry AI, Soaida S, Salah DM, Yousef AM, Morsi HA, Fadel FI and Sadek SZ


Objectives: To evaluate the effect of patient, surgical, and medical factors on surgical complications and graft function following renal transplantation (Tx) in children weighing ≤ 20 kg, because the number of this challenging group of children is increasing. Patients and Methods: Between June 2009 and October 2013, 26 patients received living donor renal allotransplant using the extraperitoneal approach (EPA). The immunosuppression regimen was composed of prednisolone, mycophenolate mofetil, and ciclosporin or tacrolimus. Results: The mean weight was 16.46 ± 2.61 kg. Mean cold ischemia time was 53.85 ± 12.35 min. The graft survival rate (GSR) and patient survival rate (PSR) were 96% at 3 years. Acute rejection episodes occurred in eight patients (30%). Postoperative surgical complications were ureteral leakage (3), vesicoureteric reflux (2), and renal vein thrombosis (2) (with one graft nephrectomy). Mean follow-up was 37.5 ± 7.4 months. Conclusion: Excellent PSR and GSR can be achieved in low weight (<20 kg) recipients. Even in very low weight patients, the EPA was used. No cases were reported with primary graft non-function due to use of living donors, increasing pre-Tx body weight to at least 10 kg and maintaining adequate filling pressure before graft reperfusion. The presence of related donors and use of induction therapy and tacrolimus decreased the rate of ARE while the presence of pre-Tx lower urinary tract surgical interventions increased the rate of ureteric complications, but this was statistically insignificant. Keywords: Renal transplantation; Extraperitoneal approach; Live donor; Low body weight children; Pediatric.

820. Human Urinary Myiasis Due To Larvae of Clogmia (Telmatoscopus) Albipunctata Williston (Diptera: Psychodidae) First Report in Egypt

El-Badry AA, Salem HK and El-Aziz Edmardash YA.

J. Vector Borne Dis, 51(3):247-249 (2014) IF: 0.647

Human myiasis is defined as “the infestation of the tissue of living human with dipterous larvae”. Parasitologically myiasis could be classified as obligatory, facultative or accidental. Clinically myiasis may be classified according to part of the body tissue invaded. Cutaneous myiasis is the commonest type. Body cavity myiasis; nasopharyngeal, ocular, aural and the gastrointestinal tract urogenital system are less common. Urethral myiasis is exceptionally rare, even in sites usually protected by clothes, inaccessible for the flies. A large number of fly species may cause urinary myiasis. Larvae of Fannia scalaris is the most frequent cause of urinary myiasis. Other fly genera Musca, Sarcophaga, Lucilia, Wohlfahrtia or Calliphora were also associated with cases of urinary myiasis. Few cases of urinary myiasis were caused by Eristalis, Psychoda and Megaselia flies. Cases of urinary myiasis were caused by larvae of Clogmia albipunctata worldwide but had never been reported before in our region. Keywords: Clogmia Albipunctata; Egypt; Human Myiasis.
Faculty of Oral Dental Medicine

Dept. of Endodontics


Hend Mahmoud Abou El Nasr and Karim Galal Abd El Kader


Introduction: Vertical root fracture is a common finding in endodontically treated teeth, notably oval roots. The aim of the present study was to determine the effect of instrumentation kinematics and the material of instrument construction of single-file systems on dentin walls and fracture resistance of oval roots.

Methods: Sixty five roots with oval canals were classified into a control group (n=5) and 3 experimental groups of 20 roots each. Group 1 was instrumented with WaveOne primary file; group 2 was prepared with F2 ProTaper files used in a reciprocating motion; and group 3 was prepared with F2 ProTaper files used in a rotation motion. For crack evaluation, half of the samples (n=30) was embedded in acrylic resin and the blocks were sectioned at 3, 6, and 9mm from the apex. The sections were examined under a stereomicroscope and scored for crack presence. The other half of the specimens (n=30) was obturated using lateral condensation of gutta percha and AdSeal sealer. The specimens were then subjected to a load of 1mm/min to determine the force required to fracture the roots. Results: WaveOne instruments induced the least amount of cracks and exhibited the greatest resistance to fracture compared to ProTaper F2 files whether used in reciprocating or rotating motions.

Conclusion: The material of manufacturing is a more important factor determining the dentin damaging potential of single-file instruments than the motion of instrumentation.

Keywords: Crack; M-Wire; Oval canals; Protaper; Reciprocation; Root fracture; Waveone.

Dept. of Operative Dentistry

822. Reinforcement of Teeth With Simulated Coronal Fracture and Immature Weakened Roots Using Resin Composite Cured by a Modified Layering Technique

Reham S Seyam and Enas H Mobarak


Objective: The purpose of this study was to evaluate the strengthening effect of resin composite, cured by a modified layering protocol, for teeth with simulated coronal fracture and weakened immature roots.

Methods: Fifty maxillary teeth were decoronated and their apices sectioned to standardize the length to 12 mm. Prepared teeth were equally distributed into five groups. Group 1VF root apices were flared with Pesso drills up to size 6. The roots were flared until a dentin thickness of only 1 ± 0.2 mm remained. Root ends were filled with mineral trioxide aggregate. The canals were backfilled with Vertise Flow following a modified layering protocol using two light-transmitting posts size 6 and 3. Next, a DT light post size 2 was cemented using the same material. Groups 2TS/MF and 3ED/PF were prepared and cured in the same way as group 1VF but filled with Clearfil Tri-S Bond/Majesty Flow and ED Primer II/Panavia F2.0 respectively. Group 4UF was similarly prepared but left unfilled (control). In group 5NW, roots were unfilled but similarly filled as in group 3ED/PF. After 24 hours of storage, the fracture load was measured. The degree of cure for each tested material was indirectly measured using microhardness at different root levels (cervical, middle, and apical). Data were analyzed using one-way analysis of variance followed by Newman-Keuls post hoc test.

Results: Fracture load results revealed that groups 1VF and 2TS/MF had no statistically significant difference from group 5NW (p>0.05). For each tested material, no significant difference was found among microhardness values at different root levels.

Conclusion: It may be possible to reinforce the teeth with coronal fracture and immature weakened roots to be comparable with unweakened ones when composite is applied and cured by the modified layering technique.

Dept. of Oral and Maxillofacial Surgery


Al-Moraissi ÊÁ, El-Sharkawy TM, El-Ghareeb TI and Chrancovic BR


The aim of the present study was to test whether there is a significant difference in the clinical outcomes between standard and three-dimensional (3D) miniplate fixation in the management of mandibular angle fractures (MAFs). An electronic search without date and language restrictions was performed in October 2013. Inclusion criteria were studies in humans including randomized controlled trials, controlled clinical trials, and retrospective studies, with the aim of comparing the two techniques. Six studies were included. The meta-analyses revealed statistically significant differences for the incidence of hardware failure and postoperative trismus. There were no significant differences in the incidence of postoperative infection, malocclusion, wound dehiscence, non-union/malunion, or paresthesia. The cumulative odds ratio was 0.42, meaning that the use of 3D miniplates in the fixation of MAFs decreases the risk of the event (postoperative complication) by 58%. The results of this meta-analysis showed lower postoperative complication rates with the use of 3D miniplate fixation in comparison with the use of standard miniplate fixation in the management of MAFs.

Keywords: Mandibular Angle Fracture; Surgical treatment; Rigid Fixation; Conventional Miniplate; 3D Miniplate; Complications.

824. Segment Tilting Associated With Surgically Assisted Rapid Maxillary Expansion

Emad Tawfik Daif


This study aimed to evaluate, via computed tomography, the direction and magnitude of the segmental tilting that may occur after surgically assisted rapid maxillary expansion (SARME) in patients with a transverse maxillary deficiency. Thirty adult patients with a transverse maxillary deficiency greater than 5 mm were treated by SARME. The procedures consisted of bilateral

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zygomatic buttress and midpalatal osteotomies combined with the use of a tooth-borne orthopaedic device postoperatively. Axial and coronal images were obtained before and 6 months after SARME to evaluate the segment tilting. The greatest expansion occurred in the most inferior (5.4 ± 1.1 mm) and anterior (4.0 ± 1.3 mm) regions of the maxilla. The expanded segment tilted outward inferiorly and anteriorly in coronal and axial images, respectively. The segment tilting was 2.0 mm (2.3%) inferiorly and 3.1 mm (12.8%) anteriorly. It can be concluded that an outward tilting occurs in the most inferior and anterior portions of the maxilla during SARME procedures. Hence the direction and magnitude of such segmental tilting must be considered preoperatively when determining the surgical objectives.

**Keywords:** Maxillary deficiency; Sarm; Segmental tilting.

### 825. Correlation of plates’ number with complications of osteosynthesis in mandibular fractures

Daif ET


**IF:** 0.676

**Objectives:** This study aimed to assess the correlation of the miniplates’ number used for fixation of single-compound symphysal and parasymphysal fractures with the osteosynthesis complications.

**Patients And Methods:** Two hundred eighty-five patients having miniplate osteosynthesis complications participated in this study. They were classified into 3 groups according to the number of miniplates used for the fixation of the fractured segments. The first group included patients having 2 miniplates, whereas the second and third groups included patients having 4 miniplates and more than 4 miniplates, respectively.

**Results:** The main osteosynthesis complications were malocclusion (32%) infection with an extraoral fistula (21%), wound dehiscence with intraoral exposure of the miniplates (17%), and combination of these (13%). Lower lip affection and intraoral bone exposure were 11% and 6%, respectively. Malocclusion was the most common complication in each group and showed the highest rate (62%) in the first group. Infection with extraoral fistula was found in all groups, with the highest rate (27%) in the first group. Wound dehiscence with intraoral exposure of the miniplates was present in the 3 groups, and the third group had the highest rate (19%). The second and third groups had equal rates of lower lip affection, numbness or weakness (12%) and intraoral bone exposure (7%). In addition, they had combined complications in rates of 16% and 13%, respectively.

**Conclusions:** The use of 2 miniplates for the fixation of single-compound symphysal and parasymphysal fractures is quite enough to avoid osteosynthesis complications such as wound dehiscence, bone or plate exposure, and lower lip affection.

### Dept. of Oral Biology

#### 826. the Ability of H1 or H2 Receptor Antagonists or their Combination in Counteracting the Glucocorticoid-Induced Alveolar Bone Loss in Rats

Bassant A. Ezzat and Marwa M.S. Abbass

*Journal of Oral Pathology and Medicine, 43: 148-156 (2014)*

**IF:** 1.87

**Objective:** The aim of the present study was to compare between three possible osteoporotic treatments in prevention of glucocorticoid-induced alveolar bone loss.

**Design:** Fifty adult female Wistar rats with an average weight 150-200 g were randomized into 5 groups, control, glucocorticoid administration, glucocorticoid administration with concomitant administration of H1 receptor antagonist, H2 receptor antagonist or H1 and H2 receptor antagonists. After 30 days, the rats have been sacrificed. The mandibles were examined histologically, histomorphometrically and histochemically. The bone mineral density was measured using DEXA.

**Results:** Histopathologically the glucocorticoid group showed wide medullary cavities with wide osteocytic lacunae. These narrow cavities were reduced in the prophylactic groups (III, IV) but increased in group V. Histomorphometric analysis showed significant reduction in area percentage of bone in groups II, IV and V (p<0.0001) and group III (p=0.0158) when compared to the control group I. Histochemical results demonstrated positive TRAP reaction in osteocytes’ lacunae and along bone resorbing surface of all experimental groups. The DEXA revealed significant reduction in the bone density in all experimental groups compared to the control group.

**Conclusions:** Patients initiating glucocorticoid treatment should be concomitantly treated with effective osteoporosis therapy to reduce fracture risk and counseled on preventive lifestyle changes.

**Keywords:** H1 Receptor Antagonist, H2 Receptor Antagonist, Dexa, Glucocorticoids.

### Dept. of Oral Medicine and Periodontology

#### 827. IL-18 Gene Polymorphisms in Aphthous Stomatitis Vs Behcets Disease in A Cohort of Egyptian Patients

Hala H. A. Hazzaa, Weam A. Rashwan and Enas A. S. Attia

*J Oral Pathol Med, 43: 746-753 (2014)*

**IF:** 1.87

A clinical investigation of the potential correlation of two single-nucleotide polymorphisms at 137 (G/C) and 607 (C/A) in the promoter region of the IL–18 gene, with the susceptibility to aphthous stomatitis and Behcet’s disease.

**Patient and Methods:** This study included 80 aphthous stomatitis patients and 80 patients with Behcet’s disease. Eighty healthy subjects were enrolled as a control group. IL-18 single-nucleotide polymorphisms at 607 and 137 regions were analyzed using polymerase chain reaction–restriction fragment length polymorphism analysis.

**Results:** The genotype and allele distributions of the two regions did not differ significantly between patients with aphthous stomatitis and controls. The genotype and allele distributions at 607 were significantly different between patients with Behcet’s disease [CC (P = 0.044), C allele (P = 0.043), A allele (P = 0.043)], and controls. The frequency of the GG genotype at position 137 in patients with Behcet’s disease was associated only with a higher rate of ocular manifestations (OR= 1.4, CI= 0.76–2.7, P = 0.031).

**Conclusion:** IL-18 gene polymorphisms were not associated with any susceptibility to aphthous stomatitis, while a positive association was found with patients with Behcet’s disease regarding 607 promoter site. Moreover, patients with Behcet’s disease carrying theGGgenotype at position 137 had a higher risk of developing ocular manifestations.
Keywords: Aphthous Stomatitis; BehcEt’S Disease; Gene Polymorphism;

Dept. of Oral Pathology

828. Chemopreventive Effect of Mentha Piperita on Dimethylbenz(a)Anthracene and Formaldehyde-Induced Tung Carcinogenesis in Mice (Histological And Immunohistochemical Study)

Rehab F. Kasem, Radwa H. Hegazy, Mona A. A. Arafa and Mona M. Abdel Mohsen

Journal of Oral Pathology and Medicine, 43: 484-491 (2014) IF: 1.87

Objective: Cancer chemoprevention is defined as the use of chemicals or dietary components to block, inhibit, or reverse the development of cancer in normal or preneoplastic tissue. Mentha extract (ME) has antioxidant and antiperoxidant properties. This study was held to investigate the protective and anticancer effect of Mentha leaves aqueous extract on oral epithelium of mice tongues.

Design: A total of 80 Egyptian albino mice were divided into three groups. Group I served as control (not subjected to any kind of treatment), and groups II and III were subjected to two-stage chemical carcinogenesis through topical application of dimethylbenz[a]anthracene (DMBA) followed by formaldehyde on dorsal and ventral surfaces of tongues for 9 weeks. Mentha leaves extract was administrated to group III at the same time of cancer induction. Histological changes were assessed in H&E sections at 3-week intervals. The anticarcinogenic effect of Mentha piperita was tested using immunostain with anticaspase antibody.

Results: The oral administration of ME reduced the appearance of dysplastic cellular changes with 61% and inhibited tumor incidence with 100%. Group I showed moderate-to-strong cytoplasmic caspase expression. At 6-week interval, group II showed weak-to-moderate caspase expression, while sections from group III showed moderate-to-strong caspase expression. High significant statistical difference in the total score of caspase 3 expression was found between specimens obtained from animals sacrificed at 6 weeks in groups I, II, and III (P = 0.001**).

Conclusion: Our study demonstrated that Mentha piperita has inhibited the initiation and promotion of oral dysplastic lesions.

Keywords: Carcinogenesis Induction; Chemoprevention; Dimethylbenz [A] Anthraceneformaldehyde; Menthapiperita; Micetongues.

Dept. of Prosthetic Dentistry

829. Evaluation of Metal Ion Release from Ti6Al4V and CO-CR-MO Casting Alloys: in Vivo and in Vitro Study

Amal A. El Sawy and Mohammed A. Shaarawy

Journal of Prosthodontics, 23(2): 89-97 (2014) IF: 0.905

Purpose: The aim of this study was to evaluate the amount of ions released from Ti6Al4V and Co-Cr-Mo alloys both in vivo and in vitro.

Materials and Methods: Twenty-one discs of each alloy were constructed and divided into seven groups. Three specimens from each group were immersed in a buffered saline solution over a period of 1, 3, 5, 7, 14, 21, and 28 days. Twenty-eight participants were also included in the study, where the study group consisted of 14 mandibular partially edentulous patients, and the control group consisted of 14 volunteers. The study group was further divided into two equal groups: the first group received removable partial dentures (RPDs) constructed from Co-Cr-Mo alloy, while the second group received RPDs constructed from Ti6Al4V alloy. Saliva samples were collected from each participant over the same study period. The conditioning media and saliva samples were analyzed using a spectrophotometer. One-way ANOVA and Tukey tests were used for statistical analysis (p < 0.05).

Results: The concentrations of metal ions released from the studied alloys were significantly higher in the in vitro than in the in vivo study group during the follow-up periods. A statistically significant increase in ion concentrations of the different elements for both alloys was found with time (p < 0.05).

Conclusion: The amounts of released metallic ions from Co-Cr-Mo and Ti6Al4V alloys were higher in the buffered saline solutions than in the studied saliva samples and control groups; however, these amounts were still within the physiological limit of trace elements in the human body.

Keywords: Ti6Al4V Alloy; Co-Cr-Mo Alloy; Metal Ion Release; Metal Ion Concentration; Removable Partial Dentures.
Faculty of Pharmacy
Dept. of Analytical Chemistry

830. Advantages of the incorporation of 2-hydroxyl propyl beta cyclodextrin and calixarene as ionophores in potentiometric ion-selective electrodes for rivastigmine with a kinetic study of its alkaline degradation
Mohamed Abdalla Elsayed

Sensors and Actuators B: Chemical, 190: 101-110 (2014) IF: 3.84

Three selective electrodes were investigated for rivastigmine (RIV). Sensor 1 was fabricated using ammonium reineckate (RNC) as a cation exchanger without incorporation of any ionophore. Sensors 2 and 3 used 2-hydroxy propyl beta-cyclodextrin and 4-sulfocalix-8-arene as ionophores respectively in addition to RNC as a cation exchanger. Linear responses of RIV within the concentration ranges of 10^{-3} to 10^{-2}, 10^{-2} to 10^{-1} and 5 \times 10^{-2} to 10^{-1} M with Nernstian slopes of 51.5 \pm 0.8, 54.6 \pm 0.7 and 56.8 \pm 0.4 mV/amp/decade over the pH range of 4–7 were obtained using sensors 1, 2 and 3, respectively. The utility of ionophores had a significant influence on increasing the membrane sensitivity and selectivity of sensors 2 and 3 compared to sensor 1. The proposed sensors displayed useful analytical characteristics for the determination of RIV in pharmaceuticals, biological fluids and in the presence of its degradation product and thus could be used for stability-indicating assays. Sensor 3 was used to study the kinetics of RIV alkaline degradation that was found to follow a pseudo first-order reaction. The activation energy could be estimated from the Arrhenius plot to be 9.864 kcal mol^{-1}.

Keywords: Rivastigmine; 2-Hydroxy propyl beta-cyclodextrin; 4-Sulfocalix-8-arene; Ionophore; Stability-indicating methods; Kinetic study.

831. Validated Liquid Chromatographic Determination of Anovel ACE Inhibitor in the Presence of its Hydrolytic and Oxidative Degradation Products as Perich Guidelines
Maha A. Hegazy, Maya S. Eissa, Osama A bdEl-Sattar and Mohamed M. AbdEl-Kawy

Imidapril hydrochloride (IMD) is a recently developed prodrug-type angiotensin-converting enzyme (ACE) inhibitor. Due to its instability under both hydrolytic and oxidative conditions, development of rapid, simple and sensitive methods for its determination in the presence of its possible degradation products is essential. We proposed two simple liquid chromatographic methods associated with ultraviolet detection. The first method is an HPTLC-densitometric one in which separation of IMD from its degradation products was achieved followed by densitometric scanning at 220 nm using silica gel F254 plates and chloroform:ethanol:acetic acid (3:0.5:0.1, v/v/v) as the developing system. The second method was based on RP-HPLC in which the separation was performed using C18 analytical column and isocratic elution system with acetonitrile: 0.15% triethylamine (pH=2.2) (40:60, v/v). The optimum flow rate was 1.5 mL min^{-1} and the detection was at 220 nm. Validation was conducted in compliance with the ICH guidelines and the methods were successfully applied for IMD determination in its commercial tablets. The obtained results were statistically compared to those obtained by applying reported HPLC method where no significant difference was found in accordance with accuracy and precision.

Keywords: AKN; DKP; Degradation products; ES; HPLC; HPTLC; IMD; Imidapril hydrochloride; OXI; Stability-indicating method; diketopiprazine; External standard; Imidapril hydrochloride; Suggested alkaline induced degradation product of imidapril hydrochloride; Suggested oxidative induced degradation product of imidapril hydrochloride.

Heba-Alla H. Abd-ElSalam, Medhat A. Al-Ghobashy, Hala E. Zaa8 and Mohamed A. Ibrahim

Epigallocatechin gallate (EGCG) is a powerful antioxidant and commonly used nutraceutical. Accelerated stability of EGCG in tablet formulations was investigated. LLE and SPE were employed for sample clean-up and enrichment of EGCG over caffeine. Samples were analysed after spiking with fixed concentration of gallic acid (GA), in order to verify reproducibility of analysis. A TLC–densitometric assay was developed and validated for determination of % loss EGCG. EGCG, GA and caffeine were resolved with Rf values 0.54, 0.69 and 0.80, respectively. LC–MS/MS was used to verify identity and purity of the EGCG band. Determination was carried out over a concentration range of 0.50–5.00 µg/band and 0.20–2.40 µg/band for GA and caffeine, respectively. Results showed significant reduction in EGCG content after one, three and six months: 24.00%, 28.00% and 52.00% respectively. Results continue to demonstrate that stability of nutraceutical products should be investigated in-depth using industry-oriented protocols before granting marketing authorization.

Keywords: Nutraceuticals; Catechins; Epigallocatechin Gallate; Solid Phase Extraction; Tlc–Densitometry; Accelerated Stability; Gallic Acid Equivalent.

833. Chromatographic and Electrophoretic Assessment of Filgrastim Biosimilars in Pharmaceutical Formulations
Eman L. Shaltout, Medhat A. Al-Ghobashy, Faten A. Fathalla and Maissa Y. Salem
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An orthogonal testing protocol was developed and validated to assess the quality of Filgrastim biosimilars. Results were compared to those obtained from the innovator product. Initial screening was carried out using reducing and non-reducing gel electrophoresis. RP-LC was employed for the determination of Filgrastim in the presence of its oxidative degradation products. SEC and CIEF were used under non-denaturing conditions to reveal high molecular weight and charged impurities, respectively. RP-LC assay was found accurate (99.78 ± 0.89) and precise over a linear concentration range of 9.38–300.00 µg/ml with a LOD of 8.26 µg/ml (0.44 mM). SEC was carried out over a molecular weight range of 5.0–150.0 kDa. CIEF was optimized.
using neutrally coated capillaries over a wide-range pH gradient (pH 3.0–10.0). Differences between the studied products were revealed using all these techniques. Impurities above the acceptable limits were detected in both biosimilar products. CIEF revealed heterogeneity in the active ingredient that has not been investigated by the manufacturers. Correlation of the obtained results indicated the presence of not only product-related impurities, but also process-related impurities. Results confirmed the need for in-house validated orthogonal testing protocols to be developed by local regulatory authorities. This should prevent access of substandard biosimilars to price-sensitive markets.

**Keywords**: Filgrastim; Biosimilars; Rp-Hplc; Capillary Isoelectric Focusing; Size exclusion; Chromatography

834. Development, Optimization and Validation of A Highly Sensitive UPLC-ESI-MS/MS Method for Simultaneous Quantification of Amlodipine, Benazepril and Benazeprilat in Human Plasma: Application to A Bioequivalence Study

Mamdouh R. Rezka and Kamal A. Badrb


A rapid, simple, sensitive and specific LC-MS/MS method has been developed and validated for the simultaneous estimation of amlodipine (AML), benazepril (BEN) and benazeprilat (BNT) using eplerenone and torsemide as internal standards (IS). The Xevo TQD LC–MS/MS was operated under the multiple-reaction monitoring mode using electrospray ionization. Sample preparation involves both extraction and precipitation techniques. The reconstituted samples were chromatographed on Acquity UPLC BEH C18 (50 mm × 2.1 mm, 1.7 m) column by pumping 0.1% formic acid and acetonitrile in a gradient mode at a flow rate of 0.45 ml/min. A detailed validation of the method was performed as per the FDA guidelines and the standard curves were found to be linear in the range of 0.1–5 ng/ml for AML; 5–1200 ng/ml for both BEN and BNT. The intra-day and inter-day precision and accuracy results were within the acceptable limits. A run time of 2.5 min for each sample made it possible to analyze more than 300 human plasma samples per day. The developed assay method was successfully applied to a bioequivalence study in human volunteers.

**Keywords**: Amlodipine; Benazepril; Benazeprilat; Bioequivalence; Uplc–Ms/MS.

835. A Comparative Study of Novel Spectrophotometric Methods Based on Isosbestic Points; Application on A Pharmaceutical Ternary Mixture

Hayam M. Lotfy, Sarah S. Saleh, Nagiba Y. Hassan and Hesham Salem


This work represents the application of the isosbestic points present in different absorption spectra. Three novel spectrophotometric methods were developed, the first method is the absorption subtraction method (AS) utilizing the isosbestic point in zero-order absorption spectra; the second method is the amplitude modulation method (AM) utilizing the isosbestic point in ratio spectra; and third method is the amplitude summation method (A-Sum) utilizing the isosbestic point in derivative spectra. The three methods were applied for the analysis of the ternary mixture of chloramphenicol (CHL), dexamethasone sodium phosphate (DXM) and tetryzoline hydrochloride (TZH) in eye drops in the presence of benzalkonium chloride as a preservative. The components at the isosbestic point were determined using the corresponding unified regression equation at this point with no need for a complementary method. The obtained results were statistically compared to each other and to that of the developed PLS model. The specificity of the developed methods was investigated by analyzing laboratory prepared mixtures and the combined dosage form. The methods were validated as per ICH guidelines where accuracy, repeatability, inter-day precision and robustness were found to be within the acceptable limits. The results obtained from the proposed methods were statistically compared with official ones where no significant difference was observed.

**Keywords**: Isosbestic Point; Absorption Subtraction Method; Amplitude Modulation Method; Chloramphenicol; Dexamethasone.


Sarah S. Saleh, Hayam M. Lotfy, Nagiba Y. Hassan and Hesham Salem


This work represents a comparative study of a novel progressive spectrophotometric resolution technique namely, amplitude center method (ACM), versus the well-established successive spectrophotometric resolution techniques namely; successive derivative subtraction (SDS); successive derivative of ratio spectra (SDR) and mean centering of ratio spectra (MCR). All the proposed spectrophotometric techniques consist of several consecutive steps utilizing ratio and/or derivative spectra. The novel amplitude center method (ACM) can be used for the determination of ternary mixtures using single divisor where the concentrations of the components are determined through progressive manipulation performed on the same ratio spectrum. Those methods were applied for the analysis of the ternary mixture of chloramphenicol (CHL), dexamethasone sodium phosphate (DXM) and tetryzoline hydrochloride (TZH) in eye drops in the presence of benzalkonium chloride as a preservative. The proposed methods were checked using laboratory-prepared mixtures and were successfully applied for the analysis of pharmaceutical formulation containing the cited drugs. The proposed methods were validated according to the ICH guidelines.

A comparative study was conducted between those methods regarding simplicity, limitation and sensitivity. The obtained results were statistically compared with those obtained from the official BP methods, showing no significant difference with respect to accuracy and precision.

**Keywords**: Amplitude center Method; Successive derivative Subtraction successive Derivative ratio Chloramphenicol; Dexamethasone; Tetryzoline.
837. Development and Validation of Simultaneous Spectrophotometric and TLC-Spectrodensitometric Methods for Determination of Beclamethasone Dipropionate and Salbutamol in Combined Dosage Form
Ahmed Samir, Hayam M. Lotfy, Hesham Salem and Mohammed Abdelkawy

Spectrophotometric and TLC-spectrodensitometric methods were developed and validated for the simultaneous determination of beclamethasone dipropionate (BEC) and salbutamol (SAL). The spectrophotometric methods include dual wavelength, ratio difference, constant center coupled with a novel method namely, spectrum subtraction and mean centering with mean percentage recoveries and RSD 99.72 ± 1.07 and 99.70 ± 1.12, 100.25 ± 1.12 and 99.89 ± 1.12, 99.66 ± 1.85 and 99.19 ± 1.32, 100.74 ± 1.26 and 101.06 ± 0.90 for BEC and SAL respectively. The TLC-spectrodensitometric method was based on separation of both drugs on TLC aluminum plates of silica gel 60 F254, using benzene: methanol: triethylamine (10:1.5:0.5 v/v/v) as a mobile phase, followed by densitometric measurements of their bands at 230 nm. The mean percentage recoveries and RSD were 99.07 ± 1.25 and 101.05 ± 1.50 for BEC and SAL respectively. The proposed methods were validated according to ICH guidelines and were applied for the simultaneous analysis of the cited drugs in synthetic mixtures and pharmaceutical preparation. The methods were found to be rapid, specific, precise and accurate and can be successfully applied for the routine analysis of BEC and SAL in their pharmaceutical formulation with no need for prior separation. The results obtained were statistically compared to each other and to that of the reported HPLC method. The statistical comparison showed that there is no significant difference regarding both accuracy and precision.

Keywords: Ratio difference; Constant center; Spectrum subtraction; Mean centering; Salbutamol; Beclamethasone; Dipropionate.

838. Different Approaches in Partial Least Squares and Artificial Neural Network Models Applied for the Analysis of A Ternary Mixture of Amlodipine, Valsartan and Hydrochlorothiazide
Darwish HW, Hassan SA, Salem MY and El-Zeany

Different chemometric models were applied for the quantitative analysis of Amlodipine (AML), Valsartan (VAL) and Hydrochlorothiazide (HCT) in ternary mixture, namely, Partial Least Squares (PLS) as traditional chemometric model and Artificial Neural Networks (ANN) as advanced model. PLS and ANN were applied with and without variable selection procedure (Genetic Algorithm GA) and data compression procedure (Principal Component Analysis PCA). The chemometric methods applied are PLS-1, GA-PLS, ANN, GA-ANN and PCA-ANN. The methods were used for the quantitative analysis of the drugs in raw materials and pharmaceutical dosage form via handling the UV spectral data. A 3-factor 5-level experimental design was established resulting in 25 mixtures containing different ratios of the drugs. Fifteen mixtures were used as a calibration set and the other ten mixtures were used as validation set to validate the prediction ability of the suggested methods. The validity of the proposed methods was assessed using the standard addition technique.

Keywords: PLS; Ann; Ga; Amlodipine; Valsartan; Hydrochlorothiazide.

839. Kinetic Study and Mechanism of Niclosamide Degradation
Hala E. Zaazaa, Maha M. Abdelrahman, Nouruddin W. Ali, Maimana A. Magdy and M. Abdelkawy

A spectrophotometric kinetic study of Niclosamide alkaline degradation as a function of drug concentration, alkaline concentration and temperature has been established utilizing double divisor-ratio spectra spectrophotometric method. The developed method allowed determination of Niclosamide in presence of its alkaline degradation products; namely, 2-chloro-4-nitro aniline (DEG I) and 5-chloro salicylic acid (DEG II) with characterization of its degradation mechanism. It was found that degradation kinetic of Niclosamide followed pseudo-first order under the established experimental conditions with a degradation rate constant (k) of 0.0829 mol/h and half life (1/2) of 8.35 h. The overall degradation rate constant as a function of the temperature under the given conditions obeyed Arrhenius equation where the activation energy was calculated to be 3.41 kcal/mol.

Keywords: Niclosamide-Double Divisor-Ratio Spectra-Spectrophotometry-Degradation.

Naguib IA, Abdelaleem EA, Draz ME and Zaazaa.

A spectrophotometric kinetic study of Niclosamide alkaline degradation as a function of drug concentration, alkaline concentration and temperature has been established utilizing double divisor-ratio spectra spectrophotometric method. The developed method allowed determination of Niclosamide in presence of its alkaline degradation products; namely, 2-chloro-4-nitro aniline (DEG I) and 5-chloro salicylic acid (DEG II) with characterization of its degradation mechanism. It was found that degradation kinetic of Niclosamide followed pseudo-first order under the established experimental conditions with a degradation rate constant (k) of 0.0829 mol/h and half life (1/2) of 8.35 h. The overall degradation rate constant as a function of the temperature under the given conditions obeyed Arrhenius equation where the activation energy was calculated to be 3.41 kcal/mol.

Keywords: Niclosamide-Double Divisor-Ratio Spectra-Spectrophotometry-Degradation.
841. Novel Spectrophotometric Methods for Simultaneous Determination of Timolol and Dorzolamide in their Binary Mixture

Hayam Mahmoud Lotfy, Maha A. Hegazy, Mamdouh R. Rezk and Yasmin Rostom Omran


Two smart and novel spectrophotometric methods namely; absorbance subtraction (AS) and amplitude modulation (AM) were developed and validated for the determination of a binary mixture of timolol maleate (TIM) and dorzolamide hydrochloride (DOR) in presence of benzalkonium chloride without prior separation, using unified regression equation. Additionally, simple, specific, accurate and precise spectrophotometric methods manipulating ratio spectra were developed and validated for simultaneous determination of the binary mixture namely; simultaneous ratio subtraction (SRS), ratio difference (RD), ratio subtraction (RS) coupled with extended ratio subtraction (EXRS), constant multiplication method (CM) and mean centering of ratio spectra (MCR). The proposed spectrophotometric procedures do not require any separation steps. Accuracy, precision and linearity ranges of the proposed methods were determined and the specificity was assessed by analyzing synthetic mixtures of both drugs. They were applied to their pharmaceutical formulation and the results obtained were statistically compared to that of a reported spectrophotometric method. The statistical comparison showed that there is no significant difference between the proposed methods and the reported one regarding both accuracy and precision.

**Keywords:** Absorbance; Subtraction; Amplitude; Modulation; Dorzolamide Hydrochloride; Ratio spectra And Timolol Maleate.

842. Simultaneous Determination of Some Anti-Hypertensive Drugs in Their Binary Mixture By Novel Spectrophotometric Methods

Yasmin Mohammed Fayez


Three simple, accurate and precise spectrophotometric methods manipulating ratio spectra were developed and validated for simultaneous determination of Irbesartan (IRB) and Hydrochlorothiazide (HCT) without prior separation namely; ratio subtraction coupled with constant multiplication (RS-CM), ratio difference (RD) and constant center (CC). The accuracy, precision and linearity ranges of the proposed methods were determined, and the methods were validated and the specificity was assessed by analyzing synthetic mixtures containing the cited drugs. The three methods were applied for the determination of the cited drugs in tablets and the obtained results were statistically compared with each other and with those of official methods. The comparison showed that there is no significant difference between the proposed methods and the official methods regarding both accuracy and precision.

**Keywords:** Hydrochlorothiazide;Benazepril Hydrochloride;Chemometrics-Pls, Svr.

843. Spectrophotometric Methods for Simultaneous Determination of Ternary Mixture of Amlodipine Besylate, Olmesartan Medoxomil and Hydrochlorothiazide

Hanan A. Merey, Nesrin K. Ramadan, Sherine S. Diab, Azza A. Moustafa


Four, accurate, precise, and sensitive spectrophotometric methods are developed for the simultaneous determination of a ternary mixture containing amlodipine besylate (AM), olmesartan medoxomil (OL) and hydrochlorothiazide (HZ), where AM is determined at its λ(max) 364.6 nm (λD), while (OL) and (HZ) are determined by different methods. Method (A) depends on determining OL and HZ by measuring the second derivative of the ratio spectra (λD) at 254.4 and 338.6 nm, respectively. Method (B) is first derivative of the double divisor ratio spectra (D-1λD) at 260.4 and 273.0 nm for OL and HZ, respectively. Method (C) based on successive spectrophotometric resolution technique (SSRT). The technique starts with the ratio subtraction method then measuring OL and HZ at their isosorptive point at 260.0 nm, while HZ is measured using the amplitude of first derivative at 335.2 nm. Method (D) is mean centering of the ratio spectra (MCR) at 252.0 nm and 220.0 nm for OL and HZ, respectively. The specificity of the developed methods is investigated by analyzing laboratory prepared mixtures containing different ratios of the three drugs and their combined dosage form. The obtained results are statistically compared with those obtained by the official or reported methods, showing no significant difference with respect to accuracy and precision at p=0.05.

**Keywords:** Ternary mixture; First derivative ratio spectra; Double Divisor;Successive Spectrophotometry; Iosabsorptive Point; Mean centering.


H. Moustafa and Y. Fayez


Three simple, specific and accurate spectrophotometric methods manipulating ratio spectra were developed and validated for simultaneous determination of Rabeprazole sodium (RB) and Domperidone (DP) in their binary mixture without prior separation. Method A, is constant center spectrophotometric method (CC). Method B is a ratio difference spectrophotometric one (RD), while method C is a combined ratio isosorptive point-ratio difference method (IRR). Linear correlations were obtained in range of 4-44µg/mL, for both Rabeprazole sodium and
Domperidone. The mean percentage recoveries of RB were 99.69±0.504 for method A, 99.83±0.483 for (B) and 100.31±0.499 for (C), respectively, and that of DP were 99.52±0.474 for method A, 100.12±0.505 for (B) and 100.16±0.498 for (C), respectively. Specificity was investigated by analysis of laboratory prepared mixtures containing the cited drugs and their combined tablet dosage form. The obtained results were statistically compared with those obtained by the reported methods, showing no significant difference with respect to accuracy and precision. The three methods were validated as per ICH guidelines and can be applied for routine analysis in quality control laboratories.

Keywords: Domperidone; Rabeprazole; Constant center; Ratio Difference; Ratio isosbestic; Spectroscopy.

### 845. Successive Spectrophotometric Resolution as a Novel Technique for the Analysis of Ternary Mixtures of Pharmaceuticals

Lotfy HM, Tawakkol SM, Fahmy NM and Shehata


A novel spectrophotometric technique was developed for the simultaneous determination of ternary mixtures, without prior separation steps. This technique was called successive spectrophotometric resolution technique. The technique was based on either the successive ratio subtraction or successive derivative subtraction. The mathematical explanation of the procedure was illustrated. In order to evaluate the applicability of the methods a model data as well as an experimental data were tested. The results from experimental data related to the simultaneous spectrophotometric determination of lidocaine hydrochloride (LH), calcium dobesilate (CD) and dexamethasone acetate (DA); in the presence of hydroquinone (HQ), the degradation product of calcium dobesilate were discussed.

The proposed drugs were determined at their maxima 202 nm, 305 nm, 239 nm and 225 nm for LH, CD, DA and HQ respectively; by successive ratio subtraction coupled with constant multiplication method to obtain the zero order absorption spectra, while by applying successive derivative subtraction they were determined at their first derivative spectra at 210 nm for LH, 320 nm or P292-320 for CD, 256 nm or P325-233 for HQ respectively. The calibration curves were linear over the concentration range of 2-20 μg/mL for both LH and DA, 6-50 μg/mL for CD, and 3-40 μg/mL for HQ. The proposed methods were checked using laboratory-prepared mixtures and were successfully applied for the analysis of pharmaceutical formulation containing the cited drugs with no interference from other dosage form additives.

The proposed methods were validated according to the ICH guidelines. The obtained results were statistically compared with those of the official BP methods for LH, DA, and CD, and with the official USP method for HQ; using student t-test, F-test, and one way ANOVA, showing no significant difference with respect to accuracy and precision.

Keywords: Lidocaine Hydrochloride; Dexamethasone Acetate; Calcium Dobesilate; Successive Ratio Subtraction; Successive Spectrophotometric Resolution Technique.

### 846. Two and Three Way Spectrophotometric-Assisted Multivariate Determination of Linezolid in the Presence of Its Alkaline and Oxidative Degradation Products and Application To Pharmaceutical Formulation

Maha Abd El-Monem Hegazy, Maya Shaaban Eissa, Osama Ibrahim El-Sattar and Mohammad Abd El-Kawy


Linezolid (LIN) is determined in the presence of its alkaline (ALK) and oxidative (OXD) degradation products without preliminary separation based on ultraviolet spectrophotometry using two-way chemometric methods; principal component regression (PCR) and partial least-squares (PLS), and three-way chemometric methods; parallel factor analysis (PARAFAC) and multi-way partial least squares (N-PLS). A training set of mixtures containing LIN, ALK and OXD; was prepared in the concentration ranges of 12-18, 2.4-3.6 and 1.2-1.8 μg mL⁻¹, respectively according to a multilevel multivariable experimental design. The multivariate calibrations were obtained by measuring the zero-order absorbance from 220 to 320 nm using the training set. The validation of the multivariate methods was realized by analyzing their synthetic mixtures. The capabilities of the chemometric analysis methods for the analysis of real samples were evaluated by determination of LIN in its pharmaceutical preparation with satisfactory results. The accuracy of the methods, evaluated through the root mean square error of prediction (RMSEP), was 0.058, 0.026, 0.101 and 0.026 for LIN using PCR, PLS, PARAFAC and N-PLS, respectively. Protolytic equilibria of LIN and its degradation products were evaluated using the corresponding absorption spectra-pH data obtained with PARAFAC. The obtained pKₐ values of LIN, ALK and OXD are 5.70, 8.90 and 6.15, respectively. The results obtained were statistically compared to that of a reported HPLC method, and there was no significant difference between the proposed methods and the reported method regarding both accuracy and precision.


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In this contribution, two novel way supported and non-supported ruthenium(II) complexes of type [RuCl₂(dppme)(NN)] where [dppme is H₂C=C(CH₂PPh₂)₂] and NN is N₁-3-(trimethoxysilyl)propyl)ethane-1,2-diamine were prepared. The NN co-ligand caused release of one of the dppme ligands from [RuCl₂(dppme)], to precursor to yield complex 1. The process of substitution of dppme by NN was monitored by ³¹P{¹H}-NMR. Taking advantage of the presence of trimethoxy silane group in the backbone of complex 1, polysiloxane xerogel counterpart, X₁, was prepared via sol-gel immobilization using tetraethoxysilane.
as cross-linker. Both complexes I and XI have been characterized via elemental analysis, CV and a number of spectroscopic techniques including FT-IR, 1H-, 13C-, and 31P-NMR, and mass spectrometry. Importantly, carbonyl selective hydrogenation was successfully accomplished under mild conditions using complex I as a homogenous catalyst and XI as a heterogeneous catalyst, respectively.

Keywords: Ru(II) Complexes; Hydrogenation; Diphosphine; Cinnamic Aldehyde; NMR.

848. Validated Simultaneous Determination of Antipyrine and Benzocaine HCl in the Presence of Benzocaine HCL Degradation Product

Hanan A. Meray and Hala E. Zaaazaa

Analytical Methods, 6: 6044-6050 (2014) IF: 1.938

Two validated, sensitive and highly selective stability-indicating methods were adopted for the simultaneous quantitative determination of antipyrine (ANT) and benzocaine HCl (BEN) in the presence of the degradation product of benzocaine HCl (p-aminobenzoic acid (PABA)). The first method was high performance liquid chromatography, where a mixture of antipyrine (ANT), benzocaine HCl (BEN) and degradation product of benzocaine HCl (PABA) is separated on a C18 ZORBAX analytical column (5 μm, 4.6 × 150 mm I.D.) using acetonitrile–phosphate buffer of pH 5.5 (25 : 75, v/v) as the mobile phase. The drugs were detected at 270 nm over a concentration range of 10–100 μg mL⁻¹ and 5–100 μg mL⁻¹, with mean percentage recoveries of 100.22% (S.D. 1.375) and 99.77% (S.D. 1.089) for antipyrine and benzocaine HCl, respectively. The second method was thin layer chromatography combined with the densitometric determination of the separated bands at 275 nm. Adequate separation was achieved using silica gel 60 F254 plates and toluene-acetone–methanol–ammonia (8 : 3 : 3 : 0.1 by volume) as the mobile phase. The proposed methods were applied for the analysis of antipyrine and benzocaine HCl in their pharmaceutical formulation, and the results were statistically compared with the reported methods.

Keywords: Antipyrine; Benzocaine; Hplc.

849. DNA Binding Test, X-Ray Crystal Structure, Spectral Studies, Tg-Dta, and Electrochemistry of [Co(2)(dmdphphen)] (dmdphphen Is 2,9-Dimethyl-4,7-Diphenyl-1,10-Phenanthroline, X = Cl, and NCS) Complexes

Mousa Al-Noaimi, Mohammed Suleiman,2 Hany W. Darwish, Ahmed H. Bakheit, Muneer Abdoh, Iyad Saadeddin, Navene Shivalingegowda, Nceurt Krishnapagowda Lokananth, Odey Bsharat, Assem Barakat and Ismail Warad


Two new neutral mixed-ligand cobalt(II) complexes, [CoCl2(dmdphphen)] 1 and [Co(NCS)2(dmdphphen)] 2, where dmdphphen is 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline, were synthesized and characterized by an elemental analysis, UV-Vis, IR, TG/DTA, cyclic voltammetry CV, and single X-ray diffraction. Complex 2 crystallized as monoclinic with a space group P21/c. Co(II) ions are located in a distorted tetrahedral environment. TG/DTA result shows that these complexes are very stable and decomposed through one-step reaction. The two complexes exhibit a quasi reversible one-electron response at −550 and 580 mV versus Cp2Fe/Cp2Fe+, which has been assigned to Co(l)/Co(II) and Co(II)/Co(III) couples. Absorption spectral studies reveal that such complexes exhibit hypochromicity during their interaction with CT-DNA.

Keywords: DNA; X-Ray; Electrochemistry.

850. Different Techniques for the Determination of Tofisopam

Nesrin K. Ramadan, Afaf O. Mohamed, Roaida M. Fouad and Azza A. Moustafa


Five simple and sensitive methods were developed for the determination of tofisopam (TF). The first four are stability-indicating depending on the determination of TF in the presence of its degradation product, while the fifth depended on the determination of TF via its degradation product. Method A was based on first and second derivative spectrophotometry, 1D and 2D, measuring the amplitude at 298 and 332 nm in the case of D¹D and at 312 and 344 nm in the case of D³D. Method B depended on measuring the peak amplitude of the first derivative of the ratio spectra D¹D at 336 nm. Method C was based on difference spectrophotometry by measuring AA at 366 nm. Method D was a TLC method using silica gel 60 F254 plates, the optimized mobile phase ethyl acetate–methanol–ammonium hydroxide 10% (8.5 + 1.0 + 0.5, v/v/v), and quantification by densitometric scanning at 315 nm. In method E, spectrofluorometry was applied for the determination of TF via its degradation product; maximum emission was 383 nm when excitation was 295 nm. Linearities were obtained in the concentration range 2–20 μg/mL for methods A, B, and C and 2–20 μg/band and 0.2–1.6 μg/mL for D and E, respectively. In method A, the mean recoveries were 99.45 ± 0.287 and 100.28 ± 0.277% at 298 and 332 nm, respectively, in the case of D¹D and 99.40 ± 0.245% and 99.50 ± 0.292% at 312 and 344 nm, respectively in the case of D³D.

The mean recovery was 100.03 ± 0.523% at 366 nm in method B. Method C showed mean recovery of 100.20 ± 0.642%. Recoveries for methods D and E were 98.98 ± 0.721 and 100.25 ± 0.282%, respectively.

The degradation product was obtained in acidic stress condition, separated, and identified by IR and mass spectral analysis, from which the degradation product was confirmed and the degradation pathway was suggested. The first four methods were specific for TF in the presence of different concentrations of its degradation product. The five proposed methods were successfully applied for the determination of TF in Nodoprine tablets. Statistical comparison among the results obtained by these methods and that obtained by the official method for the determination of the drug was made, and no significant differences were found.

Keywords: Tofisopam; Derivative; Derivative Ratio; TLC; Fluorometry.


Moustafa NM, Badawey AM, Lamie NT and El-Aleem Ael-A.


Four accurate, sensitive, and reproducible stability-indicating methods for the determination of erdosine in the presence of its...
acid degradation products are presented. The first method involves processing the spectra by using a first-derivative method at 229 nm in a concentration range of 10-70 microg/mL. The mean percentage recovery was 100.43 +/- 0.977. The second method is based on ratio-spectra first derivative spectrophotometry at 227.4 and 255 nm over a concentration range of 10-70 microg/mL. The mean percentage recovery was 99.65 +/- 1.122% and 100.02 +/- 1.306% at 227.4 and 255 nm, respectively. The third method utilizes quantitative densitometric evaluation of the TLC of erdosteine in the presence of its acid degradation products, and uses methanol-chloroform-ammonia (7 + 3 +/- 0.01, v/v/v) as the mobile phase. TLC chromatograms were scanned at 235 nm. This method analyzes erdosteine in a concentration range of 2.4-5.6 microg/spot, with a mean percentage recovery of 100.03 +/- 1.015%. The fourth method is HPLC for the simultaneous determination of erdosteine in the presence of its acid degradation products. The mobile phase consists of water-methanol (65 + 35, v/v). The standard curve of erdosteine showed good linearity over a concentration range of 10-80 microg/mL, with a mean percentage recovery of 99.90 +/- 1.207%. These methods were successfully applied to the determination of erdosteine in bulk powder, laboratory-prepared mixtures containing different percentages of the degradation products, and pharmaceutical dosage forms. The validity of results was assessed by applying the standard addition technique. The results obtained agreed statistically with those obtained by a reported method, showing no significant differences with respect to accuracy and precision. 

**Keywords:** Erdosteine; Stability-Indicating; Ratio-Spectra First Derivative; Densitometry; Hplc Technique

### 852. Stability-indicating Determination of Rebamipide in the Presence of Its Acid Degradation Products

hebatallah mohammed essam  

Four sensitive and precise stability-indicating methods for the determination of rebamipide (REB) in the presence of its acid-degradation products and in a pharmaceutical formulation were developed and validated. Method A used the first derivative of the ratio spectra (1DD) spectrophotometric method by measuring the peak amplitude at 249.4 nm (maximum) and at 259 nm (minimum), and at the total peak amplitude (from 249.4 to 259 nm). This method yielded mean recoveries of 99.87 +/- 0.83, 100.04 +/- 0.75, and 100.28 +/- 1.11%, respectively. Method B is a dual wavelength method, which allows the determination of REB in presence of its acid-degradation products by measuring the absorbance difference between 254 and 269 nm within a linearity range of 5-65 microg/mL; it showed a mean recovery of 99.84 +/- 1.06. Method C is a TLC-densitometric procedure in which REB was separated from its degradation products using a developing solution of methanol-chloroform-ammonia (8.5 + 1.5 + 0.5, v/v/v). The quantitative evaluation of REB at 329 nm was linear over the concentration range of 0.50-4.5 microg/band, with a mean recovery of 99.49 +/- 0.99% even in the presence of up to 90% degradation products. Method D is an RP-HPLC procedure. It provided the complete separation of REB from its degradation products on an XterraTM C18 column using phosphate buffer (pH 6, 0.01 M)-methanol (1 + 1, v/v) as the mobile phase (UV detection at 254 nm). Recovery was 99.28 +/- 0.78% within the range of 10-190 microg/mL. The selectivity of the proposed methods was checked using laboratory-prepared mixtures. The proposed methods have been successfully applied to the analysis of REB in pharmaceutical dosage forms without interference from other dosage form excipients.

**Keywords:** HPLC; TLC; Stability testing; Repamipide.


Heba S. Abed, Medhat A. Al-Ghobashy, Faten A. Fathalla and Maissa Y. Salem  
*Chromatographia, 77: 1661-1669 (2014) IF: 1.37*

Covalently attaching polyethylene glycol (PEGylation) to therapeutic proteins is an increasingly important tool for improving stability, pharmacokinetic and pharmacodynamic properties. In this work, degradation of pegylated interferon α-2b (mono-PEG-IFN) was induced using various physicochemical stress conditions (mechanical agitation, pH, temperature, and repeated freeze-thaw). Stability-indicating SE-HPLC assay was validated and employed for monitoring mono-PEG-IFN in the presence of all degradation products. Results were expressed in terms of percentage decrease in mono-PEG-IFN concentration (%Degradation) and peak area normalization method (%Purity). Separation was carried out using a mobile phase of phosphate buffer (100 mM, pH 6.8):1-propanol (80:20 v/v) at 1.0 mL/min and 214 nm. Incubation at pH 4.0–10.0, 37 °C for up to 4 weeks resulted in the formation of aggregates, small molecular weight peptide fragments and mostly depegylated interferon. Similar degradation pattern but to lower extent was noted under short-term storage conditions (24 h at 2–8 and 37 °C). No degradation was noted when the lyophilized powder was stored for 30 months at 2–8 °C, under real-time stability conditions. It should be noted that expression of the results using %Purity, currently employed for batch release was not a reliable approach. Alternatively, the stability of mono-PEG-IFN should be expressed as %Degradation that was shown to reveal minor changes in product stability. Results raised a concern about the efficacy and safety of reconstituted multi-dose vials of pegylated therapeutics that are stored refrigerated. The need for in-house validated testing protocols developed by local regulatory authorities to prevent access of substandard biotherapeutics to local markets is discussed.

**Keywords:** Size exclusion chromatography; Stability; Biopharmaceuticals; Pegylated interferon interferon A-2B.

### 854. Highly Sensitive Fluorimetric Method for Determination of Varenicline in Its Bulk and Tablets Via Derivatization With 7-Chloro-4-Nitrobenzoxadiazole

M. G. Kassem, I. A. Darwish and H. W. Darwish  
*Digest Journal of Nanomaterials and Biostructures, 9: 1065-1075 (2014) IF: 1.123*

This study represents the first report on the development and validation of a highly sensitive fluorimetric method for determination of varenicline (VRC) in tablets and plasma. The method was based on nucleophilic substitution reaction of VRC.
with 7-chloro-4-nitrobenzoxadiazole (NBD-Cl) in an alkaline buffered medium (pH 9) to form a highly fluorescent derivative that exhibited maximum fluorescence intensity at 550 nm after excitation at 470 nm. The factors affecting the reaction were carefully optimized. The stoichiometry of the reaction was determined, and the mechanism was postulated. Under the optimum reaction conditions, a linear relationship with good correlation coefficient (r = 0.9993) was found between the fluorescence intensity and VRC concentrations in the range of 5-250 ng ml⁻¹. The limits of detection and quantitation were 2.5 and 8.3 ng ml⁻¹, respectively. The method was reproducible as the relative standard deviations of the results did not exceed 2%.

The proposed method was successfully applied to the determination of VRC in its bulk and tablets with good accuracy; the label claim percentage was 99.17 ± 1.06%. The proposed method is valuable for routine application in quality control laboratories for determination of VRC.

**Keywords:** Varenicline; Fluorimetry; Nbd-Cl; Pharmaceutical Analysis; Tablets.

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**855. Highly Sensitive Synchronous Spectrofluorimetric Method for Determination of Stiripentol in Capsules and Human Urine: Application To In-Vitro Drug Release and Weight Variation Test**

Hany W. Darwish, Ahmed H. Bakheit and Mohamed I. Attia

*Digest Journal of Nanomaterials and Biostructures, 9: 819-829 (2014) IF: 1.123*

A highly sensitive and simple spectrofluorimetric method has been developed and validated for the determination of stiripentol (STP) in its pharmaceutical formulations and human urine. The proposed method is based on the investigation of the fluorescence spectral behaviour of STP in methanol using synchronous scan technique (Δλ=80 nm, 343nm). The fluorescence–concentration plot was rectilinear over the range 10–70 ng/mL, with lower detection limit of 2ng/mL. The proposed method was successfully applied to the assay of commercial capsules, spiked urine samples as well as weight variation testing. The application of the proposed method was extended to test the in-vitro drug release of STP capsules, according to USP guidelines.

**Keywords:** Stiripentol; Spectrofluorimetry; Human Urine; Content Uniformity; In-Vitro Release.

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**856. Simultaneous Spectrophotometric Determination of Diphenhydramine, Benzonatate, Guaifenesin and Phenylephrine in Their Quaternary Mixture Using Partial Least Squares With and Without Genetic Algorithm as A Powerful Variable Selection Procedure**


*Digest Journal of Nanomaterials and Biostructures, 9: 1359-1372 (2014) IF: 1.123*

Diphenhydramine HCl, benzonatate, guaifenesin and phenylephrine HCl are co-formulated together inBronchofree™ capsule in the ratio of 2.5:10:10:1 respectively. Literature review showed only one reported HPLC method for this mixture. Simultaneous chemometric-assisted spectrophotometric analysis of the multi-component dosage form has been carried out using two chemometric methods. These methods includes partial least squares (PLS-1) and PLS-1 proceeded by genetic algorithm (GA-PLS). Results demonstrated the efficiency of the two methods as quantitative tool of analysis of the four components without any interference of the excipient added, that eliminates the need for preliminary extraction of analytes from the pharmaceutical formulation. The four analytes were determined precisely using the afore-mentioned methods in an independent data set as well as in dosage form after optimization of the experimental conditions. Both methods are robust, accurate and precise in addition to their remarkable simplicity in comparison to other sophisticated techniques such as HPLC.

**Keywords:** Diphenhydramine Hcl, Benzonatate, Guaifenesin, Phenylephrine Hcl, Spectrophotometry, Pls, Genetic Algorithm.

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**857. A Rapid and Sensitive Hplc Assay of Some Concomitant Anti-Migraine Drugs**

Rezk MR, Michael AM, Lotfy HM, El-Kadi AO and Shehata MA

*Journal of Chromatographic Science, 52: 704-706 (2014) IF: 1.026*

This work describes a simple and sensitive method for simultaneous determination of zolmitriptan, naproxen and propranolol in their dosage forms using HPLC. The drugs were separated isocratically on a Zorbax C8 (4.6 3 250 mm with 5 mm particle size) column using a mobile phase composed of 20 mM phosphate citrate buffer [0.1% TEA (pH 3.1)];methanol:THF (5:3:2, by volumes). The detection was accomplished fluorometrically setting the excitation wavelength at 280 nm and emission wavelength at 360 nm. The method was validated over a linearity range of 100–900 ng/mL for zolmitriptan, 50–300 ng/mL for naproxen and 100–800 ng/mL for propranolol. The assay was successfully applied to the determination of the studied drugs in pharmaceutical dosage forms without interference from tablet excipients with high specificity. The method can be applied successfully in the future for the pharmacokinetic study of these drugs in the human plasma with high accuracy especially that LOQs of zolmitriptan and propranolol in the proposed method cover their Cmax.

**Keywords:** Hplc; Zolmitriptan;Naproxen; Propranolol.

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**858. Stability-Indicating Chromatographic Methods for the Determination of Sertindole**

Nariman A. El-Ragehy, Nagiba Y. Hassan, Mohamed Abdelkawy and Mahmoud A. Tantawy

*Journal of Chromatographic Science, 52: 559-565 (2014) IF: 1.026*

In this work, two chromatographic methods have been developed and validated for the determination of sertindole (an antipsychotic agent) in the presence of its oxidative degradation product. Sertindole was subjected to stress stability studies, including acid, alkali, oxidative, photolytic and thermal degradation. The chromatographic methods included the use of thin-layer chromatography (TLC–densimetry) and high-performance liquid chromatography (HPLC). The TLC method employed aluminum TLC plates precoated with silica gel G.254 as the stationary phase and methanol–ethyl acetate–33% ammonia (1:9:0.1, by volume) as the mobile phase, and the chromatograms were scanned at 227 nm. The developed HPLC method used a
reversed-phase C18 column with isocratic elution. The mobile phase was composed of phosphate buffer pH 3.0–acetoni-trile–triethylamine (45:55:0.03, by volume) and run at a flow rate of 1.0 mL/min. Quantitation was achieved with ultraviolet detection at 256 nm. The linearity ranges were found to be 2–14 mg/band and 5–200 mg/mL for TLC and HPLC, respectively. The developed methods were validated according to the International Conference on Harmonization guidelines and were applied for bulk powder and dosage forms.

**Keywords:** Spectrophotometry; TLC-Densitometry; Hplc; Sertindole.


Maha Hegazy, Amira Kessiba, Ahmed Emad El Gindy and Mohamed Abdelkawy

*Journal of Chromatographic Science, 52: 1071-1081 (2014) IF: 1.026*

A simple and sensitive stability indicating HPLC method was developed and validated for quantitative determination of Nitazoxanide (NTZ), a new antiprotazoal drug, in presence of degradation products generated under forced alkaline hydrolysis. Chromatographic separation was achieved on Inertsil C8-3 column (150 3 4.6 mm i.d.) using a mobile phase composed of acetonitrile: 50 mM ammonium acetate buffer (50:50, v/v, pH 5.0 adjusted with acetic acid) at a flow rate of 1 mL/min. Quantification was achieved with UV detection at 298 nm based on relative peak area. The method was linear over the concentration range of 0.8–50 mg/mL (r = 0.9999) with a limit of detection and quantification 0.0410 and 0.1242 mg/mL, respectively. The developed method has the requisite accuracy, selectivity, sensitivity and precision to assay NTZ in presence of its degradation products either in bulk powder or in pharmaceutical formulations. The degradation products were then identified by HPLC-MS/MS analysis using an electrospray ionization source and an ion trap analyzer.

**Keywords:** Nitazoxanide; Hplc; Degradation Products.

### 860. A Stability-Indicating Hplc-Dad Method for Determination of Stiripentol: Development, Validation, Kinetics, Structure Elucidation and Application To Commercial Dosage Form

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*Journal of Analytical Methods In Chemistry, 2014: 1-10 (2014) IF: 0.948*

A rapid, simple, sensitive, and accurate isocratic reversed-phase stability-indicating high performance liquid chromatography method has been developed and validated for the determination of stiripentol and its degradation product in its bulk form and pharmaceutical dosage form. Chromatographic separation was achieved on a Symmetry C18 column and quantification was achieved using photodiode array detector (DAD). The method was validated in accordance with the ICH requirements showing specificity, linearity (r² = 0.9996, range of 1–25 μg/mL), precision (relative standard deviation lower than 2%), accuracy (mean recovery 100.08±1.37), limits of detection and quantitation (LOD = 0.024 and LOQ = 0.081 μg/mL), and robustness. Stiripentol was subjected to various stress conditions and it has shown marked stability under alkaline hydrolytic stress conditions, thermal, oxidative, and photolytic conditions. Stiripentol degraded only under acidic conditions, forming a single degradation product which was well resolved from the pure drug with significantly different retention time values. This degradation product was characterized by 1H-NMR and 13C-NMR spectroscopy as well as ion trap mass spectrometry. The results demonstrated that the method would have a great value when applied in quality control and stability studies for stiripentol.

### 861. Determination of Fluoroquinolone Antibiotics in Industrial Wastewater by High-Pressure Liquid Chromatography and Thin-Layer Chromatography–Densitometric Methods

Fatma I. Khattab, Hesham Salem, Safaa M. Riad and Heba T. Elbalkiny

*Journal of Planar Chromatography, 27 (4): 287-293 (2014) IF: 0.67*

Two methods were described for the simultaneous determination of ciprofloxacin HCl (CIP) and moxifloxacin HCl (MOX) in their binary mixture present in industrial wastewater. A solid-phase extraction procedure (SPE) based on retention on HLB OASIS cartridges and elution with a mixture of methanol–water in acidic medium was preformed, and then both fluoroquinolones were separated using two chromatographic methods. The first method was based on high-performance liquid chromatographic separation of the two drugs on reversed-phase Zorbax C18 column. The mobile phase consisted of monobasic potassium phosphate (50 mM, pH 2.5, adjusted with phosphoric acid) and acetonitrile (80:20, v/v). Flow rate was 1 mL/min. Quantitation was achieved with ultraviolet (UV) detection at 278 nm. Linearity was found to be over the concentration range of 1–50 μg mL⁻¹ for both CIP and MOX. The second method was based on the thin-layer chromatographic (TLC) separation of the two drugs followed by densitometric measurements of their bands at 278 nm. The separation was carried out on silica gel 60 F254 plates, using methanol, ammonia, and methylene chloride (55:35:20, v/v) as a developing system. The linearity was found to be in the range of 0.25–2.5 μg band⁻¹ for both CIP and MOX. Both methods were optimized and validated as per International Conference on Har - monization (ICH) guidelines. Separation was developed on spiked water samples and checked on process wastewaters of industrial origin after SPE sample pretreatment.

**Keywords:** Ciprofloxacin hydrochloride; Moxifloxacin hydrochloride; High-performance liquid chromatography; Thin-layer chromatography–densitometry industrial wastewater.

### 862. Simultaneous Determination of Sulphadiazine Sodium and Trimethoprim in Medicated Fish Feed, Fish Tissues and in Their Veterinary Pharmaceutical Formulation by Thin-Layer Chromatography–Densitometry

Fatma I Khattab, Safaa M. Riad, Mamdouh Rezk and Hoda M. Marzouk

*Journal of Planar Chromatography, 27: 113-119 (2014) IF: 0.67*

A simple and sensitive thin-layer chromatographic method was developed and validated for the simultaneous determination of sulphadiazine sodium and trimethoprim in their binary mixture. The mobile phase was a binary mixture of acetonitrile and methanol (91:9, v/v) at a flow rate of 0.8 mL/min. The detection was achieved with UV detection at 278 nm. Linearity was achieved in the range of 0.1–50 μg mL⁻¹ for both drugs using a calibration curve method. The method was validated according to the International Conference on Harmonization guidelines and was applied for spiked and unspiked samples.
A specific, precise, and accurate thin-layer chromatographic method for the simultaneous estimation of sulphadiazine sodium (SDZ) and trimethoprim (TMP) in medicated fish feed and in fish tissues was developed and validated. This method is based on simple liquid extraction technique and employing thin-layer chromatography (TLC) as a cleanup step. In order to optimize the extraction procedure from fish tissues, several mobile phase systems and extracting solvents were tried. The method employed TLC aluminum plates precoated with silica gel 60 F254 as the stationary phase and chloroform–toluene–ethanol–glacial acetic acid (4.5:4.5:1:0.10 by volume) mixture as the developing solvent. This system was found to give compact and dense spots for both sulphadiazine sodium (RF value of 0.48) and trimethoprim (RF value of 0.16) without interference from either medicated fish feed or fish tissues co-extractives. Densitometric analysis of both drugs was carried out in the reflectance–absorbance mode at 270 nm for SDZ and 225 nm for TMP to maximize sensitivity for each drug. The linearity of the proposed method was established over the ranges 0.1–2.0 and 0.1–1.0 µg/band for sulphadiazine sodium and trimethoprim, respectively. The method was validated for linearity, specificity, precision, and accuracy. Statistical analysis proves that the method is repeatable and selective for the estimation of both drugs in various matrices. The proposed method was successfully applied for the determination of SDZ and TMP either in bulk pure powder or in their veterinary pharmaceutical formulation.

**Keywords:** Densitometry; TLC; Sulphadiazine Sodium; Trimethoprim; Medicated Fish Feed; Fish Tissues.

### 863. Thin-Layer Chromatographic Enantioreseparation Ofloxacin and Zopiclone Using Hydroxy-Propyl-Beta-Cycloexetrin as Chiral Selector and Thermodynamicstudies of Complexation

Nahla Salama, Hala E Zaaaza, Lobna Mohammed Abd El Halim, Maissa Salem and Laia E. Abd El Fattah

*Journal of Planar Chromatography, 127: 166-173 (2014) IF: 0.67*

A novel economic thin-layer chromatographic procedure for stereoselective separation of racemic mixtures of each of zopiclone and ofloxacin, and determination of their enantiomers: eszopiclone, (+)-(S)-zopiclone, and levofloxacin, (-)-(S)-ofloxacin, was described. The method was based on using normal plates and hydroxy propyl-beta-cycloexetrin (HP-beta-CD) as chiral mobile phase additive (CMPA). The spots were detected under UV lamp 254 nm, followed by densitometric measurements at 304 and 330 nm for (+)-(S)-zopiclone and (-)-(S)-ofloxacin, respectively. The mobile phase enabling successful resolution of the drugs was ethanol-acetonitrile-glacial acetic acid-diethylamine-distilled water containing 0.5% HP-beta-CD (4:2:3:3:1, by volume), pH 4, for zopiclone and ethanol-acetonitrile-glacial acetic acid-diethylamine-distilled water containing 0.3% HP-beta-CD (4:4:3:3:1, by volume), pH 4,5, for ofloxacin at 25 +/- 2 degrees C. All variables affecting the resolution, such as concentration of different chiral selectors, temperature, and pH, were investigated, and the conditions were optimized. Furthermore, some thermodynamic parameters were calculated. The procedure provided a linear response over the concentration range of 1-4 µg and 2-7 mg g(-1) for determination of pure active isomers, (+)-(S)-zopiclone and (-)-(S)-ofloxacin, respectively, with acceptable precision (relative standard deviation [% RSD] <2.0). The developed method was validated and proved to be robust. The proposed method was found to be selective and accurate for the identification and quantitative determination of enantiomeric purity of the two active isomers in their drug substances and drug products.

**Keywords:** Eszopiclone-Levofloxacin-Enantiomeric Purity-Densitometric–TLC-Chiral Mobile Phase Additive

### 864. Two Validated Liquid Chromatographic Methods for the Simultaneous Determination of Flumethasone Pivalate, its Related Substance (Flumethasone), and Clioquinol

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*Journal of Planar Chromatography, 27: 466-471 (2014) IF: 0.67*

Two liquid chromatographic methods were developed and validated. Simple and sensitive thin-layer chromatography (TLC) –densitometric and high-performance liquid chromatographic (HPLC) methods were used for the simultaneous determination of flumethasone pivate (FP), flumethasone pivate related substance and impurity, flumethasone (FL), and clioquinol (CL). The proposed TLC–densitometric method has been developed using silica gel plates 60 F254 as a stationary phase with benzene–hexane–acetonene–formic acid (5.4:2:0:13, by volume) as a developing system followed by densitometric measurements at 235 nm. The studied components were quantified in the range of 0.3–4, 0.3–3, and 1.5–5 µg band-1, respectively. For HPLC method, chromatographic separation was achieved within 11 min with the required peak symmetry, accuracy, and precision on ODS column using acetonitrile–water (70:30, v/v) as the mobile phase at a flow rate of 1 mL min-1 with ultraviolet (UV) detection at 235 nm. The calibration plots were linear over the concentration range of 5–50, 2–35, and 10–70 mg mL-1, respectively. The proposed methods were validated as per International Conference on Harmonization (ICH) guidelines; accuracy, precision, and repeatability were found to be within the acceptable limits.

**Keywords:** Flumethasone Pivate Flumethasone Clioquinol Thin-Layer Chromatography High-Performance Liquid Chromatography.

### 865. Selective Chromatographic Methods for the Determination of Rosuvastatin Calcium in the Presence of ITP Acid Degradation Products

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*Journal of Liquid Chromatography & Related Technologies, 37: 2182-2196 (2014) IF: 0.638*

Two accurate and sensitive stability-indicating methods for the determination of rosvastatin calcium in the presence of its acid degradation products are presented. The first method utilizes quantitative spectrodensitometric evaluation thin-layer chromatography (TLC) of rosvastatin calcium in the presence of its acid degradation products, using ethyl acetate/methanol/ammonia (7:3:0.01, by volume) as a mobile phase. Chromatograms are scanned at 245 nm. This method analyzes rosvastatin calcium in a concentration range of 0.6–
3.4 µg/band with mean percentage recovery of 99.78 ± 1.42. The second method is a high-performance liquid chromatography (HPLC) method for the simultaneous determination of rosuvastatin calcium in the presence of its acid degradation products. The mobile phase consists of water/acetonitrile/methanol (40:40:20, by volume). The standard curve of rosuvastatin calcium shows a good linearity over a concentration range of 10–60 µg mL⁻¹ with mean percentage recovery of 100.22 ± 0.86. These methods were successfully applied to the determination of rosuvastatin calcium in bulk powder, laboratory-prepared mixtures containing different percentages of the acid degradation products, and pharmaceutical dosage forms. The validity of results was assessed by applying standard addition technique. The results obtained were found to agree statistically with those obtained by a reported method, showing no significant difference with respect to accuracy and precision.

Keywords: Degradation, Densitometry, Hplc technique, Rosuvastatin Calcium, Stability-indicating, Tlc technique.

866. Novel Spectrophotometric Methods for Determination of salicylamide and Ascorbic Acid in Their Binary Mixture

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Journal Of Chemical Society Of Pakistan, 36: 988-995 (2014) IF: 0.612

Simple, selective and precise four spectrophotometric methods were developed and validated for quantitative determination of Salicylamide (SAD) and Ascorbic acid (ASC, Vitamin C) in their binary mixture. Method A is Area under curve spectrophotometry, in which the area under curve in the wavelength ranges 225-245 nm and 265-285 nm were selected for determination of SAD and ASC. Method B is based on dual wavelength spectrophotometry, where ASC can be determined by difference in absorbance at 249.8 and 285.8 nm.

On the same way; SAD is measured by difference in absorbance at 240.4 and 286.4 nm. Method C utilizes isosborsptive point spectrophotometry where total concentration of SAD and ASC was calculated at their isosborsptive points at 246.4 and 287 nm, while SAD concentration alone can be determined by first derivative spectrophotometry ('D') at 315.4 nm, then ASC concentration can be determined by subtraction. Method D is ratio subtraction spectrophotometry, where ASC can be determined by dividing the spectrum of the mixture by the spectrum of the SAD (as a divisor) followed by subtracting the constant absorbance value of the plateau region, then finally multiplying the obtained spectrum by the spectrum of the divisor.

The developed methods have been successfully applied for determination of the studied drugs in different laboratory prepared mixtures and in their pharmaceutical formulation. Statistical comparison between the results obtained by applying the proposed methods and the reported HPLC method was done, and it was found that there was no significant difference between them regarding both accuracy and precision.

Keywords: Ascorbic Acid; Area Under Curve; Dual Wavelength; Isosborsptive Point.

867. Smart Methods for Linezolid Determination in the Presence of Alkaline and Oxidative Degradation Products Utilizing Their Overlapped Spectral Bands

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Journal of Applied Spectroscopy, 81: 646-654 (2014) IF: 0.514

Linezolid (LIN) is considered the first available oxazolidinone antibacterial agent. It is susceptible to hydrolysis and oxidation. Five simple, accurate, sensitive and validated UV spectrophotometric methods were developed for LIN determination in the presence of its alkaline (ALK) and oxidative (OXD) degradation products in bulk powder and pharmaceutical formulation. Method A is a second derivative one (∆D) in which LIN is determined at 240.9 nm. Method B is a pH-induced differential derivative one where LIN is determined using the fourth derivative (∆D⁴) of the difference spectra (∆A) at 285.3 nm. Methods C, D, and E are manipulating ratio spectra, where C is the double divisor-ratio difference spectrophotometric one (DD-RD) in which LIN was determined by calculating the amplitude difference at 243.7 and 267.6 nm of the ratio spectra. Method D is the double divisor- first derivative of ratio spectra (DD-DD⁴) in which LIN was determined at 270.2 nm. Method E is a mean centering of ratio spectra one (MCR) in which LIN was determined at 318.0 nm. The developed methods have been validated according to ICH guidelines. The results were statistically compared to that of a reported HPLC method and there was no significant difference regarding both accuracy and precision.

Keywords: Spectrophotometry; Derivative; Ratio difference; Ratio spectra derivative; Mean centering; Linezolid; Degradation products.

868. Artificial Neural Networks And Concentration Residual Augmented Classical Least Squares for the Simultaneous Determination of Diphenhydramine, Benzonatate, Guaifenesin And Phenylephrine in Their Quaternary Mixture

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Tropical Journal Of Pharmaceutical Research, 13: 2083-2090 (2014) IF: 0.495

Purpose: To develop two multivariate calibration methods for the simultaneous spectrophotometric determination of a quaternary mixture composed of diphenhydramine HCl, benzonatate, guaifenesin and phenylephrine HCl in Bronchofree™ capsules in the ratio of 2.5 : 10 : 10 : 1, respectively.

Methods: Novel artificial neural networks (ANNs) and concentration residual augmented classical least squares (CRACLS) methods were developed for the quantitative determination of the quaternary mixture. For proper analysis, a four-level, four-factor experimental design was established resulting in a training set of 16 mixtures containing different ratios of the four analytes. A validation set consisting of six mixtures was used to validate the prediction ability of the suggested models.

Results: ANNs and CRACLS methods were successfully applied for the analysis of raw materials and capsules. For ANNs method, % recovery of diphenhydramine HCl, benzonatate, guaifenesin and phenylephrine HCl in the capsules was 102.21 ± 1.34, 100.30
± 1.17, 99.31 ± 2.00 and 98.50 ± 1.27, respectively. On the other hand, % recovery of the four analytes by CRACLS was 99.84 ± 2.22, 100.07± 0.63, 98.37 ± 1.42 and 97.99 ± 0.96, respectively. **Conclusion:** The proposed methods can be applied for the quantitative determination of the four components without interference from excipients, thus obviating the need for preliminary extraction of analytes from the pharmaceutical formulation. The ability of the methods to deconvolute the highly overlapped UV spectra of the four components’ mixtures using low-cost and easy-to-handle instruments such as UV spectrophotometer is also an advantage. **Keywords:** Artificial Neural Networks, Concentration Residual Augmented Classical Least Squares, Quaternary Mixture, Simultaneous Determination.

869. **Comparative Study of RP–HPLC Versus TLC–Spectrodensitometric Methods Applied for Binary Mixtures of Fluoroquinolones and Corticosteroids**
S. M. Elgizawy, N. Y. Hassan, H. M. Lotfy and S. S. Saleh  
*Acta Chromatographica, 26: 439-456 (2014) IF: 0.485*

Reversed phase high-performance liquid chromatography (RP–HPLC) and thin-layer chromatography (TLC)-spectrodensitometric methods have been developed and validated for the separation and quantitation of two binary mixtures: Ofloxacin (OFX) and dexamethasone (DXM) in eye preparation; ciprofloxacin hydrochloride (CIP) and hydrocortisone (HYD) in ear preparation. The linearity ranges of RP–HPLC methods were found to be (2.5–45 µg mL⁻¹) for OFX, (2.5–50 µg mL⁻¹) for DXM and (1–8 µg mL⁻¹) for both CIP and HYD. The percentage recoveries/relative standard deviation (RSD) were found to be 100.36/1.38, 100.13/1.49, 99.98/0.61 and 100.28/1.27, respectively. The linearity ranges of TLC-spectrodensitometric methods were found to be (0.5–2 µg band⁻¹), (0.5–3.5 µg band⁻¹), (0.2–1.6 µg band⁻¹), and (0.6–2 µg band⁻¹) for OFX, DXM, CIP, and HYD, respectively. The percentage recoveries/RSD were found to be 99.98/0.6, 99.93/1.18, 99.74/1.27, and 99.94/1.54, respectively. A comparative study was conducted to show the advantages of the proposed methods which showed that the TLC-spectrodensitometric methods were simpler, more sensitive, and economic, while RP–HPLC methods were more precise and robust. The methods were validated in compliance with the ICH guidelines and were successfully applied for determination of the selected drugs in their laboratory-prepared mixtures and commercial dosage forms. **Keywords:** Ofloxacin; Dexamethasone; Ciprofloxacin Hydrochloride; Hydrocortisone; HPLC; TLC-Spectrodensitometry.

870. **Electrophoretic Behavior of Charge Regulated Zwitter Ionic Buffers in Covalently And Dynamically Coated Fused Silica Capillaries**
Medhat Ahmed Abdelhamid Al-Ghobashy  
*Bulletin Of Faculty Of Pharmacy, Cairo University, 52: 71-78 (2014)*

In this work, the electrophoretic behavior of zwitterionic buffers is investigated in the absence of electroosmotic flow (EOF). Electro mobilization of capillary contents is noted when zwitterionic buffers are employed as the background electrolyte at a pH where the buffering moiety carries a net charge. The bulk flow of capillary contents was demonstrated via monitoring the migration of a neutral marker as well as a free and micellar negatively charged marker and SDS–protein complexes. This electrolyte-driven mobilization (EDM) was investigated in detail using 4-(2-hydroxyethyl)piprazine-1-ethanesulfonic acid (HEPES) buffer over a wide pH range (pH 4.0–8.0). Results confirmed that at a pH where HEPES molecules carry a net negative charge, a bulk flow toward the anode is observed. This was attributed to the migration of HEPES ions toward the anode along with their hydration shells. The relatively large difference in size and solvation number between theionic buffering moiety and its counter-migrating ions (Na⁺ or H⁺) resulted in such a net movement. Results indicated that at constant voltage, plotting the measured current versus buffer pH can be used for determination of the isoelectric point of the zwitterionic buffering moiety. Furthermore, this novel mobilization modality was demonstrated using five different HEPES analogs over pH range 5.0–8.0. More in depth investigations are required in order to explore the applicability of EDM in coated capillaries of different wall chemistries and dimensions. **Keywords:** Electrolyte-Driven Mobilization (Edm); Eof; Zwitterionic Buffers; Electrokinetic Pump.

871. **Pseudo-MS³ Approach Using Electrospray Mass Spectrometry (ESI-MS/MS) to Characterize Certain (2E)-2-[3-(1H-Imidazol-1-yl)-1-Phenylpropyldiene] Hydrazinecarboxamide Derivatives**
Ali S. Abdelhameed, Adnan A. Kadi, Mohamed I. Attia, Rihab F. Angawi, Mohamed W. Attwa and Hany W. Darwish  

An approach for the use of in-source fragmentation with electrospray ionization followed by product ion scan in a triple quadrupole mass spectrometer system is described. This approach is based on the elucidation of the various fragmentation pathways by further dissociation of each fragment ion in the ion spectrum. This can be achieved predominately, by combining fragmentor voltage induced dissociation (in-source fragmentation) with subsequent collision-induced dissociation; this process can be referred to as pseudo-MS³ scan mode. This technique permitted unambiguous assignment and provided sufficient sensitivity and specificity. It is advantageous for structure elucidation of unknown compounds. We investigate the possibility of using in-source fragmentation with the diverse novel chemical entities encompassing different substituents. This process was intended to improve the qualitative capability of tandem mass spectrometry simulating the MS³ of ion trap for studying fragmentation mechanisms. The approach is to implement the investigated technique as a well established tool for the characterization of new pharmacologically important chemical entities. The data presented in this paper provided useful information on the effect of different substituents on the ionization/fragmentation processes and can be used in the characterization of (2E)-2-[3-(1H-imidazol-1-yl)-1-phenylpropyldiene]-hydrazinecarboxamide derivatives 3a–h. **Keywords:** Esi-Ms/Ms; Hydrazinecarboxamide.
Type 1 diabetes is a multifactorial inflammatory disease in genetically susceptible individuals characterized by progressive autoimmune destruction of pancreatic β-cells initiated by yet unknown factors. Although animal models of type 1 diabetes have substantially increased our understanding of disease pathogenesis, heterogeneity seen in human patients cannot be reflected by a single model and calls for additional models covering different aspects of human pathophysiology. Inhibitor of β kinase (IKK)/nuclear factor-κB (NF-κB) signaling is a master regulator of inflammation; however, its role in diabetes pathogenesis is controversially discussed by studies using different inhibition approaches. To investigate the potential diabetogenic effects of NF-κB in β-cells, we generated a gain-of-function model allowing conditional IKK2/NF-κB activation in β-cells. A transgenic mouse model that expresses a constitutively active mutant of human IKK2 dependent on浦s-1 promoter activity (IKK2-CA(Thr(5099)→Ala)) spontaneously develops full-blown immune-mediated diabetes with insulitis, hyperglycemia, and hypoinsulinemia. Disease development involves a gene expression program mimicking virus-induced diabetes and allergic inflammatory responses as well as increased major histocompatibility complex class I/II expression by β-cells that could collectively promote diabetes development. Potential novel diabetes candidate genes were also identified. Interestingly, animals successfully recovered from diabetes upon transgene inactivation. Our data give the first direct evidence that β-cell-specific IKK2/NF-κB activation is a potential trigger of immune-mediated diabetes. Moreover, IKK2-CA(Thr(5099)→Ala) mice provide a novel tool for studying critical checkpoints in diabetes pathogenesis and mechanisms governing β-cell degeneration/regeneration.

**Keywords:** Diabetes; NF-κB; Inflammation; Beta Cells.

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**873. Direct Detection of Hyaluronidase in Urine Using Cationic Gold Nanoparticles: A Potential Diagnostic Test for Bladder Cancer**

Ahmed Ibrahim Nossier, Sanaa Eissa, Manal Fouad Ismail, Mohamed Ahmed Hamdy and Hassan Mohamed El-Said Azzary

*Biosensors and Bioelectronics, 54: 7-14 (2014) IF: 6.451*

Hyaluronidase (HAase) was reported as a urinary marker of bladder cancer. In this study, a simple colorimetric gold nanoparticle (AuNP) assay was developed for rapid and sensitive detection of urinary HAase activity. Charge interaction between polyanionic hyaluronic acid (HA) and cationic AuNPs stabilized with cetyl trimethyl ammonium bromide (CTAB) led to formation of gold aggregates and a red to blue color shift. HAase digests HA into small fragments preventing the aggregation of cationic AuNPs. The nopspecific aggregation of AuNPs in urine samples was overcome by pre-treatment of samples with the polycationic chitosan that was able to agglomerate all negatively charged interfering moieties before performing the assay. The developed AuNP assay was compared with zymography for qualitative detection of urinary HAase activity in 40 bladder carcinoma patients, 11 benign bladder lesions patients and 15 normal individuals, the assay sensitivity was 82.5% vs. 65% for zymography, while the specificity for both assays was 96.1%. The absorption ratio, A530/A620 of the reacted AuNP solution was used to quantify the HAase activity. The best cut off value was 93.5 μIUng protein, at which the sensitivity was 90% and the specificity was 80.8%. The developed colorimetric AuNP HAase assay is simple, inexpensive, and can aid noninvasive diagnosis of bladder cancer. Hyaluronidase; Hyaluronic acid; Bladder Cancer; Gold Nanoparticles; Chitosan

**Keywords:** Hyaluronidase; Hyaluronic acid; Bladder cancer; Gold nanoparticles; Chitosan.

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**874. The Adaptor Protein P66Shc Inhibits mTOR-Dependent Anabolic Metabolism**

Mohamed A. Soliman, Anas M. Abdel Rahman, Dudley A. Lamming, Kivanç Birsoy, Judy Pawling, Maria E. Frigole, Huogen Lu, I. George Fantus, Adrian Pasceulescu, Yong Zheng, David M. Sabatini, James W. Dennis and Tony Pawson


Adaptor proteins link surface receptors to intracellular signaling pathways and potentially control the way cells respond to nutrient availability. Mice deficient in p66Shc, the most recently evolved isoform of the Shc1 adaptor proteins and a mediator of receptor tyrosine kinase signaling, display resistance to diabetes and obesity. Using quantitative mass spectrometry, we found that p66Shc inhibited glucose metabolism. Depletion of p66Shc enhanced glycolysis and increased the allocation of glucose-derived carbon into anabolic metabolism, characteristics of a metabolic shift called the Warburg effect. This change in metabolism was mediated by the mammalian target of rapamycin (mTOR) because inhibition of mTOR with rapamycin reversed the glycolytic phenotype caused by p66Shc deficiency. Thus, unlike the other isoforms of Shc1, p66Shc appears to antagonize insulin and mTOR signaling, which limits glucose uptake and metabolism. Our results identify a critical inhibitory role for p66Shc in anabolic metabolism.

**Keywords:** Metabolism, Cell Signaling, Diabetes, Cancer, Oxidative Stress

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**875. Sorting of β1-adrenergic receptors is mediated by pathways that are either dependent on or independent of type I PDZ, protein kinase A (PKA), and SAP97**

Nooh MM, Chumpia MM, Hamilton TB and Bahouth SW.

*Journal of Biological Chemistry, 289: 2277-2294 (2014) IF: 4.6*

The β1-adrenergic receptor (β1-AR) is a target for treatment of major cardiovascular diseases, such as heart failure and hypertension. Recycling of agonist-internalized β1-AR is dependent on type I PSD-95/DLG/ZO1 (PDZ) in the C-tail of the β1-AR and on protein kinase A (PKA) activity (Gardner, L. A., Naren, A. P., and Bahouth, S. W. (2007) J. Biol. Chem. 282, 5085-5099). We explored the effects of point mutations in the PDZ and in the activity of PKA on recycling of the β1-AR and its binding to the PDZ-binding protein SAP97. These studies indicated that β1-AR recycling was inhibited by PKA inhibitors and by mutations in the PDZ that interfered with SAP97 binding. The trafficking effects of short sequences differing in PDZ and...
SAP97 binding were examined using chimeric mutant β1-AR, β1-AR chimera containing the type I PDZ of the β2-adrenergic receptor that does not bind to SAP97 failed to recycle except when serine 312 was mutated to aspartic acid. β1-AR chimera with type I PDZ sequences from the C-tails of aquaporin-2 or GluR1 recycled in a SAP97- and PKA-dependent manner. Non-PDZ β1-AR chimera derived from μ-opioid, dopamine 1, or GluR2 receptors promoted rapid recycling of chimeric β1-AR in a SAP97- and PKA-independent manner. Moreover, the nature of the residue at position -3 in the PDZ regulated whether the β1-AR was internalized alone or in complex with SAP97. These results indicate that divergent pathways were involved in trafficking the β1-AR and provide a roadmap for its trafficking via type I PDZs versus non-PDZs.

Keywords: Adrenergic Receptor; Confocal Microscopy; G Protein-Coupled Receptor (GPCR); Protein Kinase A (PKA); Trafficking

876. Chrysin Alleviates Testicular Dysfunction in Adjuvant Arthritic Rats Via Suppression of Inflammation and Apoptosis: Comparison With Celecoxib

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*Toxicol Appl Pharmacol, 279(2): 129-140 (2014) IF: 3.63*

Long-standing rheumatoid arthritis RA is associated with testicular dysfunction and subfertility. Few studies have addressed the pathogenesis of testicular injury in RA and its modulation by effective agents. Thus, the current study aimed at evaluating the effects of two testosterone boosting agents; chrysin, a natural flavone and celecoxib, a selective COX2 inhibitor, in testicular impairment in rats with adjuvant arthritis, an experimental model of RA. Chrysin 25 and 50mgkg and celecoxib 5mgkg were orally administered to Wistar rats once daily for 21days starting 1h before arthritis induction. Chrysin suppressed paw edema with comparable efficacy to celecoxib. More important, chrysin, dose-dependently and celecoxib attenuated the testicular injury via reversing lowered gonadotrophic hormone and histopathological alterations with preservation of spermatogenesis. Both agents upregulated steroidogenic acute regulatory StAR mRNA expression and serum testosterone with concomitant restoration of LH and FSH. Furthermore, they suppressed inflammation via abrogation of myeloperoxidase, TNF-α and protein expression of COX2 and iNOS besides elevation of IL-10. Alleviation of the testicular impairment was accompanied with suppression of oxidative stress via lowering testicular lipid peroxides and nitric oxide. With respect to apoptosis, both agents downregulated FasL mRNA and caspase-3 activity in favor of cell survival. For the first time, these findings highlight the protective effects of chrysin and celecoxib against testicular dysfunction in experimental RA which were mediated via boosting testosterone in addition to attenuation of testicular inflammation, oxidative stress and apoptosis. Generally, the 50mg kg dose of chrysin exerted comparable protective actions to celecoxib.

Keywords: Apoptosis; Celecoxib; Chrysin; Inflammation; Rheumatoid Arthritis; Testicular Dysfunction.

877. A Novel Role for Sirt-1 in L-Arginine Protection Against STZ Induced Myocardial Fibrosis in Rats

Sherine M. Rzik, Shohda A. El-Maraghy and Noha N. Nassar
*Plos One, 9(12): 1-19 (2014) IF: 3.534*

Background: L-arginine (L-ARG) effectively protects against diabetic impediments. In addition, silent information regulator (SIRT-1) activators are emerging as a new clinical concept in treating diabetic complications. Accordingly, this study aimed at delineating a role for SIRT-1 in mediating L-ARG protection against streptozotocin (STZ) induced myocardial fibrosis.

Methods: Male Wistar rats were allocated into five groups; (i) normal control rats received 0.1 M sodium citrate buffer (pH 4.5); (ii) STZ at the dose of 60 mg/kg dissolved in 0.1 M sodium citrate buffer (pH 4.5); (iii) STZ + sirtinol (Stnl; specific inhibitor of SIRT1-1; 2 mg/Kg, i.p.); (iv) STZ + L-ARG given in drinking water (2.25%) or (v) STZ + L-ARG + Stnl.

Results: L-ARG increased myocardial SIRT-1 expression as well as its protein content. The former finding was paralleled by L-ARG induced reduction in myocardial fibrotic area compared to STZ animals evidenced histopathologically. The reduction in the fibrotic area was accompanied by a decline in fibrotic markers as evident by a decrease in expression of collagen-I along with reductions in myocardial TGF-β, fibronectin, CTGF and BNP expression together with a decrease in TGF-β and hydroxyproline contents. Moreover, L-ARG increased MMP-2 expression in addition to its protein content while decreasing expression of PAI-1. Finally, L-ARG protected against myocardial cellular death by reduction in NFκ-B mRNA as well as TNF-α level in association with decline in Casp-3 and FAS expressions and Casp3 protein content in addition to reduction of FAS positive cells. However, co-administration of L-ARG and Stnl diminished the protective effect of L-ARG against STZ induced myocardial fibrosis.

Conclusion: Collectively, these findings associate a role for SIRT-1 in L-ARG defense against diabetic cardiac fibrosis via equilibrating the balance between profibrotic and antifibrotic mediators.

Keywords: L-Arginine; Diabetic impediments; Silent information regulator; Myocardial fibrosis.

878. The First Synthesis of the Antiangiogenic Homoisoflavanone, Cremastranone

Bit Lee, Halesha D. Basavarajappa, Rania S. Sulaiman, Xiang Fei, Seung-Yong Seo and Timothy W. Corson

An antiangiogenic homoisoflavanone, cremastranone, was synthesized for the first time. This scalable synthesis, which includes selective demethylation, could be used to develop lead molecules to treat angiogenesis-induced eye diseases. Synthetic cremastranone inhibited the proliferation, migration and tube formation ability of human retinal microvascular endothelial cells, important steps in pathological angiogenesis.

Keywords: Angiogenesis, Homoisoflavanone.

879. Modulatory Effects of Curcumin, Silybin-Phytosome and Alpha-R-Lipoic Acid Against Thioacetamide-Induced Liver Cirrhosis in Rats

Shimaa Omar Ali, Hebatallah Abd El-moeti Darwish and Nabilah Abd El-fattah Ismail

Liver cirrhosis is the final consequence of a progressive fibrotic process characterized by excessive collagen deposition and
destruction of the normal liver architecture. This study aimed to investigate the protective effects of curcumin, silybin-phytosomal and alpha-R-lipoic acid against thioacetamide-induced cirrhosis. Male rats were allocated into five groups of which one group received saline and served as normal control. Animals from groups 2-5 were treated with thioacetamide intraperitoneally at a dose of 200 mg kg\(^{-1}\) three times per week for 7 weeks. Group 2 was left untreated while groups from 3 to 5 were given a daily oral dose of curcumin, silybin-phytosomal or alpha-R-lipoic acid simultaneously with thioacetamide. Increases in hepatic levels of malondialdehyde, MDA and protein carbonyls Pr Co associated with thioacetamide administration were partially blocked in those groups receiving supplements. Glutathione GSH depletion, collagen deposition, matrix metalloproteinase-2 MMP-2 activity, transforming growth factor-\(\beta\) TGF-\(\beta\)1 level as well as a smooth muscle actin a-SMA and heat shock protein-47 HSP-47 gene expressions were also decreased in response to supplements administration. Serological analysis of liver function and histopathological examination reinforced the results. In conclusion, the present study highlights the antioxidant and the antifibrotic potentials of these supplements against chronic liver diseases caused by ongoing hepatic damage.

**Keywords:** Alpha-R-Lipoic Acid; Curcumin; Liver Cirrhosis; Oxidative Stress; Silybin-Phytosome; Thioacetamide

### 880. Pretreatment With Turmeric Modulates the Inhibitory Influence of Cisplatin and Paclitaxel on CYP2E1 and CYP3A1/2 in Isolated Rat Hepatic Microsomes

Enas M. Ahmed, Shohda A. EL-Maraghy, Zakaria A. Teleb and Amira A. Shaheen

**Chemico Biological Interaction**, 220: 25-32 (2014) IF: 2.982

Previous animal studies have shown that turmeric can significantly modulate the activity of several drug metabolizing enzymes, this may dramatically affect the bioavailability of several drugs resulting in over dose or less therapeutic effects. This study was directed to evaluate the inhibitory effects of cisplatin and paclitaxel on two CYP450 enzymes namely CYP2E1 and CYP3A1/2 in hepatic microsomes isolated from normal and turmeric pretreated rats. Cisplatin and paclitaxel were added by different concentrations to hepatic microsomes isolated from untreated and turmeric (100 mg/kg/day) pretreated rats for 15 days after receiving pyrazole or dexamethasone for induction of CYP2E1 and CYP3A1/2 respectively. The kinetic potency of these drugs as CYP inhibitors was determined by analysis of Lineweaver-Burk plot. Addition of cisplatin or paclitaxel by (10, 50 and 100 \(\mu\)M) to hepatic microsomes from normal or turmeric pretreated rats caused a concentration dependent inhibition of CYP2E1, with an evidence of less inhibition in hepatic microsomes in normal or turmeric pretreated microsomes particularly at higher concentration. Both drugs at 100 \(\mu\)M displayed a mixed type of inhibition of CYP2E1 in normal or turmeric pretreated microsomes which paclitaxel was the most potent inhibitor. Cisplatin (10, 50 and 100 \(\mu\)M) caused a concentration dependent inhibition of CYP3A1/2 that was enhanced by turmeric pretreatment. The inhibition of CYP3A1/2 by cisplatin (100 \(\mu\)M) was in non-competitive manner with a smaller Ki value in turmeric pretreated microsomes. The inhibitory influence of paclitaxel (10, 50 and 100 \(\mu\)M) on CYP3A1/2 decreased with increasing the drug concentration and this inhibition was augmented by turmeric pretreatment. Interestingly, the inhibition of this enzyme by paclitaxel (10 \(\mu\)M) was switched from mixed type in normal microsomes to competitive manner in turmeric pretreated ones with a marked reduction of Ki values reflecting greater inhibitory influence of paclitaxel on CYP3A1/2 by turmeric pretreatment. In conclusion, turmeric pretreatment attenuated the inhibitory influence of cisplatin and paclitaxel on CYP2E1 activity and magnified their inhibition on CYP3A1/2, thus the use of turmeric with drugs or other medications should raise concern for drugs-herb interactions.

**Keywords:** Cyp450 Isoenzyme; Cisplatin; Inhibition; Paclitaxel; Turmeric

### 881. Protective Effect of Satureja Montana Extract on Cyclophosphamide-Induced Testicular Injury in Rats

Azza M. Abd El Tawab, Nancy N. Shahin and Mona M. AbdelMohsen

**Chemico-Biological Interactions**, 224: 196-205 (2014) IF: 2.982

The present study investigated the protective effect of Satureja montana extract against cyclophosphamide-induced testicular injury in rats. Total phenolic and flavonoid contents of the extract were 1.03% and 0.34%/w/w of dry herb expressed as chlorogenic acid and quercetin, respectively. HPLC analysis identified caffeic, syringic and rosmarinic acids as the chief phenolic acids, and rutin as the major flavonoid in the extract. Oral daily administration of S.montana extract (50mg/kg/day) for 7 days before and 7 days after an intraperitoneal injection of cyclophosphamide (200mg/kg) restored the reduced relative testicular weight, serum testosterone level and testicular alkaline phosphatase activity, raised the lowered testicular sorbitol dehydrogenase and acid phosphatase activities, and decreased the elevated testicular hemoglobin absorbance. It also attenuated lipid peroxidation, restored the lowered glutathione content, glucose-6-phosphate dehydrogenase, glutathione peroxidase and glutathione reductase activities, and improved total antioxidant capacity. Moreover, S.montana extract mitigated testicular DNA fragmentation, decreased the elevated Fas and Bax gene expression, up-regulated the decreased Bcl-2 and peroxisome proliferator-activated receptor-gamma (PPAR-\(\gamma\)) gene expression and normalized Akt1 protein level. Histopathological investigation confirmed the protective effects of the extract. Conclusively, S.montana extract protects the rat testis against cyclophosphamide-induced damage via anti-oxidative and anti-apoptotic mechanisms that seem to be mediated, at least in part, by PPAR-\(\gamma\) and Akt1 up-regulation.

**Keywords:** Akt1; Apoptosis; Cyclophosphamide; Peroxisome Proliferator-Activated Receptor-Gamma; Satureja Montana Extract; Testis.

### 882. Propolis Attenuates Doxorubicin-Induced Testicular Toxicity in Rats

Sherine M. Rizk, Hala F. Zaki and Mary A.M. Mina

**Food and Chemical Toxicology**, 67: 176-186 (2014) IF: 2.61

Doxorubicin (Dox), an effective anticancer agent, can impair testicular function leading to infertility. The present study aimed to explore the protective effect of propolis extract on Dox-induced testicular injury. Rats were divided into four groups (n=10). Group I (normal control), group II received propolis extract (200 mg kg\(^{-1}\); p.o.), for 3 weeks. Group III received 18 mg kg\(^{-1}\) total cumulative dose of Dox i.p. Group IV received Dox and propolis extract. Serum and testicular samples were
collected 48 h after the last treatment. In addition, the effects of propolis extract and Dox on the growth of solid Ehrlich carcinoma in mice were investigated. Dox reduced sperm count, markers of testicular function, steroidogenesis and gene expression of testicular 3β-hydroxysteroid dehydrogenase (3β-HSD), 17β-hydroxysteroid dehydrogenase (17β-HSD) and steroidogenic acute regulatory protein (StAR). In addition, it increased testicular oxidative stress, inflammatory and apoptotic markers. Morphometric and histopathologic studies supported the biochemical findings. Treatment with propolis extract prevented Dox-induced changes without reducing its antitumor activity. Besides, administration of propolis extract to normal rats increased serum testosterone level coupled by increased activities and gene expression of 3β-HSD and 17β-HSD. Propolis extract may protect the testis from Dox-induced toxicity without reducing its anticancer potential.

**Keywords:** Doxorubicin; Propolis; Biochemical; Histopathological.

883. Effect of Simvastatin and Naringenin Coadministration on Rat Liver DNA Fragmentation and Cytochrome P450 Activity: An in Vivo and in Vitro Study


This study was designed to assess the effect of naringenin (NRG) on simvastatin (SV)-induced hepatic damage in rat and to investigate the effects of these drugs on cytochrome P450 (CYP) 2E1 and 3A1/2 isoforms in order to evaluate the possibility of their coadministration. Hepatic damage in rat was induced by SV (20 and 40 mg/kg/day, po for 30 days). The protective effect of NRG (50 mg/kg/day, po) was identified by estimating liver CYP2E1 and CYP3A1/2 activities against cancer cells viability, proliferation, apoptosis, p53 and real-time polymerase chain reaction for gene expression of survivin and caspase-3. Not only the two drugs were found to significantly reduce the viability of different cell lines, but they also were shown to have potent dose-dependent reduction of cellular proliferation. They exhibited cytotoxicity IC50 values of 3.69 and 4.16 mM for naproxen and cromolyn, respectively. Viability and proliferation results clearly correlated with apoptosis and p53 experiments in showing that both drugs significantly raised apoptotic percentages. Furthermore, we observed a significant reduction in survivin and elevation of caspase-3 gene expression upon exposure to the two drugs. It can be concluded that both naproxen and cromolyn have significant anti-cancer properties.

**Keywords:** Cancer, Caspase-3, Cromolyn, Glycogen Synthase Kinase, Naproxen, P53, Survivin

885. Biochemical Modifications and Neuronal Damage in Brain of Young and Adult Rats After Long-Term Exposure to Mobile Phone Radiations

Motawi TK, Darwish HA, Moustafa YM and Labib MM.


This study investigated the effect of exposure to mobile phone radiations on oxidative stress and apoptosis in brain of rats. Rats were allocated into six groups (three young and three adult). Groups 1 and 4 were not subjected to the radiation source and served as control groups. In groups 2 and 5, the mobile phones were only connected to the global system for mobile communication, while in groups 3 and 6, the option of calling was in use. Microwaves were generated by a mobile test phone (SAR = 1.13 W/kg) during 60 days (2 h/day). Significant increments in conjugated dienes, protein carbonyls, total antioxidant status, and oxidative stress index along with a significant reduction of total antioxidant capacity levels were evident after exposure. Bas/Bcl-2 ratio, caspase-3 activity, and tumor necrosis factor-alpha level were enhanced, whereas no DNA fragmentation was detected. The relative brain weight of young rats was greatly affected, and histopathological examination reinforced the neuronal damage. The study highlights the detrimental effects of mobile phone radiations on brain during young and adult ages. The interaction of these radiations with brain is via dissipating its antioxidant status and/or triggering apoptotic cell death.

**Keywords:** Mobile Phone Brain Oxidative Stress Apoptosis Neuronal Damage Rats

886. The Therapeutic Effects of Bone Marrow-Derived Mesenchymal Stem Cells and Simvastatin in A Rat Model of Liver Fibrosis

Tarek M. K. Motawi, Hazem M. Atta, Nermin A. H. Sadik and May Azzam

Liver fibrosis is the excessive accumulation of extracellular matrix (ECM) proteins including collagen that occurs in most types of chronic liver diseases. Studies concerning the capacity of mesenchymal stem cells (MSCs) and simvastatin (SIMV) to repair fibrotic tissues through reducing inflammation, collagen deposition, are still controversial. This study aimed to investigate the therapeutic efficacy of bone marrow (BM)-derived MSCs and SIMV on carbon tetrachloride (CCL4)-induced liver fibrosis in rats. Rats were divided into: normal, CCL4, CCL4/MSCs, CCL4/SIMV, CCL4/MSC/SIMV, and SIMV groups. BM-derived MSCs were detected by RT-PCR of CD29 and were then infused into the tail vein of female rats that received CCL4 injection to induce liver fibrosis. Sex-determining region Y (SRY) gene on Y-chromosome was assessed by PCR to confirm homing of the male stem cells in liver tissue of the female recipients. Serum liver function tests, liver procollagens I and III, tissue inhibitors of metalloproteinase-1 (TIMP-1), endoglin, matrix metalloproteinase-1 (MMP-1) gene expressions, transforming growth factor-beta (TGF-β1) immunostaining, and histopathological examination were performed. MSCs and SIMV decreased liver procollagens I and III, TIMP-1 and endoglin gene expressions, TGF-β1 immunostaining, and serum liver function tests compared with the CCL4 group. MMP-1 expression was increased in the CCL4/MSC group. Histopathological examination as well as fibrosis score supports the biochemical and molecular findings. It can be concluded that MSCs and SIMV were effective in the treatment of hepatic CCL4-induced fibrosis-rat model. Treatment with MSCs was superior to SIMV. This antifibrotic effect can be attributed to their effect on the MMP/TIMP, balance which is central in fibrogenesis.

**Keywords:** Liver Fibrosis Mesenchymal Stem Cells Simvastatin Rats.

### 887. Propolis Enhances the Effectiveness of Praziquantel in Experimental Schistosomiasis: Biochemical and Histopathological Study

Tamer Y. Mahmoud, Sherine M. Rizk, Amany S. Maghraby and Amira A. Shaheen

*Parasitology Research, 113: 4513-4523 (2014) IF: 2.327*

Despite the wide current use of praziquantel (PZQ) in treatment of schistosomiasis, low cure rates have been recorded in many studies. The aim of this study was directed to evaluate the curative effect of propolis (Pps) alone or in combination with PZQ on biochemical, immunological, parasitological, and histological changes associated with experimental schistosomiasis in mice. Schistosoma mansoni-infected mice were divided into two experimental sets, each with four subgroups: (i) untreated, (ii) treated with Pps/day p.o for 4 weeks, (iii) treated with PZQ p.o 2x500 mg/kg bd wt, and (iv) treated with Pps+PZQ as in group ii and iii; all treatments started on the 8th week postinfection, in addition to uninfected group as control for the previous groups. Treatment of infected mice with Pps, although failed to eradicate the worm, significantly reduced the hepatic granuloma number, their lymphocytic infiltration and aggregation, hepatic and splenic myeloperoxidase (MPO) activity and plasma, and liver and thymus nitric oxide (NOx) levels together with normalization of plasma proteins and alleviation of oxidative damage in the examined tissues as evidenced by reduction of malondialdehyde (MDA) and normalization of glutathione (GSH). Promising results were obtained when Pps was given in combination with PZQ, where the anti-schistosomal activity of PZQ was markedly potentiated with complete alleviation and amelioration of the histological and biochemical alteration associated with schistosomiasis. This study highlights the potential usefulness of Pps as an adjunct to PZQ in schistosomiasis.


### 888. Alterations in Circulating Angiogenic and Anti-Angiogenic Factors in Type 2 Diabetic Patients With Neuropathy

Tarek Kamal Motawi, Sherine Maher Rizk, Ibabl Abdel-Rahman Ibrahim and Yasmin Farid El-Emady


Diabetic peripheral neuropathy (DPN) is one of the most common diabetic chronic complications. There is an increased attention directed towards the role of angiogenic factors including vascular endothelial growth factor (VEGF) and anti-angiogenic factors including soluble endoglin (sEng) as contributors to diabetic microvascular complications including neuropathy. The purposes of this study were to determine the role of these angiogenesis regulators in the prognosis of DPN. The study group included 60 patients with type 2 diabetes mellitus (T2DM) and 20 clinically healthy individuals. The patients were divided into two groups. Group I included 20 T2DM patients without peripheral neuropathy, and Group II consisted of 40 T2DM patients with DPN. In all groups, plasma VEGF, sEng and endothelin-1 (ET-1), nitric oxide and ET-1 mRNA were estimated. Plasma levels of VEGF, sEng, ET-1 and nitric oxide were significantly elevated in diabetic patients (Groups I and II) compared with healthy control subjects, with a higher increase in their levels in patients with DPN compared with diabetic patients without peripheral neuropathy. Measurement of plasma levels of angiogenesis-related biomarkers in high-risk diabetic patients might identify who later develop DPN, thus providing opportunities for early detection and targets for novel treatments.

**Keywords:** Diabetic Peripheral Neuropathy; Endothelin-1; Endothelin-1 Mrna; Nitric Oxide; Soluble Endoglin; Vascular Endothelial Growth Factor.

### 889. Chronic Effects of Clozapine Administration on Insulin Resistance in Rats: Evidence for Adverse Metabolic Effects

Mohamed M. El-Seweidy, Nermin Abdel Hamid Sadik and Marwa M. Malek

*Pathology Research and Practice, 210(1): 5-9 (2014) IF: 1.562*

Chronic treatment with the atypical antipsychotics clozapine has been associated with an increased risk for deterioration of glucose homeostasis, leading to hyperglycemia and insulin resistance diabetes. The present study mainly aimed to investigate possible mechanisms underlying clozapine-induced hyperglycemia. Male Wistar albino rats were randomly divided into two groups (each consists of 12 rats). The first group received clozapine orally at a dose of 10 mg/kg body weight daily for 6 weeks, while the other group received the drug vehicle only and served as the control group. At the end of the six weeks, hyperglycemia, hyperinsulinemia and insulin resistance, as indicated by Homeostatic model assessment of insulin resistance (HOMA-IR),
were observed in the clozapine group as compared with the control group. This disturbance in glucose regulation was associated with non-significant changes in body weight, serum cortisol level, and hepatic glycogen content. The Clozapine group showed a significant increase in hepatic phosphorolase activity and in the gene expression level of hepatic glucose-6-phosphatase (G6Pase) enzymes compared to the control group. It can be concluded that clozapine-induced hyperglycemia and insulin resistance occur in a manner mostly independent of weight gain, and may be attributed to an increase in hepatic phosphorolase activity and increased expression level of G6Pase.

**Keywords:** Clozapine; Hyperglycemia; Hyperinsulinemia; Liver; Rats.

890. Visfatin -948G/T and Resistin -420C/G Polymorphisms in Egyptian Type 2 Diabetic Patients With and Without Cardiovascular Diseases

Tarek M.K. Motawi, Olfat G. Shaker, Maha M. El-Sawalhi and Zeinab M. Abdel-Nasser

*Genome, 57:* 259-266 (2014) IF: 1.558

Diabetes mellitus is one of the main threats to human health in the 21st century. Visfatin/Nampt and resistin are novel adipokines that have been implicated in the pathogenesis of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) complication. Several genetic studies have shown inconsistent results regarding association of visfatin/Nampt gene (NAMPT) and resistin gene (RETN) polymorphisms with T2DM and CVD complications. Here, we investigate whether NAMPT -948G/T and RETN -420C/G polymorphisms are associated with T2DM, its CVD complications, and serum adipokines levels in 90 Egyptian diabetic patients (44 without CVD and 46 with CVD) along with 60 healthy control subjects. Higher frequencies of NAMPT -948G/G and RETN -420G/G were observed among T2DM patients compared with controls. Furthermore, the frequencies of these genotypes were significantly higher in T2DM patients with CVD than those without CVD. Both NAMPT -948G/G and RETN -420G/G genotypes and G alleles were significantly associated with T2DM and CVD in Egyptian diabetic patients. Moreover, serum visfatin/Nampt and resistin levels were markedly elevated in T2DM patients, with the highest values observed in G/G genotypes among T2DM patients with CVD. In addition, positive correlations were observed between plasma adipokines levels and CVD risk factors. In conclusion, our data suggests that genetic variations in NAMPT -948G/T and RETN -420C/G may contribute to the disposition for T2DM and its CVD complications in Egyptian patients. However, further studies with greater sample size should be performed to verify these results.

**Keywords:** Nampt -948G/T; Retn -420C/G; Cardiovascular Disease; Diabète Sucré De Type 2; Maladies Cardiovasculaires; Polymorphism; Polymorphisms; Type 2 Diabetes Mellitus. 4

891. Simple Molecular Diagnostic Method for Fragile X Syndrome in Egyptian Patients: Pilot Study

Nagwa A. Meguid, Manal F. Ismail, Rashia S. El-Mahdy, Maged A. Barakat and Mostafa K. El-Awady


**Background:** Poor knowledge about Fragile X syndrome (FXS) may be a major barrier to early diagnosis that could improve quality of life and prognosis especially in the developing countries.

**Aim:** The aim of this study was to evaluate simple and reproducible method for premutation detection in females of fragile X families for the first time in Egypt.

**Subjects and Methods:** We have developed a rapid modified polymerase chain reaction (PCR)-based screening tool for expanded Fragile X mental retardation 1 (FMR1) alleles. This method utilizes betaine as additive to facilitate FMR 1 gene amplification. We screened fifty three males, thirty two first-degree females; twenty normal healthy controls in addition to six reference samples.

**Results:** Simple PCR method showed 16 males with abnormal CGG repeats, where 10 of their mothers and four sisters had FMR 1 premutation. Consanguineous marriage was present in 66.6% percent of the studied families. Studying the correlation between genotype and clinical manifestations showed premature ovarian failure in 40% and learning disability in 50% of the studied female carriers.

**Conclusion:** FXS has to be ruled out in families with consanguineous parents, before assuming that familial mental retardation is due to autosomal recessive gene defects. Early carrier detection may reduce the number of affected children. In conclusion, more studies are still needed of much larger sample size with known allele sizes in order to guarantee the accuracy of the method used.

**Keywords:** Key Words: Fragile X Syndrome, Consanguinity, Carrier Detection.

892. Ozone Ameliorates Age-Related Oxidative Stress Changes in Rat Liver and Kidney: Effects of Pre- and Post-Ageing Administration

M. H. Safwat, M. M. El Sawalhi1, M. N. Mausouf, and A. A. Shaheen1

*Biochemistry-Moscow, 79:* 450-458 (2014) IF: 1.353

The ageing process is known to be accompanied by increased oxidative stress and compromised antioxidant defenses. Controlled ozone administration has been shown to be effective in various pathophysiological conditions with an underlying oxidative burden. However, its effect on the biochemical alterations associated with the ageing process has been rarely studied. Therefore, the present work was carried out to study the role of ozone in counteracting the state of oxidative stress associated with ageing in rat liver and kidneys using two experimental models. In the pre-ageing model, ozone was administered prior to the onset of ageing at adulthood and continued after the start of the ageing process (3-month-old rats until the age of 15 months). While in the post-ageing model, ozone was administered after ageing has begun and lasted for one month (14-month-old rats until the age of 15 months). The pre-ageing ozone administration effectively reduced lipid and protein oxidation markers, namely, malondialdehyde and protein carbonyl levels and decreased lipofuscin pigment deposition in rat liver and kidneys. Moreover, it significantly restored hepatic and renal reduced glutathione (GSH) contents and normalized cytosolic hepatic glutathione peroxidase activity. Similar but less pronounced effects were observed in the post-ageing ozone-treated group. Nevertheless, in the latter model ozone administration failed to significantly affect liver and kidney lipofuscin levels, as well as kidney GSH contents. These data provide evidences for potentially positive effects of pre-ageing
893. Investigating the Cardio-Protective Abilities of Supplemental L-Arginine on Parameters of Endothelial Function in A Hypercholesterolemic Animal Model

Gad MZ, Abu el Maaty MA, El-Maraghy SA, Fahim AT and Hamdy MA.

*Journal of Nutritional Science and Vitamnology, 60(3): 145-151 (2014) IF: 0.868*

Endothelial dysfunction is now widely recognized as an early marker of cardiovascular disease, making its treatment, or complete avoidance, an emerging, interesting therapeutic target. This study investigated the ability of the highly intriguing amino acid L-arginine to influence endothelial function. Its therapeutic potential is also compared to that of known cardiovascular medications, namely nitroglycerin [a nitric oxide (NO) donor] and enalapril [an angiotensin-converting enzyme (ACE) inhibitor]. Fifty male New Zealand rabbits were included in the study, divided into 5 equal groups: control, hypercholesterolemia (untreated), hypercholesterolemia (+L-arginine), hypercholesterolemia (+enalapril), and hypercholesterolemia (+nitroglycerin). Biochemical investigations included measurement of circulating NOx, malondialdehyde (MDA), and lipid profile markers, as well as dimethylarginine dimethylaminohydrolase (DDAH) and ACE activities. Furthermore, aortic ACE activity and blood platelet aggregation were estimated. A histopathological examination and intimal thickness measurement were also conducted. Compared to the untreated hypercholesterolemic group, all agents were capable of positively influencing MDA levels, platelet aggregation and intimal thickness; however, only the L-arginine group was capable of beneficially and significantly altering both NOx levels and serum and aortic ACE activities. No agents were capable of modulating serum DDAH activity inhibited by hypercholesterolemia. Based on the results of this study, L-arginine appears to be a novel cardio-protective agent, illustrated by its ability to ameliorate the deleterious effects of hypercholesterolemia on endothelial function, in a manner comparable to, and sometimes more potent than, commonly used cardiovascular medications.

**Keywords:** L-Arginine Cardio-Protection Endothelial Function.

894. Antibiotic Dispensing in Egyptian Community Pharmacies: An Observational Study

Nirmeen A. Sabrya, Samer F. Farida, Dalia M. Dawoud

*Research In Social and Administrative Pharmacy, 10(1): 168-184 (2014) IF: 1.202*

**Background:** Antibiotics are commonly dispensed medications from community pharmacies, and they are frequently prescribed for inappropriate indications. In many countries, they are easily accessible without prescriptions. The inappropriate use of antibiotics results in the emergence of resistant bacterial strains, which represents a considerable public health problem, particularly in developing countries.

**Objective:** This study aimed to describe the pattern of antibiotics dispensing from Egyptian community pharmacies and to collect baseline descriptive data on the antibiotics dispensed and their appropriateness.

**Methods:** A cross-sectional, observational study of antibiotic dispensing encounters was conducted at 36 randomly selected pharmacies in Greater Cairo, Egypt. Data were collected during one shift at each pharmacy. Structured questionnaires recording patient demographics, antibiotics dispensed and reasons for dispensing were completed for each antibiotic dispensing encounter. The data were descriptively analysed.

**Results:** Overall, 1158 antibiotics were dispensed during the study period with a total cost of L.E. 24,487 (approximately 3,673 $USD). While self-medication and purchasing without medical prescriptions were common, representing around 23.3% of the antibiotics (n = 270), most antibiotics were prescribed by a doctor or dentist (n = 736, 63.6%). Pharmacist recommendations accounted for the remainder (n = 152, 13.1%). The main reasons for antibiotic use were respiratory tract ailments and gastrointestinal symptoms. The antibiotic most commonly dispensed were: penicillins, erythromycin, metronidazole, neomycin, clotrimazole and tetracyclines. Approximately 70% of the antibiotics dispensed on prescriptions were judged to be appropriate for the indications while this percentage was around 61% for antibiotics dispensed on pharmacist recommendation and patient's request.

**Conclusions:** The results of this study show that antibiotics are frequently dispensed from community pharmacies in Egypt without appropriate prescriptions and for inappropriate indications. These findings support the need for strict enforcement of pharmacy laws through improved inspection processes. They highlight the need for evidence-based guidelines and educational interventions to improve antibiotic prescribing and dispensing practices.

**Keywords:** Antibiotics; Prescription.

895. Can Zinc Levels Predict Response To Pegylated-Interferon and Ribavirin Therapy in Hepatitis C Genotype 4 Infected Egyptian Patients?

Mohamed AA, Abbassi MM, Hamed WA, EzzEl-Arab MA and Aref AM.


**Background and Aims:** Zinc has been found to be low in chronic hepatitis patients. Its level was correlated with response to Interferon/ribavirin therapy in patients infected with hepatitis C genotype 1. In Egypt, inexpensive predictors to treatment response in Hepatitis C genotype 4 infected patients are desperately needed. We aim to explore if pretreatment zinc serum levels correlate with response to pegylated-interferon and ribavirin therapy in Egyptian patients.

**Methods:** This is an observational prospective study where 57 treatment naive hepatitis C genotype 4 infected patients that were Hepatitis B and Human Immunodeficiency virus negative were recruited in a hospital setting. The study was performed from October 2010 till June 2012. Patients had Liver biopsy and basic biochemical profiles were performed pretreatment for all patients. Treatment consisted of 48 weeks of pegylated-interferon-alpha2a and ribavirin therapy. Blood samples were withdrawn from 21 healthy subjects to compare zinc levels and other biochemical markers. Patients were followed up to 72 weeks.
Results: Pretreatment serum zinc levels were significantly lower in hepatitis C infected patients compared to healthy volunteers (p < 0.05). Moreover, zinc levels correlated to sustained virological response in treated patients (p = 0.00).
Conclusion: Serum zinc levels can be used as an inexpensive predictor to effective Pegylated-interferon/ribavirin therapy in Egyptian patients infected with Hepatitis C genotype 4.
Keywords: Hepatitis C; Genotype 4; Zinc; And Egypt.

896. Factors Affecting Warfarin Dose Requirements And Quality of Anticoagulation in Adult Egyptian Patients: Role of Gene Polymorphism

Bazan NS, Sabry NA, Rizk A, Mokhtar S and Badary OA.
Irish Journal of Medical Science, 183: 161-172 (2014) IF: 0.573
Background: Warfarin is the mainstay of anticoagulation therapy worldwide. CYP2C9 and VKORC1 are two major genetic factors associated with inter-individual and inter-ethnic variability in the warfarin dose.

Aim: This study aims to assess the impact of VKORC1-1639G>A polymorphism and the most common CYP2C9 variant alleles (+2 and *3) on warfarin response in Egyptian patients.

Methods: Genetic analysis of VKORC1-1639G>A and CYP2C9*2, CYP2C9*3 was performed using real-time PCR system. Patients maintained on a constant dose targeting an international normalized ratio range of 2.3-2.5 for at least three consecutive times were considered as good candidates. A stepwise linear regression analysis was used to determine the independent effects of genetic and non-genetic factors on daily warfarin dose requirements.

Results: Patients carrying VKORC1 and CYP2C9 variant genotypes needed a 44.8 % lower mean daily warfarin dose as compared to wild types. Patients with G allele for VKORC1-1639G>A had a significantly higher number of thromboembolic complications per month during therapy. On the first 30 days of therapy, presence of a variant allele either in VKORC1 or in CYP2C9 was associated with increased time required to achieve stable dosing. Multiple regression analysis showed that, VKORC1-1639G>A, age, CYP2C9*3, and smoking status explained 43.4 % of the overall variability in the warfarin dose.

Conclusion: VKORC1-1639G>A and CYP2C9 polymorphisms contribute to the difference in warfarin dose requirements and quality of anticoagulation amongst Egyptian patients. Study results support using personalized warfarin treatment in Egyptian patients.

Keywords: Warfarin, Genetics, Polymorphism.

897. Signatures of Protective Memory Immune Responses During hepatitis C virus reinfection

Abdel-Hakeem MS, Bédard N, Murphy D, Bruneau J and Shoukry NH.

Background & Aims: Development of a vaccine against hepatitis C virus (HCV) has been hindered by our limited understanding of immune correlates of protection during real-life exposure to the virus. We studied the immune response during HCV reinfection.

Methods: We analyzed blood samples from participants in the Montreal Acute Hepatitis C Injection Drug User Cohort Study who were reinfected with HCV from 2009 to 2012. Five patients spontaneously resolved their second infection and 4 developed chronic infections. We monitored the phenotypic and functional dynamics of HCV-specific memory T cell responses in all subjects during natural re-exposure and reinfection.

Results: Populations of CD4(+) and CD8(+) T cells with HCV-specific polyfunctional memory were expanded in all 5 individuals who resolved 2 successive HCV infections. We detected CD127(hi) HCV-specific memory CD8(+) T cells before reinfection regardless of a subject’s ability to clear subsequent infections. Protection against viral persistence was associated with the expansion of a CD127(NEG), PD1lo effector memory T cells at the peak of the response. We also observed broadening of T-cell response, indicating generation of de novo T-cell responses. The 4 individuals who failed to clear their subsequent infection had limited expansion of HCV-specific CD4(+) and CD8(+) memory T cells and expressed variable levels of the exhaustion marker PD1 on HCV-specific CD8(+) T cells. Dominant epitope regions of HCV strains isolated from patients with persistent reinfection had sequence variations that were not recognized by the pre-existing memory T cells.

Conclusions: Protection from persistent HCV reinfection depends on the magnitude, breadth, and quality of the HCV-specific memory T-cell response. Sequence homology among viruses and ability of T cells to recognize multiple strains of HCV are critical determinants of protective memory.

Keywords: Cytokines; Protective immunity; Immune Regulation;
899. A Highly Abundant Bacteriophage Discovered in the Unknown Sequences of Human Faecal Metagenomes

Metagenomics, or sequencing of the genetic material from a complete microbial community, is a promising tool to discover novel microbes and viruses. Viral metagenomes typically contain many unknown sequences. Here we describe the discovery of a previously unidentified bacteriophage present in the majority of published human faecal metagenomes, which we refer to as crAssphage. Its ~97 kb genome is six times more abundant in publicly available metagenomes than all other known phages together; it comprises up to 90% and 22% of all reads in virus-like particle (VLP)-derived metagenomes and total community metagenomes, respectively; and it totals 1.68% of all human faecal metagenomic sequencing reads in the public databases. The majority of crAssphage-encoded proteins match no known sequences in the database, which is why it was not detected before. Using a new co-occurrence profiling approach, we predict a Bacteroides host for this phage, consistent with Bacteroides-related protein homologues and a unique carbohydrate-binding domain encoded in the phage genome.

Keywords: Bioinformatics; Virology; Metagenomics; Bacteriophage; Cross assembly.

900. Initial Bridges Between Two Ribosomal Subunits Are Formed Within 9.4 Milliseconds, as Studied by Time-Resolved Cryo-Em
Tanvir R. Shaikhha, Aymen S. Yassina, Zonghuan Luh, David Barnard, Xing Menga, Toh-Ming Luba, Terence Wagenknecht and Rajendra K. Agrawala

Association of the two ribosomal subunits during the process of translation initiation is a crucial step of protein synthesis. The two subunits (30S and 50S) of the bacterial 70S ribosome are held together by 12 dynamic bridges involving RNA-RNA, RNA-protein, and protein-protein interactions. The process of bridge formation, such as whether all these bridges are formed simultaneously or in a sequential order, is poorly understood. To understand such processes, we have developed and implemented a class of microfluidic devices that mix two components to completion within 0.4 ms and spray the mixture in the form of microdroplets onto an electron microscopy grid, yielding a minimum reaction time of 9.4 ms before cryofixation. Using these devices, we have obtained cryo-EM data corresponding to reaction times of 9.4 and 43 ms and have determined 3D structures of ribosomal subunit association intermediates. Molecular analyses of the cryo-EM maps reveal that eight intersubunit bridges (bridges B1a, B1b, B2a, B2b, B3, B7a, B7b, and B8) form within 9.4 ms, whereas the remaining four bridges (bridges B2c, B4, B5, and B6) take longer than 43 ms to form, suggesting that bridges are formed in a stepwise fashion. Our approach can be used to characterize sequences of various dynamic functional events on complex macromolecular assemblies such as ribosomes.

Keywords: Millisecond Time Resolution Cryo-Em; Ribosomal Intersubunit Bridges.

901. One Health People, Animals, and the Environment
Hossam M. Ashour
Clinical Infectious Diseases, 59(10): 1510 (2014) IF: 9.416

The world of emerging infectious diseases is enormous (both in scope and impact) and is comprised mainly of zoonotic diseases. The editors have gathered experts to present their perspective on different angles of the One Health concept, which addresses how complex interactions of humans, animals, and environment lead to infectious diseases. To emphasize that the authors repeatedly stress that the vast majority of emerging infectious diseases in recent decades are zoonotic in origin with a clear involvement of wildlife, highlighting the ill effects on human health. It is also pointed out that humans’ impact on the environment leads to similar ill effects on animal health. This highlights the complex multidirectional impacts of each of these domains (humans, animals, and environment) on one another. As the factors for a “microbial storm” are still in place, these ill effects are expected to be on the rise in the coming years.

Keywords: Infectious diseases; Zoonotic diseases; One health.

902. In Vitro-Induced Cell-Mediated Immune Deviation to Encephalitogenic Antigens
Shukkur M Farooq, Walid F Elkhati and Hossam M Ashour

The injection of antigens into the Anterior Chamber (AC) of the eye induces Anterior Chamber Associated Immune Deviation (ACAID), which is a potent form of immune deviation that is largely attributed to the effect of TGFβ2 in the aqueous humor on ocular antigen-presenting cells (APCs). ACAID antigen presentation via APCs and B cells leads to the generation of antigen-specific T regulatory cells. The encephalitogenic antigens Myelin oligodendrocyte glycoprotein (MOG) and Myelin basic protein (MBP) have an obvious clinical relevance. We hypothesized that the intravenous injection of in vitro-generated ACAID APCs or in vitro-generated ACAID B cells specific to the encephalitogenic antigens MOG35-55/MBP induces specific peripheral tolerance in recipient BALB/c mice. We examined the suppression of MOG35-55-specific/MBP-specific inflammatory responses using delayed-type hypersensitivity (DTH) assays and Local Adoptive Transfer (LAT) assays. Results indicated that MOG35-55-specific/MBP-specific tolerance was generated after the intravenous injections of MOG35-55-specific/MBP-specific ACAID APCs, MOG35-55-specific/MBP-specific ACAID B cells, and MOG35-55-specific/MBP-specific ACAID T regulatory cells. The specific immune deviation was in vitro-induced, cell-mediated, and specific to the encephalitogenic antigens MOG35-55/MBP. This in vitro-mediated approach for the generation of MOG35-55/MBP-specific tolerance opens up avenues for the application of ACAID as a tool for the therapy of Multiple Sclerosis, Schizophrenia, and other diseases.

Keywords: Anterior Chamber; Immune Tolerance; Myelin; B Cells.
model validity. As shown in an application to international stock markets, the model yields useful information on dependence structure of the return distributions for portfolio allocation and risk management with a reasonably good predictive power.

**Keywords:** Financial risk management; Nig distribution; T-copula.

**Dept. of Political Science**

**1247. Minorities Between State Society Dynamics in Post Revolutionary Processes**

Mai Mogib Abdel Moneim Mosad  
*Book Published by Dictus Publishing, (2014)*

The concept of “minority” has acquired new urgency. The last two decades have witnessed a widespread resurgence of the political reflections of the concept. Although the dilemmas are enduring, it’s now possible to confront them in a quite new light. Revolutionary periods are often a product of numerous events that snowball into fully fledged eruptions that lead to drastic changes in the political and social fabric of states and societies and thus to the context of minorities, and it’s clear that the case of Egypt introduced new gives to the concept and its reflections.

**Keywords:** Minorities; Egypt; Copts; State-Society Relations.

**1248. Wired Citizenship: Youth learning and activism in the Middle East**

Rehab Sakr  

Wired Citizenship examines the evolving patterns of youth learning and activism in the Middle East and North Africa (MENA). In today’s digital age, in which formal schooling often competes with the peer-driven outlets provided by social media, youth all over the globe have forged new models of civic engagement, rewriting the script of what it means to live in a democratic society. As a result, state-society relationships have shifted—never more clearly than in the MENA region, where recent uprisings were spurred by the mobilization of tech-savvy and politicized youth.

Combining original research with a thorough exploration of theories of democracy, communications, and critical pedagogy, this edited collection describes how youth are performing citizenship, innovating systems of learning, and re-imagining the practices of activism in the information age. Recent case studies illustrate the context-specific effects of these revolutionary new forms of learning and social engagement in the MENA region.

**Keywords:** Muslim brotherhood; Egypt; Children; Artists; Arab world; Cybrus; Turkey.

**Dept. of Statistics**

**1249. Chapter 4 Titled: Poverty and Inequality in the Arab Republic of Egypt’s Poorest Villages**

Sahar El Tawila, May Gadallah and Enas Ali A.El-Majeed  

This study provides a first-time assessment of the state of poverty and inequality among the poorest villages of Egypt. It used a unique survey conducted in 2009/2010 in 141 of the poorest 1,000 villages of Egypt, covering a total 10,568 households. The poverty rate in these villages is estimated at 81.7 percent against 22 percent for Egypt as a whole and 28 percent for rural Egypt. The Gini inequality across households in these villages is estimated at 29.4 percent against 31.1 percent for Egypt as a whole and 22.4 percent for rural areas. Thus, while the poverty rate in these villages is extremely high, the inequality level is very close to the national figure. The paper attempts to explain the level of inequality using a regression decomposition approach (Fiorio and Jenkins 2007) and a Gini coefficient regression in an effort to disentangle those factors that derive from household abilities such as health, education and employment (household characteristics) from those factors that derive from local opportunities such as the availability of health, education and economic facilities (village characteristics).

Factors such as higher employment and higher education, which are standard objectives of poverty reduction strategies, are found to reduce poverty but increase inequality. Other factors such as government employment and chronic illness reduce inequality but increase poverty. Hence, reducing poverty among the poorest people of Egypt may necessarily entail an increase in inequality.

**Keywords:** Poverty; Inequality; Regression based decomposition.

**Faculty of Commerce**

**Dept. of Business Administration**

**1250. Emerging Research on Islamic Marketing and Tourism in the Global Economy**

Hatem Osman Aly Salem El-Gohary  
*Publishing, 1-99 (2014)*

As the Middle East continues to grow as a predominant force within the international marketplace, research into Islamic practices and culture is necessary to promote business success in the region. Emerging Research on Islamic Marketing and Tourism in the Global Economy offers in-depth perspectives on the influence of Islam on consumer behavior, the travel industry, product development, and the promotion of goods and services. Focusing on current trends and tools, comprehensive interviews, questionnaires, and emerging research, this book is an essential reference source for academicians, entrepreneurs, policymakers, university students, and educators interested in research surrounding the impact of Islam on business.

**1251. Quality Management and Productivity**

Hatem Osman Aly Salem El-Gohary  
*Book Published by Lap Lambert Academic Publishing, (2014)*

The main aim of this book is to determine to what extent did quality management practices been effectively adopted and implemented by Pakistani manufacturing companies as well as to
Results: 60.47% (26/43) of S. aureus clinical isolates were weak biofilm producers. The CRA method detected positive-slime phenotypes (13.95%), but was unable to distinguish weak from negative producers. BLM assays demonstrated significant correlations with RES (highest), CRV and SAF (lowest). Lower coefficient of variation values indicate precision. BLM scored highest precision (coefficient of variation = 0.013) followed by RES, SAF and CRV.

Conclusion: BLM and RES detect live biomass in S. aureus biofilms (for physiological studies), SAF and CRV detect live/dead bacteria plus biofilm matrix (for monitoring overall biofilm architecture, not only its cell viability). Reliable assays are essential for effective biofilm therapy.

Keywords: Biofilm, Bioluminescence, Quantitation, Safranine, Staphylococcus Aureus.

907. Eye-Mediated Immune Tolerance To Type II Collagen in Arthritis-Prone Strains of Mice
Shukkur M. Farooq, Ashok Kumar and Hossam M. Ashour
Journal of Cellular and Molecular Medicine, 18(12); 2512-2518 (2014) IF: 3.698

Type II collagen (CII) is a cartilage structural protein that plays important roles in joint function, arthritis and ageing. In studying the ability of CII to induce eye-mediated specific immune tolerance, we have recently proven that CII is capable of inducing anterior chamber-associated immune deviation (ACAID) in Balb/c mice. Here, we study the ability of CII to induce eye-mediated immune tolerance in strains of mice that are prone to the induction of rheumatoid arthritis. Thus, we hypothesized that CII induces ACAID in DBA/1 mice and in C57BL/6 mice through the AC route (direct injection) or the intravenous route (adoptive transfer of in vitro-generated CII-specific ACAID macrophages or of CII-specific in vitro-generated T regulatory cells). Specific immune tolerance induction was assessed using both delayed-type hypersensitivity (DTH) and local adoptive transfer (LAT) assays. Results indicated the ability of CII to generate CII-specific ACAID-mediated immune tolerance in vivo and in vitro in both DBA/1 mice and C57BL/6 mice. These findings could be beneficial in studies of immune tolerance induction using CII.

Keywords: Acaid; Peripheral Tolerance; Immune Privilege; Regulatory T Cells; Collagen Type II; C57bl/6 Mice; Dba/1 Mice.

908. Protein Kinase Expression as a Predictive Factor for Interferon Response in Chronic Hepatitis C Patients
Amal A. Mohamed, Magdi A. Amin, Mai M. Ragab, Soheir A. Ismail and Amin Abdel M. Baki

Egypt has the highest prevalence of hepatitis C virus (HCV) worldwide. Currently, combined pegylated interferon and ribavirin therapy are the standard treatment. The biological activity of interferon (IFN) is mediated by the induction of intracellular antiviral proteins, such as 20–50 oligoadenylate synthetase, and dsRNA-activated protein kinase. IFN-inducible doublestranded RNA-activated protein kinase (PKR) is thought to play a key antiviral role against HCV. Some studies observed that PKR expression was higher in sustained viral responders compared with the non-responders. The PKR is considered as antiviral toward HCV and responsible for IFN’s effect against HCV while others have showed that, there were kinetic results indicate that HCV infection is not altered by reduced levels of PKR, indicating that HCV is resistant to the translational inhibitory effects of the phosphorylated forms of PKR.

This study was conducted on 50 consecutive patients with chronic HCV infection (CHC) and 20 healthy controls. All the patients were subjected to clinical and laboratory assessment, abdominal ultrasound, and liver biopsy. Determination of PKR gene quantity by using a real time PCR was done at the baseline and at the end of treatment for all patients and controls. Pre-treatment levels of protein kinase gene were significantly higher in responders in comparison with non-responders (P<0.001). It was found that 97.06% of patients who were responding to treatment had the expression of protein kinase gene greater than 26 cycle threshold.

Keywords: Chronic Hepatitis C; Pegylated Interferon; Protein Kinase Gene.

909. Pharmacomicrobiomics: the Impact of Human Microbiome Variations on Systems Pharmacology and Personalized Therapeutics
Marwa ElRakaiby, Bas E. Dutilh, Mariam R. Rizkallah, Annemarie Boleij, Jason N. Cole and Ramy K. Azziz

The Human Microbiome Project (HMP) is a global initiative undertaken to identify and characterize the collection of human-associated microorganisms at multiple anatomic sites (skin, mouth, nose, colon, vagina), and to determine how intra-individual and inter-individual alterations in the microbiome influence human health, immunity, and different disease states. In this review article, we summarize the key findings and applications of the HMP that may impact pharmacology and personalized therapeutics. We propose a microbiome cloud model, reflecting the temporal and spatial uncertainty of defining an individual's microbiome composition, with examples of how intra-individual variations (such as age and mode of delivery) shape the microbiome structure.

Additionally, we discuss how this microbiome cloud concept explains the difficulty to define a core human microbiome and to classify individuals according to their biome types. Detailed examples are presented on microbiome changes related to colorectal cancer, antibiotic administration, and pharmacomicrobiotics, or drug-microbiome interactions, highlighting how an improved understanding of the human microbiome, and alterations thereof, may lead to the development of novel therapeutic agents, the modification of antibiotic policies and implementation, and improved health outcomes. Finally, the prospects of a collaborative computational microbiome research initiative in Africa are discussed.

Keywords: Pharmacogenomics, Microbiome, Systems Biology, Genome, Bioinformatics, Human, Pharmacometrics.

910. Morphologic and Molecular Evaluation of Chlamydia Trachomatis Growth in Human Endocervix Reveals Distinct Growth Patterns
Yasser Mohamed Elsayed Metwally Abdelrahman
Frontiers in Cellular and Infection Microbiology, 4: 1-12 (2014) IF: 2.62
In vitro models of Chlamydia trachomatis growth have long been studied to predict growth in vivo. Alternative or persistent growth modes in vitro have been shown to occur under the influence of numerous stressors but have not been studied in vivo. Here, we report the development of methods for sampling human infections from the endocervix in a manner that permits a multifaceted analysis of the bacteria, host and the endocervical environment. Our approach permits evaluating total bacterial load, transcriptional patterns, morphology by immunofluorescence and electron microscopy, and levels of cytokines and nutrients in the infection microenvironment.

By applying this approach to two pilot patients with disparate infections, we have determined that their contrasting growth patterns correlate with strikingly distinct transcriptional biomarkers, and are associated with differences in local levels of IFNγ. Our multifaceted approach will be useful to dissect infections in the human host and be useful in identifying patients at risk for chronic disease. Importantly, the molecular and morphological analyses described here indicate that persistent growth forms can be isolated from the human endocervix when the infection microenvironment resembles the in vitro model of IFNγ-induced persistence.

**Keywords:** Bacterial Persistence, Chlamydia Trachomatis, Endocervix, Human, Interferon Gamma, Indole.

### 911. Monte Carlo Simulation Analysis of Ceftobiprole, Dalbavancin, Daptomycin, Tigecycline, Linezolid and Vancomycin Pharmacodynamics Against Intensive Care Unit-Isolated Methicillin-Resistant Staphylococcus Aureus

Ahmed Hamed Salem, George G Zhanel, Safaa A Ibrahim and Ayman M Noreddin

**Clinical and Experimental Pharmacology and Physiology, 41(6): 437-443 (2014) IF: 2.405**

The aim of the present study was to compare the potential of ceftobiprole, dalbavancin, daptomycin, tigecycline, linezolid and vancomycin to achieve their requisite pharmacokinetic/pharmacodynamic (PK/PD) targets against methicillin-resistant Staphylococcus aureus isolated from intensive care unit (ICU) settings.

Monte Carlo simulations were carried out to simulate the PK/PD indices of the investigated antimicrobials. The probability of target attainment (PTA) was estimated at minimum inhibitory concentration values ranging from 0.03 to 32 µg/mL to define the PK/PD susceptibility breakpoints. The cumulative fraction of response (CFR) was computed using minimum inhibitory concentration data from the Canadian National Intensive Care Unit study.

Analysis of the simulation results suggested the breakpoints of 4 µg/mL for ceftobiprole (500 mg/2 h t.i.d.), 0.25 µg/mL for dalbavancin (1000 mg), 0.12 µg/mL for daptomycin (4 mg/kg q.d. and 6 mg/kg q.d.) and tigecycline (50 mg b.i.d.), and 2 µg/mL for linezolid (600 mg b.i.d.) and vancomycin (1 g b.i.d. and 1.5 g b.i.d.). The estimated CFR were 100, 100, 70.6, 88.8, 96.5, 82.4, 89.4, and 98.3% for ceftobiprole, dalbavancin, daptomycin (4 mg/kg/day), daptomycin (6 mg/kg/day), linezolid, tigecycline, vancomycin (1 g b.i.d.) and vancomycin (1.5 g b.i.d.), respectively.

In conclusion, ceftobiprole and dalbavancin have the highest probability of achieving their requisite PK/PD targets against methicillin-resistant Staphylococcus aureus isolated from ICU settings. The susceptibility predictions suggested a reduction of the vancomycin breakpoint to 1 µg/mL.

**Keywords:** Ceftobiprole; Intensive care unit; Methicillin Resistant staphylococcus aureus; Monte carlo simulation; Vancomycin.

### 912. A Sensitive Colorimetric Assay for Identification of Acinetobacter Baumannii Using Unmodified Gold Nanoparticles


**Aims:** Acinetobacter baumannii is a global health problem, which threatens many healthcare settings. The current study aims to develop a detection assay for Ac. baumannii using unmodified gold nanoparticles (AuNPs).

**Methods and Results:** Fifty-three Ac. baumannii clinical isolates were collected from Egyptian hospitals. Bacterial isolation and biochemical identification of isolates were carried out followed by DNA extraction using boiling method and PCR amplification of the 23S–16S rRNA intergenic spacer sequences (ITS). AuNPs were synthesized using citrate reduction method. Detection and optimization of Ac. baumannii amplicons using unmodified spherical AuNPs were performed using species-specific DNA oligonucleotide. The nano-gold assay was able to colorimetrically detect and distinguish Ac. baumannii from other Gram-negative bacteria. The turnaround time of the assay is about 2 h including sample treatment and amplification. The assay detection limit is 0.8125 ng of DNA.

**Conclusions:** The developed colorimetric assay is sensitive, fast and reliable and can be used for identification of Ac. baumannii. Significance and Impact of the Study. There is a need to develop robust, rapid, and specific methods for detection of Ac. baumannii isolated from clinical specimens. The developed nanogold assay prototype allows sensitive, specific and rapid detection of amplified DNA of A. baumannii and represents a reliable diagnostic tool to aid routine laboratory identification of this pathogen.

**Keywords:** Acinetobacter baumannii; Colorimetric assay; Gold nanoparticles; In vitro detection; Pcr.

### 913. First Report of Ndm-1-Producing Pseudomonas Aeruginosa in Egypt

Shukkur M. Farooq, Ashok Kumar, Hossam M. Ashour

**International Journal of Infectious Diseases, 29: 80-81 (2014) IF: 2.33**

This work reports the occurrence of New Delhi metallo-beta-lactamase 1 (NDM-1) in metallo-beta-lactamase-producing Pseudomonas aeruginosa in Egypt for the first time, and the presence of more than one blaMBL gene in carbapenem-resistant P. aeruginosa.

**Keywords:** Pseudomonas aeruginosa; New delhi Metallo-Beta-Lactamase 1 (Ndm-1); Verona integron; Encoded Metallo-Beta-Lactamase (Vim-2); Metallo-beta-Lactamases; Carbapenem Resistance; Egypt.
914. Remediation of the Effect of Adding Cyanides on An Algal/Bacterial Treatment of A Mixture of Organic Pollutants in A Continuous Photobioreactor

Tamer Essam, Marwa ElRakaiby and Azza Agha


The effect of inorganic pollutants on the treatment of organic pollutants using algal/bacterial microcosms was investigated in a continuous photobioreactor. The microcosm was composed of Chlorella vulgaris MM1 and Pseudomonas MT1 and was able to efficiently treat artificial waste-water contaminated with 6.4 salicylate and 2.2 mM phenol at a hydraulic retention time of 4 days. No negative effect was recorded when the waste-water was supplemented with 1.6 mM thiocyanate; however, the treatment efficiency severely deteriorated when the system was challenged with 0.74 mM cyanide. Addition of 2 g NaHCO3 1-1 did not improve the efficiency of the treatment. Toxicity of the pollutants to the alga was cyanide[thiocyanate][phenol][salicylate. The high toxicity of the waste-water was eliminated either by a 25-fold dilution or by photocatalytic pre-treatment which allowed the subsequent efficient biological treatment.

Keywords: Chlorella; Cyanide; Microcosm; Photosynthesis; Thiocyanate; Photocatalytic Pretreatment; Phenol; Pseudomonas Salicylate; Thiocyanate.


Zonghuan Lu, David Barnard, Tanvir R Shaikh, Xing Meng, Carmen A Mannella, Aymen S Yassin, Rajendra K Agrawal, Terence Wagenknecht and Toh-Ming Lu

Journal of Micromechanics and Microengineering, 24 (11); (2014) IF: 1.725

Time-resolved cryo electron microscopy (TRCEM) has emerged as a powerful technique for transient structural characterization of isolated biomacromolecular complexes in their native state within the time scale of seconds to milliseconds. For TRCEM sample preparation, microfluidic device [9] has been demonstrated to be a promising approach to facilitate TRCEM biological sample preparation. It is capable of achieving rapidly aqueous sample mixing, controlled reaction incubation, and sample deposition on electron microscopy (EM) grids for rapid freezing. One of the critical challenges is to transfer samples to cryo-EM grids from the microfluidic device. By using microspraying method, the generated droplet size needs to be controlled to facilitate the thin ice film formation on the grid surface for efficient data collection, while not too thin to be dried out before freezing, i.e., optimized mean droplet size needs to be achieved. In this work, we developed a novel monolithic three dimensional (3D) annular gas-assisted microfluidic sprayer using 3D MEMS (Micro Electro Mechanical System) fabrication techniques. The microsprayer demonstrated dense and consistent microsprays with average droplet size between 6-9 µm, which fulfilled the above droplet size requirement for TRCEM sample preparation. With droplet density of around 12-18 per grid window (window size is 58x58 µm), and the data collectible thin ice region of ~50% total wetted area, we collected ~800-1000 high quality CCD micrographs in a 6-8 hour period of continuous effort. This level of output is comparable to what were routinely achieved using cryo-grids prepared by conventional blotting and manual data collection. In this case, weeks of data collection process with the previous device [9] has shortened to a day or two. And hundreds of microliter of valuable sample consumption can be reduced to only a small fraction.

Keywords: Microfluidics; Cryo Em; Microdroplet; Micronozzle; Microspray; Monolithic Device; Time-Resolved Temp

916. Application of Plackett–Burman Screening Design To The Modeling of Grafted Alginate–Carrageenan Beads for the Immobilization of Penicillin G Acylase

Magdy M. M. Elnasr, Marwa I. Wahba, Magdy A. Amin and Ahmed I. Eldiwany

Journal of Applied Polymer Science, 131 (11); (2014) IF: 1.64

Grafted alginic–carrageenan beads were used to immobilize the industrial enzyme penicillin G acylase (PGA). Sixteen factors were screened with the Placket–Burman design (PBD) to test their significance on the gel beads formation and enzyme immobilization process. The results of PBD showed a wide variation of 30-fold in the amount of immobilized penicillin G acylase (iPGA) from 11.9 to 354.16 U/g of beads; this reflected the importance of the optimizing process. Among the 16 tested factors, only 3 were proven to be significant. These factors were the enzyme buffer pH (N), enzyme soaking time (Q) with the gel beads, and enzyme concentration (P). The Pareto chart revealed that both Q and P exerted significant positive effects on the amount of iPGA, whereas N had a negative effect. We recommend further study to optimize only these three significant, distinctive enzyme factors. The PGA covalent attachment to the gel beads were proven by Fourier transform infrared spectroscopy, elemental analysis, and NaCl and reusability tests. The best gel bead formula succeeded in the immobilization of 354.16 U/g of beads and proved to be reusable 14 times, retaining 84% of the initial enzyme activity.

Keywords: Catalysts; Composites; Gels.

917. Detection, Characterization, and Molecular Typing of Human Mycoplasma Spp. from Major Hospitals in Cairo, Egypt

Mirihan A.Metwally, Aymen S. Yassin, TamerM. Essam, Hayam M. Hamouda, and Magdy A. Amin


Mycoplasmas are fastidious slow growing organisms lacking a cell wall and mostly isolated from the mucosal surfaces of the respiratory and genitourinary tracts. There is a dearth of information regarding clinical Mycoplasma spp. isolates among Egyptian patients. A total of 170 samples were collected from patients and apparently healthy personnel in local public hospitals in Cairo, Egypt. Isolation of Mycoplasma spp. was carried out using appropriate culture media and further identification was carried out by biochemical tests followed by serotyping using specific antisera. Confirmation was done by PCR for detection of different Mycoplasma spp. using genus-specific primers targeting 16S ribosomal RNA gene. Characterization of the antibiotic resistance and sensitivity pattern against different antimicrobials was carried out using disc diffusion test. The results indicated the presence of six Mycoplasma spp. in 22.94% of the samples. Mycoplasmas were detected more
frequently in throat swabs than sputum. Mycoplasma pneumoniae was highly sensitive to macrolides and quinolones but less sensitive to aminoglycosides and tetracyclines. Molecular techniques were found to be of more rapid, highly sensitive, able to detect nonviable organisms, and cost effective. These results shed light on difficulties of Mycoplasma detection and the superiority of molecular techniques over culture.

**Keywords:** Mycoplasma; Virulence; Resistance

918. Antimicrobial Resistance Pattern And Their Beta-Lactamase Encoding Genes Among Pseudomonas Aeruginosa Strains Isolated From Cancer Patients

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*Biomedical Research International, 2014: 0-9 (2014)*

This study was designed to investigate the prevalence of metallo-β-lactamases (MBL) and extended-spectrum β-lactamases (ESBL) in *P. aeruginosa* isolates collected from two different hospitals in Cairo, Egypt. Antibiotic susceptibility testing and phenotypic screening for ESBLs and MBLs were performed on 122 *P. aeruginosa* isolates collected in the period from January 2011 to March 2012. MICs were determined. ESBLs and MBLs genes were sought by PCR. The resistant rate to imipenem was 39.34%. The resistance rates for *P. aeruginosa* to cefuroxime, cefoperazone, ceftazidine, aztreonam, and piperacillin/tazobactam were 87.7%, 80.3%, 60.6%, 45.1%, and 25.4%, respectively. Out of 122 *P. aeruginosa*, 27% and 7.4% were MBL and ESBL, respectively. The prevalence of *bla*\textsubscript{VIM}-2, *bla*\textsubscript{OXA-10}, *bla*\textsubscript{TEM}, and *bla*\textsubscript{OXA-1}-like genes were found in 58.3%, 41.7%, 10.4%, 4.2%, and 2.1%, respectively. GIM, SPM, SIM, and OXA-2-like genes were not detected in this study. OXA-10-like gene was concomitant with VIM-2 and/or VEB. Twelve isolates harbored both OXA-10 and VIM-2; two isolates carried both OXA-10 and VEB. Only one strain contained OXA-10, VIM-2, and VEB. In conclusion, *bla*\textsubscript{VIM}-2 and *bla*\textsubscript{OXA-10}-like genes were the most prevalent genes in *P. aeruginosa* in Egypt. To our knowledge, this is the first report of *bla*\textsubscript{VIM}-2, *bla*\textsubscript{OXA-10}, *bla*\textsubscript{TEM}, and *bla*\textsubscript{OXA-1}-like genes in *P. aeruginosa* in Egypt.

**Keywords:** Pseudomonas Aeruginosa; Beta-Lactamase; Cancer

919. Synthesis, Bioassay, and Molecular Field Topology Analysis of Diverse Vasodilatory Heterocycles

Polina V. Oliferenko, Alexander A. Oliferenko, Adel S. Girgis, Dalia O. Saleh, Aladdin M. Sour, Riham F. George, Girinath G. Pillai, Chandramukhi S. Panda, C. Dennis Hall and Alan R. Katritzky

*Journal of Chemical Information and Modeling, 54: 1103-1116 (2014) IF: 4.068*

A diverse training set composed of 76 in-house synthesized and 61 collected from the literature was subjected to molecular field topology analysis. This resulted in a high-quality quantitative structure–activity relationships model (R^2 = 0.932, Q^2 = 0.809) which was used for the topological functional core identification and prediction of vasodilatory activity of 19 novel pyridinecarbonitriles, which turned out to be active in experimental bioassay.

**Keywords:** Qsar, Mfa, Vasodilator, Pyridinecarbonitrile.

920. Design, Synthesis and Anticancer Activity of Benzofuran Derivatives Targeting VEGFR-2 Tyrosine Kinase

Omaima M. Abdelhafiz, Kamelia M. Amin, Hamed I. Ali, Mohamed M. Abdalla and Eman Y. Ahmed

*Rsc Advances, 4: 11569-11579 (2014) IF: 3.708*

Two series of chalcone and thiopyrimidine benzofuran derivatives were designed, synthesized and evaluated in vitro for their vascular endothelial growth factor receptor (VEGFR-2) inhibitory activity, their cytotoxicity on seventeen human cancer cell lines and their in vivo antiproliferative cancer activity. The highest anti-VEGFR-2 activity was demonstrated by 1-(6-hydroxy-4-methoxybenzofuran-5-yl)-3-(4-nitrophenyl)prop-2-en-1-one (6d) exhibiting an IC\textsubscript{50} value (1.00 x 10\textsuperscript{-10} M) higher than the reference drug Sorafenib (IC\textsubscript{50} = 2.00 x 10\textsuperscript{-5} M). On the other hand, most of the synthesized compounds showed potent cytotoxicity against most of the tested cell lines and were more potent than the reference drugs, in particular, bromovisinagin (4) exhibited the best activity on the majority of the cell lines with IC\textsubscript{50} values ranging from 3.67 x 10\textsuperscript{-13} to 7.65 x 10\textsuperscript{-7} M. Moreover, the synthesized compounds showed significant in vivo antiproliferative cancer activity. The docking experiments were performed using the GOLD program on (VEGFR-2) kinase which introduced new information about the enzyme–inhibitor interaction and the potential therapeutic application of the benzofuran scaffold.

**Keywords:** Benzofuran; Tyrosine kinase


Ebeid WM, Elkady EF, El-Zaher AA, El-Bagary RI and Patonay G.

*Analytical and Bioanalytical Chemistry, 406: 6701-6712 (2014) IF: 3.578*

A RP-LC method was developed and validated for simultaneous determination of the active components, azilsartan medoxomil (AZL) and chlorthalidone (CLT), in their novel antihypertensive combined recipe. The chromatographic separation was achieved on an Eclipse XDB-C18 (4.6 x 150 mm, 5 μm) column using a mobile phase consisting of methanol/potassium hydrogen phosphate buffer (pH 8, 0.05 M) (40:60, v/v) in isocratic mode. The flow rate was maintained at 0.8 mL min\textsuperscript{-1} at ambient temperature. Detection was carried out at 210 nm. The method was validated according to the ICH guidelines. Linearity, accuracy, and precision were satisfactory over the concentration range of 5.0-50.0 and 2.5-25.0 μg mL\textsuperscript{-1} for AZL and CLT, respectively (r (2) = 0.9999). LODs for AZL and CLT were 0.90 and 0.32 μg mL\textsuperscript{-1}, whereas LOQs were 2.72 and 0.98 μg mL\textsuperscript{-1}, respectively. Both drugs were subjected to forced degradation studies under hydrolysis (neutral, acidic, and alkaline), oxidative, and photolytic extensive stress conditions. The proposed method is stability indicating by the resolution of
the investigated drugs from their degradation products. Moreover, the kinetics of the acidic degradation of AZL as well as the kinetics of the alkaline degradation of CLT were investigated. Arrhenius plots were constructed and the apparent first-order rate constants, half-life times, shelf-life times, and the activation energies of the degradation processes were calculated. The method was successfully applied for the determination of the studied drugs simultaneously in their coformulated tablet. The developed method is specific and stability indicating for the quality control and routine analysis of the cited medications in their pharmaceutical preparations.

**Keywords:** Stability; Indicating; Liquid chromatography; Degradation kinetics; Azilsartan medoxomil; Chlorthalidone; Pharmaceutical; Preparations.

### 922. Microwave Assisted Synthesis and QSAR Study of Novel Nsaid Acetaminophen Conjugates With Amino Acid Linkers

Anand D. Tiwari, Siva S. Panda, Adel S. Girgis, Sandhiyamaye Sahu, Rihann F. George, Aladdin M. Sour, Brian La Starza, Abdullah M. Asiri, C. Dennis Hall and Alan R. Karrity


Novel, non-steroidal anti-inflammatory drug (NSAID), acetaminophen conjugates 6a-1 with amino acid linkers were synthesized utilizing benzotriazole chemistry. Biological data acquired for all the novel bis-conjugates showed (a) some bis-conjugates (6d, 6e, 6h, and 6k) exhibit more potent anti-inflammatory activity than their parent drugs, (b) the potent bis-conjugates show no visible stomach lesions in contrast to parent drugs which are highly ulcerogenic, and (c) that the potent bioactive compounds have no mortality rates or toxic symptoms at 5 fold the applied anti-inflammatory dosage. A statistically significant QSAR model describing the anti-inflammatory properties of 6a-1 (N = 15, n = 3, R2 = 0.891, R2cvOO = 0.770, R2cvMO = 0.796, F = 29.904, s2 = 0.011) was obtained employing CODESSA-Pro that validated the observed bioactivity.

**Keywords:** Nsaid; Microwave; QSAR; Codessa-pro; Antiinflammatory activity.

### 923. Celecoxib Analogs Bearing Benzofuran Moiety as Cyclooxygenase-2 Inhibitors: Design, Synthesis and Evaluation as Potential Anti-Inflammatory Agents

Ghaneya Sayed Hassan, Sahar Mahmoud Abou-Seri, Gehan Kamel and Mamdouh Moawad Ali


Novel series of celecoxib analogs endowed with benzofuran moiety 3a-e and 9a-d were synthesized and evaluated for COX-1/COX-2 inhibitory activity in vitro. The most potent and selective COX-2 inhibitors - compounds 3c, 3d, 3e, 9c and 9d - were assessed for their anti-inflammatory activity and ulcerogenic liability in vivo. The 3-(pyridin-3-yl)pyrazole derivatives 3c and 3e exhibited the highest anti-inflammatory activity, that is equipotent to celecoxib. Furthermore, the tested compounds proved to have better gastric safety profile compared to celecoxib. In particular, compound 3e demonstrated about 40% reduction in ulcerogenic potential relative to the reference drug. Finally, molecular docking simulation of the new compounds in COX-2 active site and drug likeness studies showed good agreement with the obtained pharmaco-biological results.

**Keywords:** Celecoxib Analogs; Benzofuran; Pyrazole; Anti-Inflammatory Agents; Cox-1/Cox-2 Inhibitory Activity.

### 924. Design, Synthesis and Molecular Docking Study of Novel Quinoxalin-2(1H)-ones as Anti-Tumor Active Agents With Inhibition of Tyrosine Kinase Receptor and Studying Their Cyclooxygenase-2 Activity


On continuation to our work, new quinoxalin-2(1H)-ones were synthesized to study their cytotoxic effect against HepG-2 and MCF-7 with their effect on the human tyrosine kinase (TRK). Compounds 12, 18, 15, 13, 11a, 20 and 16, respectively, were found to be more potent than cisplatin against HepG2 and selective to TRK. Also, compounds 12, 18, 20, 13, 14, and 22, respectively, exhibited decidedly activity against MCF-7 and selectivity against human TRK compared to cisplatin. A molecular docking study was also performed to gain comprehensive understanding into plausible binding modes and to conclude the structure activity relationships of the synthesized compounds. Moreover, anti-inflammatory activity was studied. Compounds 12, 15, 18 and 22 were found to be potent and selective against COX-2.

**Keywords:** Synthesis; Quinoxalines; Antitumor; Activity; Cyclooxygenase-2 Docking protein tyrosine kinase

### 925. Design, Synthesis and Structure–Activity Relationship of Novel Semi-Synthetic Flavonoids as Antiproliferative Agents


Various flavonoid scaffold based derivatives viz furoxalones (3a-e, 6a-d and 9a-d), furoflavones (10a-d, 11a-d, 12a-d, 18a&b), flavones (21a-d), furoarones (13a,b, 14a-d and 15a-d) and 7-styrylfurochromones (22a and 25a-e) were designed and synthesized. The novel compounds were evaluated for their antiproliferative activity against a panel of 60 cancer cell lines comprising 9 types of tumors. Ten compounds belonging to the major subgroups of flavonoids viz furoxalones (3a, 3d, 6b, 9a and 9b), furoflavones (12a and 12c), furoarones (15d), styrylfurochromones (25b and 25e) showed very promising activity. These active compounds were also evaluated in vitro as kinase inhibitors against CDK2/cyclin E1, CDK4/cyclin D1 and GSK-3β and the best inhibition was displayed against GSK-3β with the allylfuroxalene derivative 9b exhibiting 80% decrease in GSK-3β catalytic activity. On the other hand, the styrylfurochromone 25e interestingly showed a 13% enhancement of GSK-3β catalytic power and a 12% reduction in CDK4/cyclin D1 activity.
Finally, the in vivo anti-tumor activity of 25e was evaluated against breast cancer induced in mice. The results showed a profound anti-tumor effect of 25e that accompanies a significant increase and decrease in the levels of GSK-3β and cyclin D1, respectively.

Keywords: Furochalcones; Furoflavonones; Furoaurones; Furostyrilflurochromones; Cytotoxicity; Kinase; Inhibition.

926. Novel Sulfonamides Bearing Pyrrole and Pyrrolopyrimidine Moieties As Carbonic Anhydrase Inhibitors: Synthesis, Cytotoxic Activity and Molecular Modeling

Mostafa M. Ghorab, Mariangela Ceruso, Mansour S. Alsaied, Yassin M. Nissan, Reem K. Arafa and Claudiu T. Supuran


Novel pyrrole and pyrrolopyrimidine scaffold-based sulfonamides were designed and synthesized. The carbonic anhydrase (CA) inhibition ability of all derivatives was assessed against the human (h) cytosolic isofoms hCA I and II and the transmembrane, tumor-associated isofoms hCA IX and XII. Some of these sulfonamides were 6-8 fold more potent than the reference drug acetazolamide (AZA, K_i = 5.7 nM)) against hCA XII showing subnanomolar activity. The in vitro cytotoxicity of these derivatives was evaluated against MCF-7, where some derivatives were more cytotoxic than doxorubicin (IC_{50} = 8.02 mM) displaying IC_{50} values between 6.46 and 7.56 mM. Docking of these sulfonamides with CA XII was performed and their binding modes were comparable with that of AZA.

Keywords: Pyroles, Pyrrolopyrimidines, Sulfonamides, Carbonic Anhydrase, Cytotoxic Activity.

927. Part I. Synthesis, Biological Evaluation and Docking Studies of New 2-Furylbenzimidazoles as Antiangiogenic Agents


2-(2-Furyl)-1H-benzimidazoles 3-11 were synthesized and tested for their in vitro VEGF inhibition in MCF-7 cancer cell line. Compound 5a was more potent than Tamoxifen, and compounds 3b, 5a, 5c, 6b, 7a and 10 showed promising potency. Furthermore, compounds (6b, 7a and 10) showed remarkable selective inhibition of COX-2 enzyme close to that of Celecoxicib. Additionally, docking studies were performed using AutoDock 4.2 into the VEGFR2 kinase. Significant correlation exists between the biological activity (IC_{50} and %VEGF inhibition) against MCF-7 cell line and the molecular docking results (K_i and ΔGb) with correlation coefficients (r^2) of 0.5513 and 0.4623 respectively. Accordingly, most of the synthesized 2-(2-furyl)-1H-benzimidazoles showed strong antiangiogenic activity against VEGFR2 kinase.

Keywords: 2-(2-Furyl)-1H-Benzimidazoles Angiogenesis Vascular Endothelial Growth Factor (Vegf) Vegrfr2 Kinase Cytotoxicity.


Mohamed Fares, Sahar Mahmoud Abou-Seri, Hatem A. Abdel-Aziz Safinaz E.-S. Abbas, Mohieldin Magdy Youssef and Radwa Ahmed Eladwy


New series of 2-(2-arylidenehydrazinyl)pyrido[2,3-d]pyrimidines 5a-e and pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidines 6-15 were synthesized and evaluated for their cytotoxic activity against two cancer cell lines, namely PC-3 prostate cancer and A-549 lung cancer. Some of the tested compounds displayed high growth inhibitory activity against PC-3 cells. Whereas, compounds 5b and 15f showed relatively potent antitumor activity against PC-3 and A-549 cell lines. In particular, 4-(3-acetyl-5-oxo-6-phenyl-8-(thiophen-2-yl)pyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-1(5H)-yl)benzenesulfonamide 15f exhibited superior antitumor activity against both cell lines at submicromolar level (IC_{50} = 0.36, 0.41 μM, respectively). Moreover, the potential mechanisms of the cytotoxic activity of the promising compound 15f on the more sensitive cell line PC-3 were studied. The data indicated that 15f was able to cause cell cycle arrest at least partly through enhancing the expression level of the cell cycle inhibitor p21 and induced cancer cell apoptosis via caspase-3 dependent pathway.

Keywords: Pyrido [2,3-D] Pyrimidine; Pyrido [2,3-D][1,2,4]Triazolo [4,3-A] Pyrimidine; Antitumor Activity; Apoptosis; Cell Cycle Arrest.

929. Anticancer, Antioxidant Activities, and DNA Affinity of Novel Monocationic Bithiophenes and Analogues

Mohamed A.Ismail, R.eem K.Arafa Magdy M Youssef andWael M El-Sayed

Drug Design, Development and Therapy, 8: 1659-1672 (2014) IF: 3.026

A series of 15 monocationic bithiophenes and isosteres were prepared and subjected to in vitro antiproliferative screening using the full National Cancer Institute (NCI) 60 cell line panel, representing nine types of cancer. Among the nine types of cancer involved in a five-dose screen, non-small cell lung and breast cancer cell lines were the most responsive to the antiproliferative effect of the tested compounds, especially cell lines A549/ATCC, NCI-H322M, and NCI-H460, whereas compounds 1a, 1c, 1d, and 7 exhibited potent activity, with GI_{50} values (drug concentration that causes 50% inhibition of cell growth) from less than 10 nM to 102 nM. In addition, compounds 1c and 1d gave GI_{50} values of 73 nM and 79 nM, respectively, against the MDA-MB-468 breast cancer cell line. Structure–activity relationship findings indicated that the mononitriles were far less active than their corresponding monoamidines and, within the amidines series, the bioisosteric replacement of a thiophene ring by a furan led to a reduction in antiproliferative activity. Also, molecular manipulations, involving substitution on the phenyl ring, or its replacement by a pyridyl, or alteration of the
position of the amidine group, led to significant alteration in antiproliferative activity. On the other hand, DNA studies demonstrated that these monoamidine bichalcophenes have promising ability to cleave the genomic DNA. These monoamidines show a wide range of DNA affinities, as judged from their DNA cleavage effect, which are remarkably sensitive to all kinds of structural modifications. Finally, the novel bichalcophenes were tested for their antioxidant property by the ABTS (2,2'-azino- bis(3-ethylbenzthiazoline-6-sulfonic acid) diaminonium salt) assay, as well as lipid and nitric oxide scavenging techniques, and were found to exhibit good-to-potent antioxidant abilities.

Keywords: Bithiophenes, Anticancer, Dna Cleavage, Antioxidant, Suzuki Coupling, Stille Coupling.

930. Novel Pyrazolopyrimidine Derivatives Targeting COXs and iNOS Enzymes; Design, Synthesis and Biological Evaluation as Potential Anti-Inflammatory Agents

Ahmed H. Abdelazem, Shaimaa A. Abdelatef, Mohammed T. El-Saadi, Hany A. Omar, Shabana I. Khan, Christopher R. McCurdy and Samir M. El-Moghazy


A novel set of 4-substituted-1-phenyl-pyrazolo[3,4-d]pyrimidine and 5-substituted-1-phenyl-pyrazolo[3,4-d]pyrimidin-4-one derivatives were synthesized and evaluated as potential anti-inflammatory agents.

The newly prepared compounds were assessed through the examination of their in vitro inhibition of four targets: cyclooxygenases subtypes (COX-1 and COX-2), inducible nitric oxide synthase (iNOS) and nuclear factor kappa B (NF-kB). Compounds 8a, 10c and 13c were the most potent and selective ligands against COX-2 with inhibition percentages of 79.6%, 78.7% and 78.9% at a concentration of 2 μM respectively, while compound 13c significantly inhibited both COX subtypes.

On the other hand, fourteen compounds showed high iNOS inhibitory activities with IC50 values in the range of 0.22–8.5 μM where the urea derivative 11 was the most active compound with IC50 value of 0.22 μM. Most of the tested compounds were found to be devoid of inhibitory activity against NF-kB.

Moreover, almost all compounds were not cytotoxic, (up to 25 μg/mL), against a panel of normal and cancer cell lines. The in silico docking results were in agreement with the in vitro inhibitory activities against COXs and iNOS enzymes. The results of in vivo anti-inflammatory and antinociceptive studies were consistent with that of in vitro studies which confirmed that compounds 8a, 10c and 13c have significant anti-inflammatory and analgesic activities comparable to that of the control, ketorolac. Taken together, dual inhibition of COXs and iNOS with novel pyrazolopyrimidine derivatives is a valid strategy for the development of anti-inflammatory/analgesic agents with the probability of fewer side effects.

Keywords: Anti-Inflammatory, Analgesic, Cox, Inos, Nf-Kb, Pyrazolopyrimidines.

931. Carbonic Anhydrase Inhibitors: Synthesis, Molecular Docking, Cytotoxic and Inhibition of the Human Carbonic Anhydrase Isoforms I, II, IX, XII With Novel Benzenesulfonamides Incorporating Pyrrole, Pyrrolopyrimidine and Fused Pyrrolopyrimidine Moieties

Mostafa M. Ghorab, Mansour S. Alsaid, Mariangela Ceruso, Yasmin M. Nissan and Claudiu T. Supuran


A series of novel pyroles, pyrrolopyrimidines, pyrazolopyrrolopyrimidine, triazolopyrrolopyrimidines, tetrazolopyrrolopyrimidine, triazinopyrrolopyrimidines and pyrrolopyrimidotriazinepses bearing the biologically active benzenesulfonamide moiety were synthesized by using pyrole-o-amino-carbonitrile as key intermediate. All the synthesized compounds were evaluated for their in vitro carbonic anhydrase (CA, EC 4.2.1.1) inhibitory effects against the human (h) isoforms hCA I, II, IX and XII. Among the tested derivatives, compounds 16, 18 and 20–24 showed potent activity as inhibitors for the tumor associated transmembrane isoforms (hCA IX and XII) in the nanomolar and subnanomolar range, with high selectivity. All compounds underwent cytotoxic activity assays on human breast cancer cell line (MCF-7) showing effective activity, comparable to that of the clinically used drug doxorubicin.

Keywords: Pyrrolopyrimidines, Sulfonamide, Cytotoxic Activity, Carbonic Anhydrase Inhibitors, Molecular Docking.

932. Synchronized Separation of Seven Medications Representing Most Commonly Prescribed Antihypertensive Classes By Using RP-LC: Applied To Analysis in Their Combined Formulations

Waleed Ebeid, Ehab F Elkady, Ehab F Elkady, Asmaa Ahmed El-Zaher, Ramzia El-Bagary and Gabor Patonay


An RP-HPLC method was developed for the simultaneous determination of the diuretic, hydrochlorothiazide, along with six drugs representing the most commonly prescribed antihypertensive pharmacological classes such as atenolol, a selective β1 blocker, amlodipine besylate, a calcium channel blocker, moexipril hydrochloride, an angiotensin-converting enzyme (ACE) inhibitor, valsartan and candesartan cilexetil which are angiotensin II receptor blockers and aliskiren hemifumarate, a renin inhibitor, using irbesartan as an internal standard. The chromatographic separation was achieved using acetonitrile: sodium phosphate dibasic buffer (0.02 M, pH 5.5) at a flow rate of 1 mL/min (-1) in gradient elution mode at ambient temperature on a stationary phase composed of Eclipse XDB-C18 (4.6 × 150 mm, 5 μm) column. UV detection was carried out at 220 nm. The method was validated according to ICH guidelines. Linearity, accuracy and precision were satisfactory over the concentration ranges of 2-40 μg/mL(-1) for hydrochlorothiazide and candesartan cilexetil, 20-200, 10-160, 5-40, 20-250 and 5-50 μg/mL(-1) for atenolol, valsartan, moexipril hydrochloride, aliskiren hemifumarate and amlodipine besylate, respectively. The method was successfully applied for the determination of each of the studied medications in their combined formulations with hydrochlorothiazide. The developed method is suitable for the quality control and routine analysis of the cited drugs in their
pharmaceutical dosage forms. This article is protected by copyright. All rights reserved.

**Keywords**: Antihypertensive Medications; Pharmaceuticals; Liquid Chromatography; Simultaneous; Validation.

**933. Anticonvulsant Profiles of Certain New 6-Aryl-9-Substituted-6,9-Diazaspiro[4.5]Decane-8,10-Diones and 1-Aryl-4-Substituted-1,4-Diazaspiro[5.5]Undecane-3,5-Diones**

Mohamed N. Aboul-Enein, Aida A. El-Azzouony, Mohamed I. Attia, Yousreya A. Maklad, Mona E. Aboutabl, Fatma Ragab and Walaa H. A. Abd El-Hamid


Synthesis and anticonvulsant potential of certain new 6-aryl-9-substituted-6,9-diazaspiro[4.5]decane-8,10-diones (6a-l) and 1-aryl-4-substituted-1,4-diazaspiro[5.5]undecane-3,5-diones (6m-x) are reported. The intermediates 1-(6-aryl)cycloalkanecarboxamides (3a-f) were prepared via adopting Streeker synthesis on the proper cycloalkanone followed by partial hydrolysis of the obtained nitrile functionality and subsequent N-cyanomethylation. Compounds 3a-f were subjected to complete nitrile hydrolysis to give the respective carboxylic acid derivatives 4a-f which were cyclized under mild conditions to give the spiro compounds 5a-f. Ultimately, compounds 5a-f were alkylated or aralkylated to give the target compounds 6a-i and 6m-u. On the other hand, compounds 6j-l and 6v-x were synthesized from the intermediates 5a-f through alkylation, dehydration and finally tetrazole ring formation. Anticonvulsant screening of the target compounds 6a-x revealed that compound 6g showed an ED$_{50}$ of 0.0043 mmol/kg in the scPTZ screen, being about 14 and 214 fold more potent than the reference drugs, Phenytoin (ED$_{50}$ = 0.06 mmol/kg) and Ethosuximide (ED$_{50}$ = 0.92 mmol/kg), respectively. Compound 6e exhibited an ED$_{50}$ of 0.019 mmol/kg, being about 1.8 fold more potent than that of the reference drug, Diphenylhydantoin (ED$_{50}$ = 0.034 mmol/kg) in the MES screen. Interestingly, all the test compounds 6a-x did not show any minimal motor impairment at the maximum administered dose in the neurotoxicity screen.

**Keywords**: Cycloalkanones; Streeker Synthesis; Alkylation; Spiro Compounds; Tetrazole; Anticonvulsant.

**934. Synthesis, Docking and Biological Activities of Novel Hybrids Celecoxib and Anthraquinone Analogs as Potent Cytotoxic Agents**

Maha S. Almutairi, Gahan H. Hegazy, Mogeeda E. Haiba, Hamed I. Ali, Nagy M. Khalifa and Abd El-mohsen M. Soliman


Herein, novel hybrid compounds of celecoxib and 2-aminoanthraquinone derivatives have been synthesized using condensation reactions of celecoxib with 2-aminoanthraquinone derivatives or 2-aminoanthraquinon with celecoxib derivatives. Celecoxib was reacted with different acid chlorides, 2-chloroethyl isocyanate and bis (2-chloroethyl) amine hydrochloride. These intermediates were then reacted with 2-aminoanthraquinone. Also, the same different acid chlorides and 2-chloroethyl isocyanate were reacted with 2-aminoanthraquinone and the resulting intermediates were reacted with celecoxib to give isomers for the previous compounds. The antitumor activities against hepatic carcinoma tumor cell line (HEPG2) have been investigated in vitro, and all these compounds showed promising activities, especially compound 3c, 7, and 12. Flexible docking studies involving AutoDock 4.2 was investigated to identify the potential binding affinities and the mode of interaction of the hybrid compounds into two protein tyrosine kinases namely, SRC (Pp60v-src) and platelet-derived growth factor receptor, PDGFR (c-Kit). The compounds in this study have a preferential affinity for the c-Kit PDGFR PTK over the non-receptor tyrosine kinase SRC (Pp60v-src).

**Keywords**: Antitumor; Anthraquinone; Celecoxib; Hepg2; Docking; Protein kinase activities.

**935. Simultaneous Determination of Sildenafil Citrate and Some Nitric Oxide Releasing Drugs in Human Plasma Using Uplc Ms/Ms**

Ramzia El-Bagary, Hassan M.E. Azzazy, Ehab F. Elkady and Faten Farouk

*Clinical Biochemistry, 47*: 654-656 (2014) IF: 2.229

Objectives: The inadvertent combination of sildenafil (SLD) and nitric oxide releasing compounds (NRC) may cause a life-threatening hypotension and conversion of coital angina into an irreversible one. The aim of this study was to develop and validate a UPLC MS/MS method for the simultaneous quantitative analysis of SLD, nicorandil (NRD), and ARG in human plasma to determine the safety margins for drug combinations.

**Design and Method**: Chromatographic elution was achieved in 4 min using gradient elution and an injection volume of 10 µL. Electro-spray positive ionization (ESI+ve) detection and multiple-reaction monitoring mode (MRM) were used for detection.

**Results**: The method was found to be linear (10–900 ng/mL for SLD and NRD while 1–30 µg/mL for ARG), accurate and precise (99.35 ± 1.58, 99.62 ± 1.13, and 100.04 ± 1.22% for SLD, NRD and ARG; respectively) and met all other validation requirements.

**Conclusion**: The developed UPLC MS/MS method is suitable for fast, sensitive, accurate and simultaneous determinations of SLD, NRD, and ARG in plasma.

**Keywords**: Drug interactions; LC–MS/MS; Nicorandil; Sildenafil citrate; l-Arginine.

**936. Molecular Design and Synthesis of 1,4-Disubstituted Piperazines as A1-Adrenergic Receptor Blockers**


*Bioorganic Chemistry, 54*: 21-30 (2014) IF: 2.141

A new series of 4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylic acid amide and 3,5,6,8-tetrahydropyrido [4,3-4'5]thieno[2,3-d]pyrimidin-4-one derivatives were designed, synthesized, their binding and functional properties as a1-adrenoceptors blockers were evaluated. A new validated a1-adrenoceptor blocker pharmacophore model (hypothesis) was generated using Discovery Studio 2.5. The compare-fit study for the designated molecules with the generated hypothesis was fulfilled and several compounds showed significant high fit values. Compounds IVa-c, VIIa–d, VIIia–c, Xa–c, Xla–d have shown blocking activity ranging from 46.73% up to 94.74% compared to 99.17% for prazosin.
Keywords: Phenylpiperazines; Pyridothenopyrimidine; A1-Adrenoreceptors Blockers.

937. New Series of 6-Substituted Coumarin Derivatives as Effective Factor Xa Inhibitors: Synthesis, in Vivo Antithrombotic Evaluation and Molecular Docking

Kamelia M. Amin, Nagwa M. Abdel Gawad, Doaa E. Abdel Rahman and Mohamed K.M. El Ashry

Despite recent progress in antithrombotic therapy, there’s still an unmet medical need for safe and orally available anticoagulants. Encouraged by the marked antithrombotic and anticoagulant activities of some coumarin derivatives, twenty-three new N-coumarinyl-4-amidinobenzamides 4a-f and 6-heterocycle substituted coumarin derivatives 5, 6a,b, 10a-e, 12a-e and 14a-d were synthesized and evaluated for their in vivo antithrombotic activity.

The most active congeners were the unsubstituted amide 4a (36.5 s), coumarinyl oxadiazole 5 (42.3 s), bis coumarinyl oxadiazole 6b (37.8 s) and coumarinyl pyrazole 10b (38.5 s) that presented prothrombin time (PT) values comparable to the reference drug warfarin (42.3 s). Furthermore, docking studies were undertaken to gain insight into the possible binding mode of these compounds with the coagulation factor Xa (FXa) binding site.

Keywords: Coumarin.

938. Synthesis, Docking and in Vitro Anticancer Evaluation of Some New Benzopyrone Derivatives

Sohair L. El-Ansary, Mohammed M. Hussein, Doaa E. Abdel Rahman and Lina M.A. Abdel Ghany

The synthesis of some new 3-alkyl-7-hydroxy-4-methyl-8-substituted-1H-benzo[p]pyran-2-ones, 6-alkyl-7-methyl-2-substituted amino-5H-pyran[6,5-e] benzoazol-5-ones, 7-alkyl-8-methyl-3-substituted-2,6-dihydropyran[6,5-f]-1,4-benzoxazin-6-ones, 7,8-disubstituted-3-ethyl-4-methyl-1H-benzo[b]pyran-2-ones and 3-alkyl-4-methyl-7-substituted-1H-benzo[b]pyran-2-ones were described. Fourteen compounds were selected by National Cancer Institute (NCI), Bethesda, and evaluated for their in vitro anticancer activity in the full NCI 60 cell lines panel assay by a single dose test. Compounds 4a, 18a, 18b and 23a were found to be broad-spectrum antitumors showing effectiveness toward numerous cell lines that belong to different tumor subpanels. Furthermore, docking studies were undertaken to gain insight into the possible binding mode of these compounds with the binding site of the casein kinase II (CK2) enzyme which is involved in cell survival and proliferation through a number of downstream effectors.

Keywords: Benzopyrones; Anticancer; Docking Studies; Casein Kinase II.

939. Synthesis, Cytotoxic Activity and 2D-Qsar Study of Some Imidazoquinazoline Derivatives

Hanan Georgey
Molecules, 19: 3777-3792 (2014) IF: 2.095

A novel series of 4-substituted amino-7,8-dimethoxy-1-phenylimidazo[1,5-a]quinazolin-5(4H)-one derivatives was designed, synthesized and tested for their antitumour activity against a human mammary carcinoma cell line (MCF7). Compound 5a was found to be the most active derivative. Physico-chemical parameters were also determined and revealed that most of the compounds obeyed the “rule of five” properties with good absorption percentages. 2D-QSAR studies revealed a well predictive and statistically significant and cross validated QSAR model that helps to explore some expectedly potent compounds.

Keywords: Imidazolone; Imidazo[1,5-A]Quinazoline; Antitumor Activity; Lipinski’S Parameters; 2D-Qsar.

940. Steady-State and Synchronous Spectrofluorimetric Methods for Simultaneous Determination of Aliskiren Hemifumarate and Amlodipine Besylate in Dosage Forms

Walid M. Ebeid, Ehaf F. Elkady, Asmaa A. El-Zaher, Ramizia El-Bagary and Gabor Patonay

Aliskiren hemifumarate (ALS) and amlodipine besylate (AML) were simultaneously determined by two different spectrofluorimetric methods. The first technique depends on direct measurement of the steady-state fluorescence intensities of ALS and AML at 313 nm and 452 nm upon excitation at 290 and 375 nm, respectively, in a solvent composed of methanol and water (10: 90, v/v). The second technique utilizes synchronous fluorimetric quantitative screening of the emission spectra of ALS and AML at 272 and 366 nm, respectively using 2.2 of 97 nm. Effects of different solvents and surfactants on relative fluorescence intensity were studied. The method was validated according to ICH guidelines. Linearity, accuracy and precision were found to be satisfactory in both techniques over the concentration ranges of 1–15 and 0.4–4 µg/mL for ALS and AML, respectively. In the first technique, limit of detection and limit of quantification were estimated and found to be 0.256 and 0.776 µg/mL for ALS as well as 0.067 and 0.204 µg/mL for AML, respectively. Also, limit of detection and limit of quantification were calculated in the synchronous method and found to be 0.293 and 0.887 µg/mL for ALS as well as 0.034 and 0.103 µg/mL for AML, respectively. The methods were successfully applied for the determination of the two drugs in their co-formulated tablets. The results were compared statistically with reference methods and no significant difference was found. The developed methods are rapid, sensitive, inexpensive and accurate for the quality control and routine analysis of the cited drugs in bulk and in pharmaceutical preparations without pre-separation.

Keywords: Spectrofluorimetry; Synchronous; Aliskiren hemifumarate; Amlodipine besylate; Pharmaceutical preparations; Validation.

941. Synthesis, Biological Evaluation, and Docking Studies of New 2-Furylbenzimidazoles as Anti-Angiogenic Agents: Part II

The 2-(5-methyl-2-furyl)-1H-benzimidazole moiety has shown promising activity against vascular endothelial growth factor (VEGF)-induced angiogenesis. In Part I of this study, we have synthesized new analogs and tested their anti-angiogenic potentials. Here, we continue our previous study with different new analogs. Some compounds show promising cytotoxic activity against the human breast cancer cell line MCF-7, with IC\textsubscript{50} in the range of 7.80-13.90\textmu M/mL, and exhibited remarkable in vitro inhibition against VEGF in the MCF-7 cancer cell line, with 95-98% of inhibition in comparison to tamoxifen as reference (IC\textsubscript{50}: 8.00\textmu M/mL, % of inhibition= 98%). Additionally, a molecular docking study was carried out to gain insight into plausible binding modes and to understand the structure-activity relationships of the synthesized compounds.

**Keywords:** 2-(2-Furyl)-1H-Benzimidazoles; Angiogenesis; Cytotoxicity; Molecular Modeling; Vascular endothelial growth Factor (Vegf).

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**942. Design, Synthesis and in Vitro Anti-Tumor Evaluation of Novel Acrylohydrozide Thioglycosides**

Galal H. Elgemeie, Nahed M. Fathy, Ayman B. Farag, Ossama M. El-Badry, Ghaneia S. Hassan, Kamelia M Amin and Fathi Halaweis

*Medicinal Chemistry, 4: 400-406 (2014) IF: 1.387*

A facile, convenient and high yielding synthesis of novel acrylohydrozide thioglycosides via one-pot reaction of the potassium thiolate salts of acglycon part - prepared from readily available starting materials - with 2,3,4,6-tetra-O-acetyl- a-D-gluco- and galactopyranosyl bromides. Pharmacological evaluation of compounds 8j, 8b, 8h, 8k, 8f and 5b in vitro against (MCF-7) cell line (Breast carcinoma cell line) showing high-moderate anti-tumor activities with IC\textsubscript{50} values ranging from 3.69-14.93 (\mu M), moreover molecular modeling of these compounds revealed that they have high binding affinitivity through hydrophobic-hydrophobic interaction and moderate selectivity through the hydrogen bond interaction with the atypical nucleotide binding pocket in the amino terminus of Hsp90.

**Keywords:** Acrylohydrozide; Anti; Tumor activity; Hsp90

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**943. Benzofuran–Morpholinomethyl–Pyrazoline Hybrids as A New Class of Vasorelaxant Agents: Synthesis and Quantitative Structure–Activity Relationship Study**

Ghaneya Sayed Hassan, Doaa Ezzat Abdel Rahman, Dalia Osama Saleh and Gehad Abdel Raheem Abdel Jaleel


A variety of benzofuran-morpholinomethyl-pyrazoline hybrids 4a-e, 5a-e and 6a-j were synthesized via reaction of \( \alpha, \beta \)-unsaturated carbonyl compounds 3a-e with hydrazine hydrate, semicarbazide or thiosemicarbazide. Mannich reaction to 5-(4-aryl-4,5-dihydro-1H-pyrazol-3-yl)-4-methoxybenzofuran-6-ol 7a-e with morpholine hydrochloride and paraformaldehyde afforded two positional isomers 7-morpholinomethyl derivatives 4a-e and N-morpholinomethyl derivatives 8a-e. All the synthesized compounds showed significant vasodilatation properties using isolated thoracic aortic rings of rats precontracted with norepinephrine hydrochloride standard technique. Compounds 3d, 3e, 5a, 5b, 5c, 6b, 6c, 6f, 6h and 6i exhibited activity (IC\textsubscript{50} 0.3185-0.4577 mM) superior to prazocin (IC\textsubscript{50} 0.487 mM), while 5d, 6j and 8c showed comparable activity (IC\textsubscript{50} 0.4789-0.4951 mM). QSAR study revealed a correlation between the observed vasorelaxant activities of the newly synthesized compounds and their different physicochemical parameters, especially solubility, in addition to structure connectivity and energetic quantities calculated from stored 3D conformations. ADME evaluation showed good agreement with the obtained biological results.

**Keywords:** Benzofuran; Morpholinomethyl; Pyrazoline; Vasorelaxant; Quantitative Structure–Activity Relationship Study.

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**944. Synthesis, Molecular Modeling, and Biological Evaluation of Novel Benzimidazole Derivatives As Inhibitors of Hepatitis C Virus RNA Replication**


In this study, synthesis and docking studies of a series of new benzimidazole derivatives linked to substituted pyrimidines either through the methylenethio linkage or its bioisosteric methylene amino bridge were carried out. All the synthesized compounds were evaluated for their hepatitis C virus (HCV) RNA replication-inhibitory activity. Compounds 4d, 4f, and 4h were found to be more potent than VX-950 (IC\textsubscript{50}/90 of 4d=0.123/0.321, 4f=0.145/0.345, 4h=0.129/0.432, VX-950=0.20/0.45 \mu M, respectively) and 6d (IC\textsubscript{50}/90=0.116/0.452 \mu M) displayed activity very similar to that of the standard. Compounds 4d, 4f, and 4h were potent HCV RNA replication inhibitors and are good drug candidates for further investigations.

**Keywords:** Synthesis; Benzimidazole; Pyrimidine; Hepatitis c Virus; Viral RNA replication inhibitor.

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**945. Ion-Pair LC Method for Simultaneous Determination of Aliskiren Hemifumarate, Amlodipine Besylate and Hydrochlorothiazide in Pharmaceuticals**

Ramzia I. El-Bagary, Gabor Patonay, Asmaa A. Elzahr, Elhaf Eldaky and Walid A. Ebed

*Chromatographia, 77: 257-264 (2014) IF: 1.37*

A rapid and precise LC method was developed for the simultaneous determination of aliskiren hemifumarate (ALS), amlodipine besylate (AML) and hydrochlorothiazide (HCZ) using acetonitrile:25 mM octane sulfonic acid sodium salt monohydrate in water (60:40 v/v) as the mobile phase. The flow rate was maintained at 1.2 mL min\(^{-1}\) on a stationary phase composed of Supelco, Discovery\textsuperscript{®} HS (C18) column (25 cm x 4.6 mm, 5 \mu m). Isocratic elution was applied throughout the analysis. Detection was carried out at \( \lambda_{max} (232 \text{ nm}) \) at ambient temperature. The method was validated according to ICH guidelines. Linearity, accuracy and precision were satisfactory over the concentration ranges of 32-320, 2-44 and 4-64 \mu g mL\(^{-1}\) for ALS, AML and HCZ, respectively. LOD and LOQ were estimated and found to be 0.855 and 2.951 \mu g mL\(^{-1}\), respectively, for ALS, 0.061 and 0.202 \mu g mL\(^{-1}\), respectively, for AML, as well as 0.052 and 0.174 \mu g mL\(^{-1}\), respectively, for HCZ. The method was successfully applied for the determination of the three drugs in...
their co-formulated tablets. The results were compared statistically with reference methods and no significant difference was found. The developed method is specific and accurate for the quality control and routine analysis of the cited drugs in pharmaceutical preparations.

Keywords: Column; Liquid; Chromatography; Aliskiren Hemifumarate; Amlodipine Besylate; Hydrochlorothiazide; Pharmaceuticals.

946. Field-Amplified Sample Stacking β-Cyclodextrin Modified Capillary Electrophoresis for Quantitative Determination of Diastereomeric Saponins


Successful simultaneous diastereomeric separation and sensitive determination of two pairs of triterpenoidal saponins have been achieved by capillary electrophoresis (CE) using β-cyclodextrin (β-CD) as a stereoselective agent to cooperate with borate complexation. A usual technique for isolation and group separation of saponins was developed as an appropriate purification step prior to the determination of individual saponins by CE. Soyasaponin I (S1:), azukisaponin V (S2:), bersimidoside I (S3:) and bersimidoside II (S4:) could be well separated within 14 min in a fused-silica capillary (60 cm long to the detector with an additional 10 cm to the cathode; 75 µm i.d.). The background electrolyte was borate buffer (80 mM, pH 10), containing 24 mM β-CD. The separation voltage was 14 kV with a detection wavelength of 195 nm. The sample was electrokinetically injected using a voltage of 16 kV for 12 s. Methanol (70%) was used as the diluent for field-amplified sample stacking after hydrodynamic injection of short water plug (5 cm, 4 s). The method was partially validated for linearity, repeatability, reproducibility, limits of detection and limits of quantification. The correlation coefficients of the calibration curves were all >0.998, and the recoveries were from 98.23 to 96.21%.

Keywords: Capillary; Electrophoresis; Triterpenoidal; Saponins; B-Cyclodextrin.

947. Design, Synthesis and Potential Anti-Proliferative Activity of Some Novel 4-Aminoquinoline Derivatives

Mostafa m. ghobar mansour s. al-said and reem k. araфа


Novel nineteen compounds based on a 4-aminoquinoline scaffold were designed and synthesized as potential antiproliferative agents. The new compounds were N-substituted at the 4-position by aryl or heteroaryl (1-9), quinolin-3-yl (10), 2-methylquinolin-3-yl (11), thiadiazol-2-yl (12), and dapsone moieties (13, 14 and 18). Bis-compounds 15, 16 and 19 were also synthesized to assess their biological activity. All the newly synthesized compounds were tested for in vitro antiproliferative activity against the MCF-7 breast cancer cell line. Seventeen of the novel compounds showed higher activity than the reference drug doxorubicin. The corresponding 7-(trifluoromethyl)-N-[3,4,5-trimethoxyphenyl] quinolin-4-amine 1, N-(7-(trifluoromethyl)quinolin-4-yl)quinolin-3-amine (10), 2-methyl-N-(7-trifluoromethyl)quinolin-4-yl)quinolin-3-amine (11) and N-(4-(4-aminophenylsulfonyl) phenyl)-7-chloroquinolin-4-amine (13) were almost twice to thrice as potent as doxorubicin. Biological screening of the tested compounds could offer an encouraging framework in this field that may lead to the discovery of potent anticaner agents.

Keywords: 4-Aminoquinolines; Bis-Compounds; Dapsone; Antiproliferative Activity.

948. Spectrofluorimetric Determination of Gemifloxacin Mesylate and Linezolid in Pharmaceutical Formulations: Application of Quinone-Based Fluorophores and Enhanced Native Fluorescence

Bahia Abbas Moussa, Marianne Alphonse, Mahrouse Mahmoud Ali Hassan and Michael Gamal Fawzy


Quinone-based fluorophores and enhanced native fluorescence techniques were applied for a fast quantitative analysis of gemifloxacin mesylate (GEM) and linezolid (LIN) in pharmaceutical formulations. For this purpose, three sensitive, accurate and precise spectrofluorimetric methods were developed. GEM, as an n-electron donor, reacts with 7,7,8,8-tetracyanoquinodimethane (method A) and 2,5-dichloro-3,6-dihydroxy-p-benzoquinone (method B) as π-electron acceptors, forming charge transfer complexes that exhibit high fluorescence intensity at 441 and 390 nm upon excitation at 260 and 339 nm, respectively. Method C depends on measurement of enhanced native fluorescence of LIN in phosphate buffer (pH 5) at 380 nm upon excitation at 260 nm. Experimental factors affecting fluorescence intensity were optimized. Linearity was obtained over concentration ranges 50–500, 10–60 and 20–400 ng mL⁻¹ for methods A, B and C, respectively. The developed methods were validated and successfully applied for determination of the cited drugs in tablets.

Keywords: Gemifloxacin mesylate; Linezolid; 7,7,8,8-Tetracyanoquinodimethane; 2,5-Dichloro-3,6-Dihydroxy-P-Benz-oquinone, Fluorimetry; Charge transfer complex.

949. Novel Quinazolone Derivatives Bearing A Sulfonylpyridine Moiety As Anticancer and Radiosensitizing Agents

Mostafa M. Ghorab, Fatma A. Ragab, Helmi l. Heiba and Ahmad A. Bayomi

Journal of Heterocyclic Chemistry, 51 (S1): E255–E262 (2014) IF: 0.873

Quinazoline derivatives posses many types of biological activities and have recently been reported to show substantial antitumor activity in vitro and/or in vivo. There is a variety of mechanisms for their anticaner activity. The present work reports the possible utility of methyl antranilate in the synthesis of some new quinazoline derivatives, bearing a substituted sulfonamide moiety. All the newly synthesized compounds were evaluated for their in vitro anticancer activity against human liver cancer cell line, using doxorubicin as a reference drug. In addition, the most active compounds 14 and 15 were selected and evaluated for their ability to enhance the cell killing effect of γ-radiation.

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950. Synthesis and Molecular Docking of Some Novel Anticancer Sulfonamides Carrying A Biologically Active Pyrrole and Pyrrolopyrimidine Moieties

Mostafa M. Ghorab, Mansour S. Alsaid and Yassin M. Nissan

_Acta Pol Pharm_, 71 (4): 603-614 (2014) IF: 0.693

A novel series of pyrroles and pyrrolopyrimidines carrying a biologically active sulfonamide moiety have been synthesized. The structures were confirmed by elemental analyses and spectral data. All the target compounds were subjected to in vitro cytotoxic screening on breast cancer cell line (MCF-7). Most of the synthesized compounds showed good activity as cytotoxic agents with better IC50 than doxorubicin as a reference drug. In order to suggest a mechanism of action for their activity, molecular docking on the active site of human c-Src was performed for all synthesized compounds.

**Keywords**: Sulfonamide Derivatives, Anticancer Activity.


Ramzia I. El-Bagary , Ehab F. Elkady , Marwa A. Fouad , Zeinab Abdelaziz El-Sherif , Ahmed M. Kadry and Bassam M. Ayoub

_Journal Of Liquid Chromatography & Related Technologies, 37: 1895-1908 (2014) IF: 0.638_

A simple, selective, and precise stability-indicating reversed-phase liquid chromatographic method has been developed and validated for the determination of nilotinib. Nilotinib was subjected to acid and alkali hydrolysis, oxidation, thermal, and photo-degradation. The degradation products were well separated from the pure drug. The method was based on isocratic elution of nilotinib and its degradation products on reversed phase C18 column (100 mm × 4.6 mm, 3.5 µm) — Zorbax Eclipse Plus using a mobile phase consisting of 10 mM KH2PO4:acetonitrile (54.5:45.5, v/v) at a flow rate of 1 mL min⁻¹. Quantitation was achieved with UV detection at 265 nm. Linearity, accuracy and precision were found to be acceptable over the concentration range of 0.1–80 µg mL⁻¹. The drug was found to be susceptible to acid and base hydrolysis but resistant to oxidation, dry heat degradation, and photodegradation. The proposed method was successfully applied to the determination of nilotinib in bulk and in its pharmaceutical preparation.

**Keywords**: Nilotinib; Reversed:Phase Liquid chromatography; Stability;Indicating Assay; Capsules; Anticancer drugs.

Dept. of Pharmaceutical Organic Chemistry


Marwa Ahmed Fouad Said Elfeky

_Acta Chromatographica, 26: 637-647 (2014) IF: 0.485_

A simple, selective, and precise stability-indicating reversed-phase liquid chromatographic method was developed and validated for the determination of nilotinib. Nilotinib was subjected to acid and alkali hydrolysis, oxidation, thermal, and photo-degradation. The degradation products were well separated from the pure drug. The method was based on isocratic elution of nilotinib and its degradation products on reversed phase C18 column (100 mm × 4.6 mm, 3.5 µm) — Zorbax Eclipse Plus using a mobile phase consisting of 10 mM KH2PO4:acetonitrile (54.5:45.5, v/v) at a flow rate of 1 mL min⁻¹. Quantitation was achieved with UV detection at 265 nm. Linearity, accuracy and precision were found to be acceptable over the concentration range of 0.1–80 µg mL⁻¹. The drug was found to be susceptible to acid and base hydrolysis but resistant to oxidation, dry heat degradation, and photodegradation. The proposed method was successfully applied to the determination of nilotinib in bulk and in its pharmaceutical preparation.

**Keywords**: Nilotinib; Reversed:Phase Liquid chromatography; Stability;Indicating Assay; Capsules; Anticancer drugs.

953. Recent Progress in the Identification of Braf Inhibitors As Anti-Cancer Agents

Hala Bakr Ali El-Nassan


The “RAS/BRAF/MEK/ERK” pathway has been associated with human cancers due to the frequent oncogenic mutations identified in its members. In particular, BRAF is mutated at high frequency in many cancers especially melanoma. This mutation leads to activation of the MAPK signaling pathway, inducing uncontrolled cell proliferation, and facilitating malignant transformation. All these facts make BRAF an ideal target for antitumor therapeutic development. Many BRAF inhibitors have been discovered during the last decade and most of them exhibit potent antitumor activity especially on tumors that harbor BRAF V600E mutations. Some of these compounds have entered clinical trials and displayed encouraged results. The present review highlights the progress in identification and development of BRAF inhibitors especially during the last five years.

**Keywords**: BRAF; Inhibitors; Anti-cancer agents.

954. Synthesis and Evaluation of 4-Anilinoquinazoline Biososteres as Potential Anti-Breast Cancer Agents

Afael K. El-Ansary, Aliaa M. Kamal and Mokhtar AbdHafiz Al-Ghorafi


Based on one of the four major categories of scaffold hopping theory namely heterocycle replacements, a series of 5-
arylthieno[2,3-d]pyrimidines had been prepared and evaluated as anti-breast cancer agents. Optimization by combination of different pharmacophores with the thienopyrimidine scaffold led to discovery of biologically active compounds.

**Keywords:** Breast Cancer Cytotoxic Activity Scaffold Hopping

**Synthesis Thienopyrimidines**

955. Synthesis of Novel 1,2,4-Triazoles, Triazolothiadiazines and Triazolothiadiazoles as Potential Anticancer Agents

Mona M. Kamel and Nadia Y. Megally Abdo

*European Journal of Medicinal Chemistry, 86: 75-80 (2014) IF: 3.432*

A series of new N-substituted-3-mercapto-1,2,4-triazoles (3a,b and 7a)ed, triazolo[1,3,4]thiadiazines (5a,b) and triazololo[1,3,4]thiadiazoles (4a, 6 and 8aed) have been synthesized starting from isonicotinic acid hydrizide.

The structure of the newly synthesized compounds was confirmed on the basis of their spectral data and elemental analyses. All the compounds were screened for their in vitro anticancer activity against 6 human cancer cell lines and normal fibroblasts. Seven of the tested compounds (3a,b, 4c, 5a and 8bed) exhibited significant cytotoxicity against most cell lines. Among these derivatives compound 4c exhibited equivalent cytotoxic effect to the standard reference compound.

Synthesis, Molecular Docking, Biological Evaluation of Some Novel Pyrazolones and Pyrazole Derivatives as Anti-Inflammatory Agents

Nadia Abdalla Khalil, Eman Mohamed Ahmed, Khaled Omar Mohamed, Yassin Mohammed Nissan and Sawsan Abo-Bakr Zaitone


A new series of pyrazolone–pyridazine conjugates 3 and 4a–l were synthesized and characterized by spectroscopic means and elemental analyses. All compounds were tested in vivo for their anti-inflammatory and analgesic properties against dicyclofenac, as reference compound.

The synthesized compounds were also evaluated for their ability to inhibit the production of certain inflammatory cytokines such as TNF-α and IL-6 in serum samples. The ulcerogenic potential of the synthesized compounds was also determined. IC50 values for inhibition of COX-1 and COX-2 enzymes were investigated in vitro for the most active candidates. Molecular docking was performed on the active site of COX-2 to predict their mode of binding to the amino acids. Among the synthesized derivatives, compounds 4c and 4e showed good analgesic and anti-inflammatory activities with lower ulcer index than the reference drug.

**Keywords:** Pyrazolone; Pyridazine; Analgesic; Anti-Inflammatory.
clinically approved drug as AChEI used in the treatment of AD. In this paper, we synthesized new tacrine analogs to act on catalytic and peripheral sites of AChE. Their inhibitory activity was evaluated. All novel compounds except 7a showed promising results toward AChE.

Two compounds, 10b and 11b, are more potent than tacrine. Furthermore, molecular-modeling studies were performed for these two compounds to rationalize the obtained pharmacological activity. Moreover, various drug-likeness properties of the new compounds were predicted.

**Keywords:** Acetylcholinesterase; Alzheimer’s Disease; Drug-Likeness; Molecular-Modeling; Tacrine.

### 960. Synthesis and Antitumour Activity of Certain Pyrido[2,3-D]Pyrimidine and 1,8-Naphthyridine Derivatives

Afaf K. Elansary, Astral A. Moneer, Hanan H. Kadry and Ehab M. Gedawy

*Journal of Chemical Research, 38: 147-153 (2014) IF: 0.697*

In an effort to establish new candidates with improved anticancer activity, we report here the synthesis of various series of 2,4,5,7-tetrasubstituted pyrido[2,3-d]pyrimidines and their related isosteres substituted 1,8-naphthyridines. The cytotoxic activity of the newly synthesised compounds against human breast cancer cell line, MCF7 was investigated. Most of the tested compounds exploited potent to moderate growth inhibitory activity, in particular 7-(4-chlorophenyl)-5-(3-nitrophenyl)pyrido[2,3-d]pyrimidin- 4-amino exhibited superior potency to the reference drug doxorubicin (IC50 = 7.54 and 8.48 µM respectively).

**Keywords:** Synthesis, Pyrido[2,3-D]Pyrimidine, Naphthyridine, Inhibitor, Substituent Effect, Antitumour.

### 961. Synthesis, Biological Evaluation of Certain Pyrazolo [3,4-D]Pyrimidines as Novel Anti-Inflammatory and Analgesic Agents

Hanan H. Kadry

*Medicinal Chemistry Research, 23: 5269-5281 (2014)*

In the present study, a series of pyrazolo[3,4-d]pyrimidin-4(5H)-ones linked at 5-position to thiazoline or thiazolidinone ring systems through imino linkage (5-8) was designed and synthesized.

The compounds were assessed for their anti-inflammatory activity and analgesic in vivo. Also, their ability to inhibit ovine COX-1/COX-2 isoforms was evaluated using in vitro cyclooxygenase (COX) inhibition assay. The newly synthesised compounds 7, 8d, and 8e showed potent anti-inflammatory and analgesic activity. Moreover, compound 7 displayed preferential COX-2 inhibitory potency (IC50 = 0.53 IM and COX-2 selectivity index = 10.07) which is more potent than the standard drug meloxicam. Interestingly, the tested compounds showed excellent gastrointestinal safety profile and were well tolerated by experimental animals with high safety margins than the reference drug meloxicam.

**Keywords:** Pyrazolo[3,4-D]Pyrimidine; Thiazolidinone; Anti-Inflammatory; Analgesic; COX-2 Inhibition; Ulcerogenic Effect.

### Dept. of Pharmaceutical Technology and Industrial Pharmacy

#### 962. Continuous Intrajejunal Infusion of Levodopa-Carbidopa Intestinal Gel for Patients With Advanced Parkinsons Disease: A Randomised, Controlled, Double-Blind, Double-Dummy Study


**Background:** Levodopa is the most effective therapy for Parkinson’s disease, but chronic treatment is associated with the development of potentially disabling motor complications. Experimental studies suggest that motor complications are due to non-physiological, intermittent administration of the drug, and can be reduced with continuous delivery. We aimed to assess efficacy and safety of levodopa-carbidopa intestinal gel delivered continuously through an intrajejunal percutaneous tube.

**Methods:** In our 12-week, randomised, double-blind, double-dummy, double-titration trial, we enrolled adults (aged ≥30 years) with advanced Parkinson’s disease and motor complications at 26 centres in Germany, New Zealand, and the USA. Eligible participants had jejunal placement of a percutaneous gastrojejunostomy tube, and were then randomly allocated (1:1) to treatment with immediate-release oral levodopa-carbidopa plus placebo intestinal gel infusion or levodopa-carbidopa intestinal gel infusion plus oral placebo. Randomisation was stratified by site, with a mixed block size of 2 or 4.

The primary endpoint was change from baseline to final visit in motor off-time. We assessed change in motor on-time without troublesome dyskinesia as a prespecified key secondary outcome. We assessed efficacy in a full-analysis set of participants with data for baseline and at least one post-baseline assessment, and imputed missing data with the last observation carried forward approach. We assessed safety in randomly allocated patients who underwent the percutaneous gastrojejunostomy procedure. This study is registered with ClinicalTrials.gov, numbers NCT00660387 and NCT0357994.

**Findings:** From baseline to 12 weeks in the full-analysis set, mean off-time decreased by 4.04 h (SE 0.76; p=0.0015). Mean on-time without troublesome dyskinesia increased by 4.11 h (SE 0.75) in the intestinal gel group and 2.24 h (SE 0.76) in the immediate-release oral group (difference 1.86 [95% CI 0.56 to 3.17]; p=0.0059). In the safety analyses 35 (95%) of 37 patients allocated to the levodopa-carbidopa intestinal gel group had adverse events (five [14%] serious), as did 34 (100%) of 34 patients allocated to the immediate-release oral levodopa-carbidopa group (seven [21%] serious), mainly associated with the percutaneous gastrojejunostomy tube.

**Interpretation:** Continuous delivery of levodopa-carbidopa with an intestinal gel offers a promising option for control of advanced Parkinson’s disease with motor complications. Benefits noted with intestinal gel delivery were of a greater magnitude than were those obtained with medical therapies to date, and our study is, to
our knowledge, the first demonstration of the benefit of continuous levodopa delivery in a double-blind controlled study.

Keywords: Levodopa; Carbidopa; Leig; Parkinson's Disease; Intestinal Gel.

963. A Randomized Trial of the Efficacy and Safety of the H3 Antagonist Abt-288 in Cognitive Impairment Associated With Schizophrenia

George M. Haig, Earle Bain, Weinig Robieson, Ahmed A. Othman, Jeffrey Baker and Robert A. Lenz


Introduction: ABT-288 is a highly potent histamine-3 receptor antagonist that has demonstrated pro-cognitive effects in preclinical models relevant to schizophrenia. This study evaluated the efficacy and safety of two doses of ABT-288 in the treatment of cognitive impairment associated with schizophrenia.

Methods: A randomized, double-blind, placebo-controlled, parallel-group 12-week study was conducted at 23 centers in the United States. Clinically stable subjects with schizophrenia were randomized in an equal ratio to ABT-288 10mg; ABT-288 25mg, or placebo once daily while continuing their antipsychotic regimen. The primary efficacy measure was the change from baseline to day 84 evaluation on the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MCCB) composite score vs placebo. Secondary measures included cognitive functioning and psychiatric scales. Safety assessments and sparse pharmacokinetic sampling were also conducted.

Results: A total of 214 subjects were randomized. The mean baseline MCCB composite score was 28.4. Approximately 80% of subjects completed the study. The MCCB composite score mean change from baseline to day 84 was numerically worse for both the 10mg (1.90, P = .618) and 25mg (0.64, P = .946) doses of ABT-288 vs placebo (2.19). Results from the secondary measures were consistent with the primary analysis. Subjects’ schizophrenia symptoms remained stable throughout the study as evidenced by stable Positive and Negative Syndrome Scale scores. Overall, study medication was tolerated; however, an increased incidence of psychosis-related and sleep-related adverse events was associated with ABT-288.

Discussion: Neither dose of ABT-288 resulted in cognitive improvement in clinically stable adults with schizophrenia

Keywords: Histamine-3 Receptor; Cognition Disorders; Cognitive Dysfunction; Humans; Therapy

964. Exploiting Oxidative Microenvironments in the Body as Triggers for Drug Delivery Systems

Shivanjali Joshi-Barr, Caroline de Gracia Lux, Enas Mahmoud and Adah Almutairi

Antioxidants & Redox Signaling, 21: 730-754 (2014) IF: 7.667

Significance: Reactive oxygen species and reactive nitrogen species (ROS/RNS) play an important role in cell signaling pathways. However, the increased production of these species may disrupt cellular homeostasis, giving rise to pathological conditions. Biomaterials that are responsive to ROS/RNS can be strategically used to specifically release therapeutics and diagnostic agents to regions undergoing oxidative stress.

Recent Advances: Many nanocarriers intended to exploit redox micro-environments as triggers for drug release, summarized and compared in this review, have recently been developed. We describe these carriers’ chemical structures, strategies for payload protection and oxidation-selective release, and ROS/RNS sensitivity as tested in initial studies.

Critical Issues: ROS/RNS are unstable, so reliable measures of their concentrations in various conditions are scarce. Combined with the dearth of materials shown to respond to physiologically relevant levels of ROS/RNS, evaluations of their true sensitivity are difficult.

Future Directions: Oxidation-responsive nanocarriers developed thus far show tremendous potential for applicability in vivo; however, the sensitivity of these chemistries needs to be fine tuned to enable responses to physiological levels of ROS and RNS.

965. Population Pharmacokinetics of Daclizumab High-Yield Process in Healthy Volunteers: Integrated Analysis of Intravenous and Subcutaneous, Single- and Multiple-Dose Administration

Ahmed A. Othman, Jonathan Q. Tran, Meina T. Tang and Sandeep Dutta


Background and Objective: Daclizumab is a humanized monoclonal antibody that blocks the α-subunit of the interleukin-2 receptor with demonstrated benefits in the treatment of multiple sclerosis. The present work aimed to characterize the pharmacokinetics of daclizumab high-yield process (HYP) in healthy volunteers.

Methods: Three double-blind, randomized, placebo-controlled, phase I studies evaluated the pharmacokinetics of daclizumab HYP in healthy volunteers following single subcutaneous administration (50, 150, or 300 mg), multiple subcutaneous administrations (100 or 200 mg biweekly with a 200 mg loading dose), or single intravenous administration (200 or 400 mg). Measurable serum concentrations (n = 925) from 70 subjects treated with daclizumab HYP in the three studies were analyzed using non-linear mixed-effects modeling.

Results: A two-compartment model with a first-order absorption and elimination adequately described daclizumab HYP pharmacokinetics. Daclizumab HYP clearance, inter-compartmental clearance, and central and peripheral volumes of distribution were 10 mL/h, 44 mL/h, 3.89 L, and 2.52 L, respectively, scaled by [bodyweight (kg)/70] with 0.54 and 0.64 exponents for clearance and volume parameters, respectively. Lag-time, mean absorption time, and absolute bioavailability (100–300 mg) for subcutaneous administration were 2 h, 4.6 days, and 84 %, respectively. Bodyweight explained only ~20 % of daclizumab HYP pharmacokinetic variability. With this limited dataset, sex, age, race, or presence of antibodies did not correlate with daclizumab HYP clearance. The estimated effective half-life was 21–25 days. The developed model was robust in bootstrap evaluation and predicted the data adequately in stochastic simulations.

Conclusions: Daclizumab HYP is characterized by slow clearance, linear pharmacokinetics (at doses =100 mg), high subcutaneous bioavailability, and a half-life suitable for monthly administration.

Keywords: Daclizumab hyp; Population pharmacokinetics; Multiple sclerosis; Antibody.
966. Hot-Melts in Buccoadhesive Patches: an Approach for Bioavailability Enhancement of Highly-Metabolized Drugs With Short Elimination Half-Life

Galal M. El Mahrouk, Omaima N. ElGazayerly, Ahmed A. Aboelwafa and Maie S. Taha


The present study deals with the inclusion or incorporation of hot-melts into buccoadhesive patches. Our aim is to develop a patient-friendly dosage form that is capable of extending release of short elimination half-life drugs so to decrease dosing frequency and to increase the bioavailability of highly-metabolized drugs with the ultimate aim of dose reduction. Tizanidine hydrochloride (TIZ) was used as a model drug. TIZ was incorporated into Compritol-based hot-melts, and then further formulated into buccal patches prepared using HPMC, PVA and Polyox. A Central Composite Face-centered Design was employed to statistically optimize the formulation variables; HPMC solution/PVA solution weight ratio, Compritol/TIZ ratio in the hot-melts and percentage Polyox. The optimized formula suggested by the software was successful in controlling drug release, where 85% of TIZ was released after 4 h and the patch showed acceptable mucoadhesion properties. Pharmacokinetic parameters of TIZ from the optimized formula were compared to those of the immediate release tablet, Sirdalud, as reference in human volunteers using a randomized crossover design. Significant increase was observed for Cmax, Tmax, AUC(0–12) and AUC(0–1). The increase in relative bioavailability of TIZ from the optimized formula was 2.57 folds. 

Keywords: Buccoadhesive Patch-Hot-Melts Central Composite Face-Centered Design Lc–Ms/Ms Mucus Glycoprotein Assay.

967. Silver Sulfadiazine Based Cubosome Hydrogels for Topical Treatment of Burns: Development and in Vitro/in Vivo Characterization

Mohammed Abdallah Ahmed Abdallah


The present study is concerned with the development and characterization of a novel nanoaparticlect system; cubosomes, loaded with silver sulfadiazine (SSD), which is the metallic salt of a sulfonamide derivative, and is considered as the drug of choice for topical treatment of infected burns. Cubosome dispersions were formulated by an emulsification technique using different approaches, emulsification of glyceryl monoolein (GMO) and poloxamer (P407) in water followed by ultrasonication, and the dilution method using a hydrotrope. Three different concentrations of GMO were used to formulate the cubosome dispersions using the first method, 5% (D1), 10% (D2) and 15% w/w (D3). 

In the second technique an isotropic liquid was produced by combining GMO with ethanol, and this isotropic liquid was then diluted with a P407 solution (D4). The dispersions were characterized by zeta potential, light scattering techniques, optical and transmission electron microscopy, encapsulation efficiency and in vitro drug release. Results showed that D4 was not a uniform dispersion and that D1, D2 and D3 were uniform dispersions, in which by increasing the GMO content in the dispersion, the size of the cubosomes decreased, zeta potential became more negative, encapsulation efficiency increased up to 86.48% and the drug release rate was slower. P407 gels were prepared using the cold method. Two concentrations of P407 gel were fabricated, 20 and 30% w/w. P407 gels were loaded with either ALA or dispersions containing ALA cubosomes. P407 gels were characterized by critical gelation temperature, rheological measurements and in vitro drug release studies. Results suggested that by increasing P407 concentration, the gelation temperature decreases and viscosity increases. Drug release in both cases was found to follow the Higuchi square root model. Gel loaded with ALA cubosomes provided a significantly lower release rate than the gel loaded with the un-encapsulated ALA. A double blinded placebo controlled clinical study was conducted, aiming to evaluate the efficacy as an anti-wrinkle agent and volunteer’s satisfaction upon application of topical 30% P407 gel loaded with ALA cubosomes. Results indicated reduction in facial lines, almost complete volunteer’s satisfaction upon application of topical 30% P407 gel loaded with ALA cubosomes. Results indicated reduction in facial lines, almost complete

Keywords: Liquid crystals; Drug release; Antioxidant; Alpha lipoic acid; Glyceryl monooleate; Cubosomes; Poloxamer gel; Cosmeceutical application; Clinical study.
969. Follicular Delivery of Spironolactone Via Nanostructured Lipid Carriers for Management of Alopecia

Rehab Nabil Shamma and Mona Hassan Aburahma


Spironolactone (SL) is a US Food and Drug Administration-approved drug for the treatment of hypertension and various edematous conditions. SL has gained a lot of attention for treating androgenic alopecia due to its potent antiandrogenic properties. Recently, there has been growing interest for follicular targeting of drug molecules for treatment of hair and scalp disorders using nanocolloidal lipid-based delivery systems to minimize unnecessary systemic side effects associated with oral drug administration. Accordingly, the objective of this study is to improve SL efficiency and safety in treating alopecia through the preparation of colloidal nanostructured lipid carriers (NLCs) for follicular drug delivery. SL-loaded NLCs were prepared by an emulsion solvent diffusion and evaporation method using 23 full factorial design. All of the prepared formulations were spherical in shape with nanometric size range (215.6–834.3 nm) and entrapment efficiency >74%. Differential scanning calorimetry thermograms and X-ray diffractograms revealed that SL exists in amorphous form within the NLC matrices. The drug release behavior from the NLCs displayed an initial burst release phase followed by sustained release of SL. Confocal laser scanning microscopy confirmed the potential of delivering the fluorolabeled NLCs within the follicles, suggesting the possibility of using SL-loaded NLCs for localized delivery of SL into the scalp hair follicles.

**Keywords:** Spironolactone; Androgenic alopecia; Nanostructured lipid carriers; Follicular targeting; Confocal laser scanning microscopy.

970. Nanosizing of A Poorly Soluble Drug: Technique Optimization, Factorial Analysis, and Pharmacokinetic Study in Healthy Human Volunteers

Ibrahim Elsayed, Aly Ahmed Abdelbary and Ahmed Hassen Elshafey


**Context:** Diacerein (DCN) has low aqueous solubility (3.197 mg/L) and, consequently, low oral bioavailability (35%–56%). To increase both the solubility and dissolution rate of DCN while maintaining its crystalline nature, high pressure homogenization was used but with only a few homogenization cycles preceded by a simple bottom-up technique.

**Methods:** The nanosuspensions of DCN were prepared using a combined bottom-up/top-down technique. Different surfactants – polyvinyl alcohol, sodium deoxycholate, and sodium dodecyl sulfate – with different concentrations were used for the stabilization of the nanosuspensions. Full factorial experimental design was employed to investigate the influence of formulation variables on nanosuspension characteristics using Design-Expert® Software. Particle size (PS), zeta potential, saturation solubility, in vitro dissolution, and drug crystallinity were studied. Moreover, the in vivo performance of the optimized formula was assessed by bioavailability determination in healthy human volunteers.

**Results:** The concentration of surfactant had a significant effect on both the PS and polydispersity index values. The 1% surfactant concentration showed the lowest PS and polydispersity index values compared with other concentrations. Both type and concentration of surfactant had significant effects on the zeta potential. Formula F8 (containing 1% sodium deoxycholate) and Formula F12 (containing 1% sodium dodecyl sulfate) had the highest desirability values (0.952 and 0.927, respectively). Hence, they were selected for further characterization. The saturated solubility and mean dissolution time, in the case of F8 and F12, were significantly higher than the coarse drug powder. Techniques utilized in the nanocrystals’ preparation had no effect on DCN crystalline state. The selected formula (F12) showed a higher bioavailability compared to the reference market product with relative bioavailability of 131.4%.

**Conclusion:** The saturation solubility, in vitro dissolution rate and relative bioavailability of DCN were significantly increased after nanocrystallization. Less time and power consumption were applied by the combination of bottom-up and top-down techniques.

**Keywords:** Nanocrystals, High Pressure Homogenization, Diacerein, Factorial Analysis, Pharmacokinetic Study.

971. Compritol 888 Ato: A Multifunctional Lipid Exciptent in Drug Delivery Systems and Nanopharmaceuticals

Aburahma MH and Badr-Eldin SM.

*Expert Opin. 11 (12): 1865-1883 (2014)* IF: 4.116

**Introduction:** Compritol® 888 ATO is a lipid excipient that is generally used in cosmetic industry as a surfactant, emulsifying agent and viscosity-inducing agent in emulsions or creams. Based on its chemical composition, Compritol 888 ATO is a blend of different esters of behenic acid with glycerol.

**Areas Covered:** Recently, there has been great interest in the multiple roles that Compritol 888 ATO plays in various pharmaceutical delivery systems. Accordingly, this review aimed at summarizing the current and potential applications of Compritol 888 ATO in various drug delivery areas.

**Expert Opinion:** Different researches have highlighted the feasibility of using Compritol 888 ATO as a lubricant or coating agent for oral solid dosage formulations. It has also been explored as a matrix-forming agent for controlling drug release. At present, the most common pharmaceutical application of Compritol 888 ATO is in lipid-based colloidal drug delivery system such as solid lipid nanoparticles, solid lipid nanoparticles and nanostructured lipid carriers. Although, Compritol 888 ATO has acceptable regulatory and safety profiles and although the number of articles that emphasize on its applicability as an innovative excipient in pharmaceutical technology is continuously increasing, it is not widely used in the pharmaceutical market products and its use is limited to its sustain release ability in extended release tablets.

**Keywords:** Compritol 888 Ato, Glycerol Behenate, Lipid Excipients, Pharmaceutical.
972. Metronidazole and Pentoxifylline Films for the Local Treatment of Chronic Periodontal Pockets: Preparation, in Vitro Evaluation and Clinical Assessment
Labib GS, Aldawsari HM and Badr-Eldin SM.

Objective: Periodontitis is one of the most important chronic inflammatory dental diseases arising from the destructive actions caused by a variety of pathogenic organisms presented in the oral cavity. The aim of this study is the preparation and in vitro evaluation of films for the local treatment of periodontal pockets.

Methods: The prepared films contained either metronidazole (Mtr), for its antimicrobial effect in periodontal diseases, using a mixture of polymers namely hydroxypropyl methyl cellulose, Carbopol 934 or locally applied Pentoxifylline (PTX), for its anti-inflammatory activity, using chitosan. All films were prepared using solvent casting technique and were evaluated for their physical characteristics, drug content uniformity, surface pH, swelling behavior, mechanical properties and in vitro release. Further characterization was done on the selected formulations using differential scanning calorimetry and scanning electron microscopy for surface structure. Clinical evaluation tests were also performed.

Result: Appropriate physical characteristics and mechanical properties for most formulations and their suitability for periodontal application were observed. In vitro drug release from most films showed a burst release rate for both Mtr and PTX during the first 2 h after which the release rate was markedly decreased. Clinical trials on patients revealed the advantageous use of Mtr and PTX as an adjunct treatment with traditionally used dental techniques.

Conclusion: The effectiveness of the co-therapy of either drug could add benefit in the eradication of chronic periodontal hazards.

Keywords: Chitosan; Clinical Assessment; Hydroxypropyl Methyl Cellulose; In Vitro Release; Local Drug Delivery; Metronidazole; Pentoxifylline; Solvent Casting Technique.

973. Chitosan Lactate Wafer As A Platform for the Buccal Delivery of Tizanidine HCl: in Vitro and in Vivo Performance
Gallal M. El-Mahrouk, Omaima N. El-Gazayerly, Ahmed A. Aboelwafa and Maie S. Taha

International Journal of Pharmaceutics, 467: 100-112 (2014) IF: 3.785

Tizanidine HCl is a skeletal muscle relaxant that suffers from extensive hepatic metabolism resulting in 34–40% oral bioavailability. It also suffers from short half-life (2.1–4.2 h) that necessitates frequent administration thus reducing patient compliance. In addition, tizanidine HCl is water soluble, so it is a challenging candidate for controlled drug delivery. In our study, tizanidine was encapsulated in chitosan lactate beads cross-linked with sodium tripolyphosphate. The beads were further incorporated into chitosan lactate wafer to be easily applied to buccal mucosa, aiming to bypass the hepatic metabolism. A central composite face-centered design was applied to statistically optimize the formulation variables; tripolyphosphate concentration, chitosan lactate concentration and polymer/drug ratio. The optimized formula suggested by the software composed of: 3.03% tripolyphosphate, 4.92% chitosan lactate and 2.13 polymer/drug ratio. It provided encapsulation efficiency of 56.5% and controlled tizanidine release over 8 h. It is also characterized by being mucoadhesive and nonirritant. Pharmacokinetic parameters of tizanidine from the optimized formula were compared to those of the immediate release tablet, Sirdalud1, as reference in human volunteers using a randomized crossover design. Significant increase was observed for Tmax and AUC(0–1). The increase in relative bioavailability of TIZ from the optimized formula was 2.27 fold.

Keywords: Chitosan Lactate Na Tripolyphosphate Buccoadhesive Wafer Containing Beads Central Composite Facecentered Design.

974. Controlled-Release Triple Anti-Inflammatory Therapy Based on Novel Gastroretentive Sponges: Characterization and Magnetic Resonance Imaging in Healthy Volunteers
Tadros MI. and Fahmy RH.


The current work aimed to develop novel composite sponges of chitosan (CH)–chondroitin sulfate (CS) as a low-density gastroretentive delivery system for lornoxicam (LOR). This triple anti-inflammatory therapy-loaded matrices are expected to expand and float upon contact with gastric fluids for prolonged times. CH and CS solutions (3%, w/w) were prepared, mixed in different ratios, lyophilized, coated with magnesium stearate and compressed. The CH:CS interpolymer complex (IPC) was evaluated via FT-IR, DSC, and XRD. The compressed-sponges were evaluated for appearance, structure, porosity, pore diameter, density, wetting-time, floating characteristics, adhesion-retention, and LOR-release. The gastroretentivity of the best achieved magnetite-loaded sponges was monitored in healthy volunteers via MRI. The interaction between CH (protonated amino groups) and CS (anionic carboxylate/sulfate groups) proved IPC formation. DSC and XRD studies confirmed loss of LOR crystallinity. The sponges possessed interconnecting porous-network structures. The porosity, mean pore diameter, and bulk density of CH:CS (10:3) IPC sponges were 11.779%, 25.4 nm, and 0.670 g/mL, respectively. They showed complete wetting within seconds, gradual size-expansion within minutes and prolonged adhesion for hours. Controlled LOR-release profiles were tailored over 12 h to satisfy individual patient needs. Monitoring of sponges via MRI proved their gastroretentivity for at least 5 h.

Keywords: Lornoxicam; Chitosan–chondroitin sulfate interpolymer; Complex; Triple anti-inflammatory therapy; Gastroretentive sponges; Magnetic resonance imaging.

975. Design of Lipotomes As A Novel Dual Functioning Nanocarrier for Bioavailability Enhancement of Lacidipine: in-Vitro and in Vivo Characterization
Nermeen Adel ElKasabgy, Ibrahim Elsayed and Ahmed Hassen Elshafeey


www.gsrdis.ae.edu.eg
Lipotomes were designed to enhance lacidipine’s oral bioavailability by improving its solubility and enhancing the oral lymphatic uptake. Lipotomes were prepared using cetyl alcohol and Tween 1 80 using a thin film hydration technique. Cetyl alcohol was chosen for imparting a lipophilic environment that would enhance the lymphatic uptake while Tween 1 80 would improve drug solubility within the lipotomes. Lipotomes were characterized by analyzing their particle size, solubilization efficiency and in vitro drug release. Central composite design was applied to statistically optimize the formulations using Design-Expert software. The optimum formula (OLT) was made up of excipients: drug ratio of 36:59:1 w/w and Tween 1 80: cetyl alcohol ratio of 4:1 w/w. OLT was lyophilized and filled into Eudragit-L100 enteric coated capsules. Mannitol (10% w/v) was the ideal cryoprotectant to retain the physicochemical characteristics of the OLT formulation after lyophilization. In conclusion, the selected lyophilized formula (L3) succeeded in enhancing drug’s oral bioavailability in human volunteers compared to the commercial product confirming the success of lipotomes as a novel oral nanocarrier for insoluble drugs having extensive first pass metabolism.

**Keywords:** Lipotomes, Lacidipine, Central Composite, Lyophilization, Enteric Coating.

**976. Effect of Surface Charge on the Brain Delivery of Nanostructured Lipid Carriers in Situ Gels Via the Nasal Route**

Yasmine M. Gaba, Amany O. Kamel, Omaima A. Sammoura, and Ahmed H. Elshafeey


The aim of this study was to investigate the influence of the nanocarrier surface charge on brain delivery of a model hydrophilic drug via the nasal route. Anionic and cationic nanostructured lipid carriers (NLCs) were prepared and optimized for their particle size and zeta potential. The optimum particles were incorporated in poloxamer in situ gels and their in vivo behavior was studied in the plasma and brain after administration to rats. Optimum anionic and cationic NLCs of size <200 nm and absolute zeta potential value of ≈ 34 mV were obtained. Toxicity study revealed mild to moderate reversible inflammation of the nasal epithilium in rats treated with the anionic NLCs (A7), and destruction of the lining mucosal nasal epithilium in rats treated with the cationic NLCs (C7L). The absolute bioavailability of both drug loaded anionic and cationic NLCs in situ gels was enhanced compared to that of the intranasal solution (IN) of the drug with values of 44% and 77.3%, respectively. Cationic NLCs in situ gel showed a non significant higher Cmax (maximum concentration) in the brain compared to the anionic NLCs in situ gel. Anionic NLCs in situ gel gave highest drug targeting efficiency in the brain (DTE%) with a value of 158.5 which is nearly 1.2 times that of the cationic NLCs in situ gel.

**Keywords:** Nanostructured Lipid Carriers; Surface Charge; Brain Delivery; Intranasal; In Vivo.

**977. Enhanced Bioavailability of Buspirone Hydrochloride Via Cup and Core Buccal Tablets: Formulation and in Vivo Evaluation**

Mohamed A.A. Kassem, Aliaa N. ElMeshad and Ahmed R. Fares


This work aims to prepare sustained release buccal mucoadhesive tablets of buspirone hydrochloride (BH) to improve its systemic bioavailability. The tablets were prepared according to 5 x 3 factorial design where polymer type was set at five levels (carbopol, hydroxypropyl methylcellulose, sodium alginate, sodium carboxymethyl cellulose and guar gum), and polymer to drug ratio at three levels (1:1, 2:1 and 3:1). Mucoadhesion force, *ex vivo* mucoadhesion time, percent BH released after 8 h (Q8h) and time for release of 50% BH (T50) were chosen as dependent variables. Additional BH cup and core buccal tablets were prepared to optimize BH release profile and make it unidirectional along with the tablets mucoadhesion. Tablets were evaluated in terms of content uniformity, weight variation, thickness, diameter, hardness, friability, swelling index, surface pH, mucoadhesion strength and time and *in vitro* release. Cup and core formula (CA10) was able to adhere to the buccal mucosa for 8 h, showed the highest Q8h (97.91%) and exhibited a zero order drug release profile. Pharmacokinetic study of formula CA10 in human volunteers revealed a 5.6 fold increase in BH bioavailability compared to the oral commercial Buspar® tablets. Conducting level A in *in vitro/in vivo* correlation showed good correlation (*r*² = 0.9805) between fractions dissolved in *in vitro* and fractions absorbed in *in vivo*.

**Keywords:** Buspirone HCl; Mucoadhesive dosage forms; Buccal tablets; Cup and core tablets; Pharmacokinetic study; LC/MS/MS.


Dina B. Mahmoud, Marwa H. Shukr and Ehab R. Bendas


The current investigation was aimed to improve the solubility of poorly soluble drug, cilostazol (CLZ), Self-nanoemulsifying drug delivery system (SNEDDS) composed of oil, surfactant and co-surfactant for both oral and parenteral administration of CLZ was formulated. The components for SNEDDS were identified by solubility studies, and pseudo-ternary phase diagrams were plotted to identify the efficient self-emulsification regions. The optimum formula, composed of Capryol 90 as an oil phase, Cremporph EL as a surfactant, and Transcutol HP as a cosurfactant in a ratio of 19.8:30.5:49.7 by weight, was able to solubilize CLZ 2000 times higher than its solubility in water. This formula was able to form grade “A” nanoemulsion when diluted with water, resulted in emulsification time of 50 1.1 s, particle size of 14.3 nm, PDI of 0.5 and % transmittance was 97.40% 0.65. It showed excellent in vitro dissolution of 93.1% and 81.5% after 5 min in 0.3% sodium lauryl sulphate solution and phosphate buffer pH 6.4, respectively when compared with the marketed tablet formulation and drug suspension as the tablets showed only 44.3% and 9.9% while CLZ suspension showed 33.9% and 8.8% in 0.3% sodium lauryl sulphate solution and phosphate buffer pH 6.4, respectively. It was found to be robust to low viscosity values of 14.20 0.35 cP. In vivo study revealed significant increase in bioavailability of CLZ in rabbits to 3.94 fold compared with the marketed tablet formulation after oral administration. This formula could be sterilized by autoclaving and did not cause significant hemolysis to human blood which indicates its safety for intravenous administration with a 1.12 fold increase in bioavailability compared with its oral administration. Our study
illustrated the potential use of SNEDDS of poorly soluble CLZ orally, and its successful administration of parenterally when required in acute cases of myocardial and cerebral infarction.

**Keywords:** Cilostazol; Self-Nanoemulsifying Systems; Pharmacokinetics; Oral Administration; Intravenous Administration.


Ehab R. Bendas and Aly A. Abdelbary

*International Journal of Pharmaceutics, **472:** 304-314 (2014) IF: 3.785

Recently, great attention has been paid to nanocapsules. The interest of these structures is due to their promising applications as drug delivery systems. The objective of this study was to develop novel enteric coating technique based on instantaneous encapsulation of the acid-labile drug, omeprazole in innovative enteric nanocapsules. Omeprazole enteric nanocapsules were formulated by varying the type and amount of the enteric polymer. The particle size (PS), polydispersity index (PDI), zeta potential (ZP) and encapsulation efficiency (EE) values of the prepared enteric nanocapsules were determined. A full 2131 factorial design was used for planning and analysis of the experimental trials to select the optimized formulation. The highest desirability value was 0.7463 for formula E3 (containing 200 mg hydroxypropyl methylcellulose phthalate (HPMCP)). The stability of omeprazole was reflected by the absence of the exothermal peak when the drug was encapsulated as detected by differential scanning calorimetry (DSC) thermograms. In vitro drug release study confirmed the USP specifications required to meet the key formulation characteristics of gastro-resistance. In vivo pharmacological assessment showed that the optimized nanocapsules were able to protect rat stomach against ulcer formation compared to the aqueous suspension of the drug which showed less significant protection.

**Keywords:** Enteric Nanocapsules; Omeprazole; Hydroxypropyl Methylcellulose Phthalate; In Vivo Antiulcer Activity.

980. Nano-Transfersomal Ciprofloxacin Loaded Vesicles for Non-Invasive Trans-Tympanic Ototopical Delivery: in-Vitro Optimization, Ex-Vivo Permeation Studies, and in-Vivo Assessment

Abdulaziz Mohsen Al-mahlawi, Omnaya Mohammed Khowessah and Raguia Ali Shoukri

*International Journal of Pharmaceutics, **472:** 304-314 (2014) IF: 3.785

Ciprofloxacin is a synthetic fluoroquinolone antibiotic that has been used for systemic treatment of otitis media in adults. It was approved for topical treatment of otitis in children with tympanostomy tubes. The aim of this work was to enhance the local non-invasive delivery of ciprofloxacin to the middle ear across an intact tympanic membrane (TM) in an attempt to treat acute otitis media (AOM) ototopically. In order to achieve this goal, ciprofloxacin nano-transfersomal vesicles were prepared by thin film hydration (TFH) technique, using several edge activators (EAs) of varying hydrophilic-lipophilic balance (HLB) values. A full factorial design was employed for the optimization of formulation variables using Design-Expert® software. The optimal formulation was subjected to stability testing, ex-vivo permeation studies (through ear skin and TM of rabbits), and in-vivo evaluation. Results revealed that the optimal formulation (composed of phospholipid and sodium cholate as an EA at a molar ratio of 5:1) exhibited enhanced ex-vivo drug flux through ear skin and TM when compared with the commercial product (Ciprocin® drops). It demonstrated a greater extent of in-vivo drug deposition in the TM of albino rabbits relative to Ciprocin®. Consequently, transfersomes could be promising for the non-invasive trans-tympanic delivery of ciprofloxacin.

**Keywords:** Transfersomes; Thin Film hydration; Acute otitis Media; Ex-Vivo Tympanic membrane permeation; In-Vivo drug Deposition studies.

981. Ocular Supersaturated Self-Nanoemulsifying Drug Delivery Systems (S-SNEDDS) to Enhance Econazole Nitrate Bioavailability

Nermeen Adel ElKasabgy

*International Journal of Pharmaceutics, **460:** 33-44 (2014) IF: 3.785

Econazole nitrate (ECO) is a poorly water soluble antifungal drug. Having low aqueous solubility affects negatively its use for ocular treatment. This work aimed to prepare ocular supersaturated selfnanoemulsifying drug delivery systems (S-SNEDDS) of ECO employing hydroxypropyl methylcellulose as a precipitation inhibitor to improve the drug solubility by avoiding its precipitation after administration. Various oils, surfactants and co-surfactants were used to construct SNEDDS. The SNEDDS were evaluated for globule size, polydispersity index and their irritation potential using hen’s egg test-chorioallantoic membrane (HET-CAM). The best SNEDDS was loaded with ECO and HPMC to prepare S-SNEDDS. In vitro precipitation test of the S-SNEDDS showed that the selected S-SNEDDS was done to study the effect of the precipitation inhibitor, ECO permeation in rabbits’ eyes from the selected S-SNEDDS (with and without HPMC) was evaluated. The results showed that SNEDDS-X consisting of 20% Capmul® C10 as an oil, 60% Cremophor RH40® as a surfactant and 20% Transcutol® HP as co-surfactant possessed the lowest PDI value and a non-irritant effect on the CAM. The in-vitro precipitation test showed that the use of HPMC successfully sustained the supersaturated state by avoiding ECO precipitation. Higher Cmax, AUC0–8 and longer tmax confirm the development of a successful ECO-loaded S-SNEDDS.

**Keywords:** Econazole Nitrate; S-Egg Test-Chorioallantoic Membrane Supersaturated Self-Nanoemulsifying Systems Precipitation Inhibitor In-Vitro Precipitation Test.


Rania Moataz El-Dahmy, Ibrahim Elsayed Ahmed Hassen Elshafeey, Nabaweya Abdelaziz Abd El Gawad and Omaima Naim El-Gazayerly


The aim of this study was to increase the in vivo mean residence time of vinpocetine after IV injection utilizing long circulating mixed micellar systems. Mixed micelles were prepared using Pluronics L121, P123 and P127. The systems were characterized
by testing their entrapment efficiency, particle size, polydispersity index, zeta potential, transmission electron microscopy and in vitro drug release. Simple lattice mixture design was planned for the optimization using Design-Expert 1 software. The optimized formula was lyophilized, sterilized and imaged by scanning electron microscope. Moreover, the in vivo behavior of the optimized formula was evaluated after IV injection in rabbits. The optimized formula, containing 68% w/w Pluronic L121 and 32% w/w Pluronic F127, had the highest desirability value (0.621). Entrapment efficiency, particle size, polydispersity index and zeta potential of the optimized formula were 50.74 ± 3.26%, 161.50 ± 7.39 nm, 0.21 ± 0.03 and 22.42 ± 1.72 mV, respectively. Lyophilization and sterilization did not affect the characteristics of the optimized formula. Upon in vivo investigation in rabbits, the optimized formula showed a significantly higher elimination half-life and mean residence time than the market product. Finally, mixed micelles could be considered as a promising long circulating nanocarrier for lipophilic drugs.

**Keywords:** Pluronic, Vinpocetine micelles lyophilization; Sterilization; Vivo Mean Residence Time.

**983. Population Pharmacokinetics of Levodopa in Subjects With Advanced Parkinsons Disease: Levodopa-Carbidopa Intestinal Gel Infusion Vs. Oral Tablets**

Ahmed A. Othman and Sandeep Dutta


**Aims:** Levodopa-carbidopa intestinal gel (LCIG) provides continuous levodopa-carbidopa delivery through intrajejunal infusion. This study characterized the population pharmacokinetics of levodopa following a 16h jejunal infusion of LCIG or frequent oral administration of levodopa-carbidopa tablets (LC-oral) in subjects with advanced Parkinson’s disease (PD).

**Methods:** A non-linear mixed-effects model of levodopa pharmacokinetics was developed using serial plasma concentrations from an LCIG phase 1 study and a phase 3 double-blind, double-dummy study of the efficacy and safety of LCIG compared with LC-oral in advanced PD patients (n=68 for model development; 45 on LCIG and 23 on LC-oral). The final model was internally evaluated using stochastic simulations and bootstrap and externally evaluated using sparse pharmacokinetic data from 311 subjects treated in a long-term safety study of LCIG.

**Results:** The final model was a two-compartment model for absorption, first order elimination, bioavailability for LCIG (97%; confidence interval = 95% to 98%) relative to LC-oral, different first order transit absorption rate constants (LCIG = 9.2h (-1) vs. LC-oral= 2.4h(-1); corresponding mean absorption time of 7 min for LCIG vs. 25/min for LC-oral) and different residual (intra-subject) variability for LCIG (15% proportional error, 0.3µg ml-1 additive error) vs. LC-oral (29% proportional error, 0.59µg ml-1 additive error). Estimated oral clearance and steady-state volume of distribution for levodopa were 24.8 l (-1) and 1311, respectively.

**Conclusions:** LCIG administration results in faster absorption, comparable levodopa bioavailability and significantly reduced intra-subject variability in levodopa concentrations relative to LC-oral administration.

**Keywords:** Duodopa; Intestinal gel; Levodopa; Parkinson’s disease; Population pharmacokinetics.

**984. The H3 Antagonist ABT-288 is Tolerated at Significantly Higher Exposures in Subjects With Schizophrenia Than in Healthy Volunteers**

Ahmed A. Othman, George Haig, Hana Florian, Charles Locke, Lev Gertsik and Sandeep Dutta


**Aims:** ABT-288 is a potent and selective H3 receptor antagonist with proconvulsive effects in several preclinical models. In previous studies, 3mg once daily was the maximal tolerated dose in healthy volunteers. This study characterized the safety, tolerability and pharmacokinetics of ABT-288 in stable subjects with schizophrenia.

**Methods:** This was a randomized, double-blind, placebo-controlled, dose-escalating study of ABT-288 (10 dose levels, from 1 to 60 mg once daily for 14 days) in stable subjects with schizophrenia treated with an atypical antipsychotic. In each dose group, five to seven and two to three participants were assigned to ABT-288 and placebo, respectively.

**Results:** Of the 67 participants enrolled, nine participants (on ABT-288) were prematurely discontinued, in seven of these due to adverse events. ABT-288 was generally safe and tolerated at doses up to 45 mg once daily. The most common adverse events, in decreasing frequency (from 31 to 5%), were abnormal dreams, headache, insomnia, dizziness, somnolence, dysgeusia, dry mouth, psychotic disorder, parosmia and tachycardia. Adverse events causing early termination were psychotic events (four) and increased creatine phosphokinase, pyrexia and insomnia (one each). The half-life of ABT-288 ranged from 28 to 51h, and steady state was achieved by day 12 of dosing. At comparable multiple doses, ABT-288 exposure in subjects with schizophrenia was 45% lower than that previously observed in healthy subjects. At trough, ABT-288 cerebrospinal fluid concentrations were 40% of the total plasma concentrations.

**Conclusions:** ABT-288 was tolerated at a 15-fold higher dose and 12-fold higher exposures in subjects with schizophrenia than previously observed in healthy volunteers. The greater ABT-288 tolerability was not due to limited brain uptake.

**Keywords:** ABT-288; Cognitive Deficits; Histamine H3 Receptors; Schizophrenia; Tolerability.

**985. A Randomized Study of H3 Antagonist ABT-288 in Mild-To-Moderate Alzheimer’s Dementia**

George M. Haig, Yili Pritchett, Andreas Meier, Ahmed A. Othman, Coleen Hall, Laura M. Gault and Robert A. Lenz

*Journal of Alzheimer’s Disease, 42 (3): 959-971 (2014) IF: 3.612*

**Background:** ABT-288, a highly selective histamine-3 receptor antagonist, demonstrated efficacy across several preclinical cognitive domains, and safety in healthy subjects and elderly volunteers. Objective: Evaluate the efficacy and safety of ABT-288 in subjects with mild-to-moderate Alzheimer’s dementia.

**Methods:** The study used a randomized, double-blind, placebo-and active-controlled, parallel group design with pre-defined futility criteria to permit early study termination. A total of 242 subjects were randomized in an equal ratio to ABT-288 1 mg or 3
mg, donepezil 10 mg, or placebo once daily for 12 weeks. The primary efficacy endpoint was the change from baseline to final evaluation on the 13-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) total score.

**Results:** The study was prematurely terminated because futility criteria were met. Point estimates on the ADAS-Cog scores for both ABT-288 dose groups were numerically inferior to placebo but no statistical differences were detected. Donepezil demonstrated statistically significant improvement. Adverse events were generally mild and self-limiting.

**Conclusion:** ABT-288 did not demonstrate efficacy in the symptomatic treatment of Alzheimer's dementia.

**Keywords:** Abt-288, Alzheimer's Dementia, Cognition, Drug Therapy, H3 Antagonists, Humans

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**986. Design and Optimization of Self-Nanoemulsifying Delivery System to Enhance Quercetin Hepatoprotective Activity in Paracetamol-Induced Hepatotoxicity**

Osama A. A. Ahmed, Shaimaa M. Badr-Eldin, Mona K. Tawfik, Tarek A. Ahmed, Khalid M. El-Say and Jihan M. Badr

*Journal Of Pharmaceutical Sciences, 103(2): 602-612 (2014) IF: 3.007*

He present study aimed to develop optimized quercetin (QT)-loaded self-nanoemulsifying drug delivery system (SNEDDS) that offers protective effect against liver damage. Solubility study of QT in different oils, surfactants, and cosurfactants was performed. Ternary phase mixtures of the selected components were constructed to select a suitable range for each component. Experimental mixture design was utilized to optimize SNEDDS that possess smaller globule size with enhanced emulsification and dissolution rates. QT SNEDDS was compared with QT suspension control and silymarin. In vivo evaluation and histopathological study of the selected QT SNEDDSs were achieved after administration of paracetamol over dosage to albino rats. Two optimized formulations were selected; one based on Sefsol and the other based on linoleic acid as an oily phase, Tween® 80 and polyethylene glycol 400 as surfactant and cosurfactant, respectively. Both Sefsol and linoleic-acid-optimized SNEDDS formulation showed no symptoms associated with toxicity and offered protective effect against paracetamol-induced hepatotoxicity by scavenging free radicals, attenuating lipid peroxidation, and enhancing the activity of antioxidants. The histopathological observations revealed that the inflammatory infiltrations induced by paracetamol were significantly ameliorated.

**Keywords:** Snedds; Dynamic Light Scattering; Emulsion; Hepatoprotective Activity; Mixture Design; Nanoparticles; Nanotechnology; Optical Activity; Quercetin.

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Sami Ahmed, Doaa Ahmed El-Setouhy, Alia Abd El-Latif Badawi and Mohamed Ahmed El-Nabarawi

*European Journal of Pharmaceutical Sciences, 60: 10-23 (2014) IF: 3.005*

Granisetron hydrochloride (granisetron) is a potent antiemetic that has been proven to be effective in acute and delayed emesis in cancer chemotherapy. Granisetron suffers from reduced oral bioavailability (60%) due to hepatic metabolism. In this study the combined advantage of provesicular carriers and buccal drug delivery has been explored aiming to sustain effect and improve bioavailability of granisetron via development of granisetron provesicular buccoadhesive tablets with suitable quality characteristics (hardness, drug content, in vitro release pattern, ex vivo bioadhesion and in vivo bioadhesion behavior).

Composition of the reconstituted niosomes from different prepared provesicular carriers regarding type of surfactant used and cholesterol concentration significantly affected both entrapment efficiency (%EE) and vesicle size. Span 80 proniosome-derived niosomes exhibited higher encapsulation efficiency and smaller particle size than those derived from span 20. Also, the effect of %EE and bioadhesive polymer type on in vitro drug release and in vivo performance of bucchoadhesive tablets was investigated.

Based on achievement of required in vitro release pattern (20–30% at 2 h, 40–65% at 6 h and 80–95% at 12 h), in vivo swelling behavior, and in vivo adhesion time (>14 h) granisetron formulation (F19, 1.4 mg) comprising HPMC:carbopol 974P (7:3) and maltodextrin coated with the vesicular precursors span 80 and cholesterol (9:1) was chosen for in vivo study.

In vivo pharmacokinetic study revealed higher bioavailability of buccal formulation relative to conventional oral formulation of granisetron (AUC0–1 is 89.97 and 38.18 ng h/ml for buccal and oral formulation, respectively). A significantly lower and delayed Cmax (12.09 ± 4.47 ng/ml, at 8 h) was observed after buccal application compared to conventional oral tablet (31.66 ± 10.15 ng/ml, at 0.5 h). The prepared provesicular buccoadhesive tablet of granisetron (F19) might help bypass hepatic first-pass metabolism and improve bioavailability of granisetron with the possibility of reducing reported daily dose (2 mg) and reducing dosing frequency.

**Keywords:** Granisetron hydrochloride; Proniosomes; Provesicular Powder; Buccal Delivery; Bioavailability Study.

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**988. Feasibility of Optimizing Trimetazidine Dihydrochloride Release from Controlled Porosity Osmotic Pump Tablets of Directly Compressed Cores**

Basant A. Habib, Randa T. Abd El Rehim and Samia A. Nour


The aim of this study was to develop and optimize Trimetazidine dihydrochloride (TM) controlled porosity osmotic pump (CPOP) tablets of directly compressed cores. A23 full factorial design was used to study the influence of three factors namely: PEG400 (10% and 25% based on coating polymer weight), coating level (10% and 20% of tablet core weight) and hole diameter (0 “no hole” and 1 mm). Other variables such as tablet cores, coating mixture of ethylcellulose (4%) and dibutylphthalate (2%) in 95% ethanol and pan coating conditions were kept constant. The responses studied (Yi) were cumulative percentage released after 2 h (Q%2h), 6 h (Q%6h), 12 h (Q%12h) and regression coefficient of release data fitted to zero order equation (RSQz ero), forY1,Y2,Y3, and Y4, respectively. Polynomial equations were used to study the influence of different factors on each response individually. Response surface methodology and multiple response optimization were used to search for an optimized formula. Response variables for the optimized formula were
restricted to 10% 6 Y1 6 20%, 40% 6 Y2 6 60%, 80% 6 Y3 6 100%, and Y4>0.9. The statistical analysis of the results revealed that PEG400 had positive effects on Q%2h, Q%6h and Q%12h. hole diameter had positive effects on all responses and coating level had positive effect on Q%6h, Q%12h and negative effect on RSQzero. Full three factor interaction (3FI) equations were used for representation of all responses except Q%2h which was represented by reduced (3FI) equation. Upon exploring the experimental space, no formula in the tested range could satisfy the required constraints. Thus, direct compression of TMCores was not suitable for formation of CPOP tablets. Preliminary trials of CPOP tablets with wet granulated cores were promising with an intact membrane for 12 h and high RSQzero. Further improvement of these formulations to optimize TM release will be done in further studies.

**Keywords:** Trimeprazine; Controlled porosity osmotic Pump Tablets; Factorial design; Response surface methodology.

**989. Antioxidant and Hepatoprotective Effects of Silymarin Phytosomes Compared To Milk Thistle Extract in CCl4 Induced Hepatotoxicity in Rat**

O. N. El-Gazayerly, A. I. A. Makhlouf, A. M. A. Soelm, and M. A. Mohmoud


Milk thistle extract is a well-known hepatoprotectant with low bioavailability (20–50%). The objective of the present study is to prepare and characterize silymarin phytosomes and to test the hepatoprotective effect of the phytosomes in CCl4 induced liver injury in rats compared to milk thistle extract. Phytosomes were prepared using lecithin from soybeans and from egg yolk. The prepared phytosomes were examined using scanning electron microscopy, transmission electron microscopy, differential scanning calorimetry, Fourier transform infrared spectroscopy and proton nuclear magnetic resonance spectroscopy (H1NMR). The loading efficiency was 485% in all phytosomal formulations. Formula P2 (with the molar ratio of soybean lecithin to silybin 1:1) and P4 (with the molar ratio of egg-yolk lecithin to silybin 0.25:1) exhibited significantly (p<0.05) faster release than milk thistle extract. The in vivo study revealed that phytosomes significantly (p<0.05) decreased glutamic pyruvic transaminase (SGPT) and super oxide dismutase activities compared to milk thistle extract.

**Keywords:** Liver enzymes; Phosphatidylcholine; Silybin.

**990. Pharmaceutical and Pharmacokinetic Evaluation of A Novel Fast Dissolving Film Formulation of Flupentixol Dihydrochloride**

Ahmed Abdelbary, Ehab R. Bendas, Afaf A. Ramadan and Dalia A. Mostafa

*Aaps Pharmucitech, 15: 1603-1610 (2014) IF: 1.776*

The objective of the present study was to develop fast dissolving oral film of the antipsychotic drug, flupentixol dihydrochloride, to enhance its bioavailability, optimize its therapeutic effect when used to treat depression with anxiety, and increase the convenience and compliance by the mentally ill, developmentally disable, elderly, and pediatric patients. Six formulae were prepared with different concentrations of water-soluble polymers viz. hydroxpropyl methylcellulose (HPMC E5) and carboxymethyl cellulose (CMC) by solvent casting technique. The prepared films were subjected to characterization for folding endurance, weight variations, thickness, disintegration time, drug release pattern, and drug content. Physical compatibility between the drug and excipients was guaranteed in the selected formulation (2% HPMC) by means of differential scanning calorimetry analysis and Fourier transform infrared spectroscopy. This formulation revealed high stability after testing according to the International Conference on Harmonisation guidelines. In vivo studies based on single phase parallel design were carried out for the optimized formulation in healthy human volunteers. The concentration of flupentixol dihydrochloride in plasma samples was analyzed by a developed validated LC-MS/MS assay method and the pharmacokinetic parameters of the established formulation were compared with the commercially available oral tablets. Faster rate of absorption of flupentixol could be obtained from the oral film formulation and the relative bioavailability was found to be 151.06% compared to the marketed product.

**Keywords:** Fast dissolving; Flupentixol dihydrochloride; LC-MS/MS Analysis; Oral Film; Pharmacokinetics.

**991. Design of Innovated Lipid-Based Floating Beads Loaded With An Antispasmodic Drug: in-Vitro and in-Vivo Evaluation**

Sally Adel and Nermene Adel ElKasaby

*Journal of Liposome Research, 24: 136-149 (2014) IF: 1.533*

**Context:** Drotaverine hydrochloride (DRT) is used to treat gastrointestinal spasms accompanied with diarrhoea. Hence, the drug suffers from brief residence in the highly moving intestine during diarrhoea which leads to poor bioavailability and frequent dosing.

**Objective:** This study aimed to extend DRT residence in the stomach.

**Methods:** Calcium alginate floating beads were prepared using sodium alginate, isopropylmyristate (oil), and Gelucire43/01 (lipid) adopting emulsion gelation technique. The beads were evaluated for their floating ability, DRT entrapment efficiency and in-vitro release. Gelucire43/01 /oil-based beads of the selected formula were coated using ethylcellulose and different plastics as polyethylene glycol 400 and triethyl citrate to retard the drug release.

The coated beads were re-characterized. Finally, the best formulae were investigated for their in-vivo floating ability in dogs besides their delivery to the systemic circulation compared to drug powder in human volunteers.

**Results:** Incorporation of Gelucire43/01 to oil-based beads enhanced the in-vitro performance of the beads. Coated beads prepared using drug:sodium alginate ratio of 1:3 (w/w), 20% (w/v) isopropylmyristate, 20% (w/v) Gelucire43/01 showed promising in-vitro performance. The beads floated for 12 h in the dogs' stomach and produced three-fold increase of the total amount of DRT absorbed within 24 h compared to that of DRT powder.

**Conclusions:** Gelucire43/01 isopropylmyristate-based calcium alginate floating beads coated with ethylcellulose using either PEG 400 or TEC as plasticizers proved to be a successful dosage form in extending DRT release.

**Keywords:** Drotaverine Hydrochloride; Glass Transition Temperature; Isopropylmyristate; Pharmacokinetics.
992. Formulation and Preclinical Evaluation of 99mTc–Gemcitabine as a Novel Radiopharmaceutical for Solid Tumor Imaging

A. B. Ibrahim, T. M. Sakr, O. M. A. Khoeysya, M. A. Motaleb, A. Abd El-Bary and M. T. El-Kolaly


The aim of this study is the formulation of a new radiopharmaceutical for imaging solid tumor bearing. Gemcitabine is a nucleoside analogue used as chemotherapeutic agent. Gemcitabine was formulated and radiolabeled with one of the most important diagnostic radioactive isotopes (technetium-99m) to be investigated in solid tumor imaging. The labeling parameters such as gemcitabine amount, stannous chloride amount, pH of the reaction mixture, and reaction time were optimized. 99mTc–gemcitabine was prepared at pH 9 with a maximum labeling yield of 96 ± 0.3 % without any notable decomposition at room temperature over a period of 8 h. The preclinical evaluation and biodistribution in solid tumor bearing mice showed that 99mTc–gemcitabine had solid tumor selectivity, preclinical high biological accumulation in tumor cells and high retention. Tumor:normal muscle (T/NT) ratios increased with time showing high T/NT ratio (T/NT = 4.9 ± 0.27 at 120 min post injection) and high Tumor/ Blood ratio (3.4 ± 0.06), suggesting 99mTc–gemcitabine as a novel solid tumor imaging agent.

Keywords: Gemcitabine; Technetium-99M; Formulation; Tumor.

993. Preparation of Radioiodinated Ritodrine as a Potential Agent for Lung Imaging

H. M. Rashed, I. T. Ibrahim, M. A. Motaleb and A. Abd El-Bary


Ritodrine (a beta-2 adrenergic receptor agonist) was successfully labeled with 125I via direct electrophilic substitution reaction at ambient temperature. 125I-ritodrine was obtained with a maximum labeling yield of 97 ± 0.163 % and in vitro stability up to 24 h. Biodistribution studies showed that maximum in vivo uptake of 125I-ritodrine in lungs was 20.4 ± 0.22 % injected activity/g tissue at 1 h post-injection, whereas the clearance from mice appeared to proceed mainly via the renal pathway. 125I-ritodrine is not a blood product and so it is more safe than the currently available 99mTc-MAA, and its lung uptake is higher than that of the recently discovered 99mTc(CO)5I and 99mTc-DHPM. As a conclusion, radioiodinated ritodrine could be used as a novel radiopharmaceutical for lung perfusion scan safer than the currently available 99mTc-MAA and more potential than the recently discovered 99mTc(CO)5I and 99mTc-DHPM.

Keywords: Ritodrine; 125I; Chloramine-T; Lung imaging.

994. Adoption of Polymeric Micelles To Enhance the Oral Bioavailability of Dexamprofen: Formulation, in-Vitro Evaluation and in-Vivo Pharmacokinetic Study in Healthy Human Volunteers

Ghada Abdelbary and Amal Makhlouf


This work aimed to incorporate Dexamprofen (DXI), the pharmacologically active and more potent form of ibuprofen, into polymeric micelles based tablets with enhanced oral bioavailability. Thin film hydration technique was employed to prepare DXI polymeric micelles using Pluronic® F127 and/or P123 solutions in different ratios (ranging from 1:1 up to 1:10). Prepared micelles were characterized regarding particle size, drug loading and entrapment efficiency. Selected formulae were lyophilized in presence of cryoprotectants and subjected to solid-state characterization as well as scanning and transmission electron microscopy. Subsequently, tablets were prepared and evaluated in-vitro regarding physical properties and drug release. An in-vivo pharmacokinetic study was performed in six healthy human volunteers in comparison to the commercially available tablet of DXI. Solid-state characterization proved that DXI was homogeneously dispersed in Pluronic micelles’ matrices. Formula T5 tablets comprising lyophilized micelles (F5; DXI: Pluronic F127 in 1:1 ratio and 0.25% mannitol) showed higher Cmax and earlier tmax values than those of the commercial formula, where the relative bioavailability was calculated to be 160.15%. The experimental evidence in this research leads to the conclusion that polymeric micelles present enabling properties for oral delivery of drugs with low solubility.

Keywords: Dexamprofen; Healthy human volunteers; Pharmacokinetic study; Pluronic; Polymeric micelles.

995. Comparison of Nanomilling and Coprecipitation on the Enhancement of in Vitro Dissolution Rate of Poorly Water-Soluble Model Drug Aripiprazole

Abdelbary AA, Li X, El-Nabarawi M, Ellassasy A and Jasti B.


The aim of this study was to evaluate the effect of coprecipitation and nanomilling on the crystallinity of a model drug, aripiprazole and evaluate the in vitro dissolution rate (IDR). Aripiprazole compositions were prepared by physical mixing, coprecipitation and nanomilling using hydroxypropylcellulose (HPC), polyvinylpyrrolidone (PVP) K17 and pluronic F127. The particle size, solubility, IDR and drug crystallinity were studied. Aripiprazole pluronic compositions were compressed into tablets and dissolution rate was evaluated. The particle size of nanomilled compositions was significantly smaller than that of the other compositions. The saturation solubility of aripiprazole from nanoparticle (NP) and coprecipitate (CP) from PVP and Pluronic was comparable, however, NP of HPC containing composition showed higher solubility when compared to its CP compositions. The crystallinity of aripiprazole decreased from physical mixtures to coprecipitates and further in NPs. The increased aripiprazole IDR was due to decreased crystallinity from coprecipitate compositions and disruption of crystallinity from nanomilled compositions. Aripiprazole tablets prepared from nanomilled powder dissolved >75% within 10 min compared with 17% and 20% for tablets prepared from physical mixture and coprecipitate powders, respectively. The increase in IDR due to nanomilling was more significant than coprecipitation and NPs retained the IDR after compression into tablets.

Keywords: Aripiprazole; Crystallinity; Dissolution rate; Nanoparticles; Particle size; Tablets.
996. Nanostructured Lipid Carriers (NLCs) Versus Solid Lipid Nanoparticles (SLNs) for Topical Delivery of Meloxicam
Rawia M. Khalil, A. Abd-Elbaray, Mahfouz A. Kassem, Mamdouh M. Ghorab and Mona Basha


Objective: The aim of this study was to develop nanostructured lipid carriers (NLCs) as well as solid lipid nanoparticles (SLNs) and evaluate their potential in the topical delivery of meloxicam (MLX). Materials and methods: The effect of various compositional variations on their physicochemical properties was investigated. Furthermore, MLX-loaded lipid nanoparticles-based hydrogels were formulated and the gels were evaluated as vehicles for topical application. Results and discussion: The results showed that NLC and SLN dispersions had spherical shapes with an average size between 215 and 430 nm. High entrapment efficiency was obtained ranging from 61.94 to 90.38% with negatively charged zeta potential in the range of 19.1 to 25.7 mV. The release profiles of all formulations exhibited sustained release characteristics over 48 h and the release rates increased as the amount of liquid lipid in lipid core increased. Finally, Precirol NLC with 50% Miglyol1812 and its corresponding SLN were incorporated in hydrogels. The gels showed adequate pH, non-Newtonian flow with shear-thinning behavior and controlled release profiles. The biological evaluation revealed that MLX-loaded NLC gel showed more pronounced effect compared to MLX-loaded SLN gel.

Conclusion: It can be concluded that lipid nanoparticles represent promising particulate carriers for topical application.

Keywords: Hydrogels; Meloxicam; Nanostructured lipid Carriers; Solid lipid nanoparticles; Topical delivery.

Rania H. Fahmy and Shaimaa M. Badr-Eldin


Orally dissolving films (dissolphins) have gained increasing popularity and attention due to their ease of administration and avoidance of first pass metabolism. Ketotifen fumarate (KF) bioavailability is reported to be only ~50% due to hepatic first-pass metabolism. Aiming to surmount this drawback and improve patients’ compliance, a 3rd full factorial design was applied to formulate KF Orodispersible films, and to investigate the effects and interactions of the concentrations of the novel film former; Lyco Ng73® and the film modifier; maltodextrin (MDX) on the characteristics of the films prepared using solvent casting technique. The dissolphins were thoroughly evaluated regarding their weight uniformity, content uniformity, moisture uptake, in vivo mouth dissolving time (MDT) and their thermal behavior via differential scanning calorimetry. Statistical analysis revealed the significant influence of Lyco Ng73® concentration on percent elongation, percent KF dissolved after 5 min, and in vivo MDT, while MDX concentration had significant effect only on percent elongation. Further, storage of the optimal selected formula (15% Lyco Ng73 and 0% MDX) at 40°C/75% relative humidity for 12 weeks caused no significant change in appearance, KF content or drug dissolution profile. Pharmacokinetic study revealed that the orally dissolving films showed significantly higher absorption extent than the reference marketed product, while no significant difference was observed for Cmax.

Keywords: Ketotifen Fumarate; Lyco Ng73; Maltodextrin; Mouth-Dissolving Films; Orodispersible Films.

998. Utility of Mannitol and Citric Acid for Enhancing the Solubilizing and Taste Masking Properties of β-Cyclodextrin: Development of Fast-Dissolving Tablets Containing Extremely Bitter Drug
Emad B. Basalious, Asmaa Abdullah and Magdy Ibrahim


Introduction: Development of Fast dissolved tablets (FDTs) in which taste is masked, and drug dissolution is improved, is a major challenge especially in case of extremely bitter drug with poor water solubility such as aceclofenac.

Purpose: The purpose of this study was to enhance the taste masking and solubilizing properties of β-cyclodextrin using citric acid and mannitol through preparation of acid soluble taste masked granules of aceclofenac (ASTMGA).

Methods: General factorial design was applied to optimize FDTs containing ASTMGA so to have short disintegration time (<30 sec.), acceptable taste and enhanced drug dissolution in gastric fluid. Three formulation variables; the type of sugar / cellulose based diluents, X1 (Galen IQ® and Prosolv®), supersolubilization type, X2 (Crosopolvone®, Glycols® and Ac-Di-Sol®) and superdisintegrant concentration, X3 (10 % and 20 %) were included in the design. The systems were assessed for hardness, friability, in vitro disintegration, wetting time, in vitro dissolution and in vivo oral study.

Results: The combination of Prosolv® and Crosopolvone® in the formulation of FDT gave optimum disintegration time. The stability of the optimized FDT in different package materials was retained after storage at 40°C/75% RH for six months. Contrary to FDT containing conventional aceclofenac β-cyclodextrin inclusion complex, FDT containing ASTMGA showed highest dissolution rate in both simulated salivary and gastric fluids and excellent ability to mask the bitterness of drug.

Conclusions: Our results propose that the combination of citric acid, mannitol and β-cyclodextrin could be promising to improve taste masking and solubilizing properties of β-cyclodextrin.

Keywords: Aceclofenac; β-Cyclodextrin; Mannitol; Fast:Dissolving tablet; Citric acid; Taste masking.

999. Radiiodinated Acebutolol as A New Highly Selective Radiotracer for Myocardial Perfusion Imaging
M. M. Swidan, T. M. Sakr, M. A. Motaleb, A. Abd El-Bary and M. T. El-Kolaly


Acebutolol was successfully labeled with 125I via direct electrophilic substitution reaction. Radiiodinated acebutolol was prepared with a maximum radiochemical yield of 96.5 ± 0.3% and in vitro stability up to 72 h. The in vivo biological distribution of radiiodinated acebutolol showed high heart uptake of 37.8 ± 0.14% injected activity/g organ with low lungs and liver uptakes at 5 min post-injection. In vivo receptor imaging...
blocking study was carried out in mice to evaluate its selectivity to heart. Radioiodinated acebutolol showed fast heart accumulation with high heart/liver ratio, which provides the ability for fast myocardial imaging with significant decrease in the radiation hazards risk on patients. So, radioiodinated acebutolol could be displayed as a radiotracer drug of choice in case of emergency patients for myocardial perfusion imaging.

Keywords: Myocardial Perfusion Imaging; Radioiodination; Acebutolol; Chloramin-T

1000. Chromium Picolinate Loaded Superporous Hydrogel and Superporous Hydrogel Composite as A Controlled Release Device: in Vitro and in Vivo Evaluation
S.A. Abdel Halim, S.A.Yehia and M.A. El-Nabarawi

The aim of this work was to develop chromium picolinate (CP) loaded gastroretentive device using superporous hydrogel (SPH) and superporous hydrogel composite (SPHC). The drug was considered as good candidate for such systems owing to its narrow absorption window. Swelling ratio, apparent density, scanning electron microscopy (SEM), drug content and drug release in pH 1.2 were evaluated for hydrogels. SEM of hydrogels showed interconnected pores with extensive capillary insertion. Swelling ratio for CP-SPH was higher than that of SPHC while apparent densities were lower. Both SPH and SPHC retarded drug release as values of half-life attained 3.64 and 2.94 h, respectively, while plain drug 0.22 h. The mechanical strength of SPHC was higher than SPH, so it was selected for in vivo studies in dogs. Radiographic examination in dogs showed that gastric retention persisted for 24 h. Percentage relative bioavailability was 298.8 %. SPHC could be thus considered as good gastroretentive device for CP.

Keywords: Controlled release formulations ; Chromium Picolinate ; Superporous hydrogel composite ; Gastric retention ; Radiographic examination.

1001. Development of Nanoparticulate Formulations for Ocular Delivery of Prednisolone Acetate: Preparation and Characterization
S.A. Abdel Halim and S. Salah
Journal of Drug Delivery Science and Technology, 24(2): 159-165 (2014) IF: 0.734

This study describes the development and characterization of biodegradable prednisolone acetate nanoparticles indicated for ocular use. Nanoparticles were prepared by oil-in-water emulsion/solvent evaporation and nanoprecipitation techniques using poly lactide-co-glycolide (50:50) and poly DL-lactide. A 24 factorial design was applied to optimize the drug formulation. The effect of independent variables such as polymer type, drug-to-polymer ratio, surfactant concentration and method of preparation on entrapment efficiency (EE%), particle size, zeta potential and drug release were investigated. Further studies such as differential scanning calorimetry (DSC), X-ray diffraction (XRD) and transmission electron microscope were carried out on the selected formula. O/W emulsion/solvent evaporation technique was superior to the nanoprecipitation method in terms of EE%. In vitro release study showed extended drug release. DSC and XRD indicated the dispersion of the drug within the nanoparticles. These results demonstrate the feasibility of encapsulating prednisolone acetate inside biodegradable nanoparticles for ocular delivery.

Keywords: Prednisolone Acetate; Biodegradable Nanoparticles; Factorial design; O/W solvent evaporation; Nanoprecipitation technique; Intravitreal injection.

1002. Olmesartan Medoxomil Surface Solid Dispersion-Based Orodispersible Tablets: Formulation And in Vitro Characterization
A. Abd-El Bary, D. Louis and S. Sayed
Journal of Drug Delivery Science and Technology, 24: 665-672 (2014) IF: 0.734

This work aims to improve the dissolution of the poorly water soluble drug olmesartan medoxomil by using the surface solid dispersion (SSD) technique. Insoluble carriers, namely Avicel PH 102, Aerosil 200, silicified microcrystalline cellulose, Lycatab, Starlac, sodium starch glycolate (SSG), and Kyron T-314, were used at three different drug: carrier ratios (1:1, 1:5, and 1:9 w/w) to prepare SSDs by solvent evaporation method. SSD18 consisting of drug;SSG at 1:9 ratio and SSD20 consisting of drug;Kyron T-314 at 1:5 ratio showed the highest enhancement in the dissolution rate and efficiency compared to the plain drug and the physical mixture. The selected dispersion was formulated into orodispersible tablets (ODTs) by using four different disintegrants. F3 DC ODT (consisting of SSD20 and 5 % crospovidone) and F6 DC ODT (consisting of SSD18 and no disintegrant) exhibited low in vitro disintegration time and high percentage of olmesartan medoxomil dissolved within 10 min.

Keywords: Olmesartan Medoxomil; Poorly water soluble; Surface solid dispersion; Co-evaporation technique; Solvent evaporation; Dissolution rate; Kyron T-314; Sodium starch glycolate; Orodispersible tablet.

1003. Recrystallized Agglomerated Meloxicam: Evaluation of Anti-Nociceptive Effect
M. Farid, D.A. El-Setouhy, M.A. El-Nabarawi and T. El-Bayomi

Meloxicam (Mel) is a non steroidal anti-inflammatory drug belonging to BCS class II category. Hence, its pharmacological effect is affected by its low water solubility. The aim of this study was to improve the solubility and dissolution rate of meloxicam. Mel was recrystallized into spherical agglomerates (SA) with or without different polymers (PEG 4000; Inutec SP1, PVP k30, Pluronic F127 and HPβCD) at three different concentrations (0.0125, 0. 025 and 0.05 % w/v) using quasi emulsion solvent diffusion (QESD) and neutralization techniques (NT). Mel SA containing low concentration level of polymer (0.0125 % w/v) showed highest solubility and dissolution rate enhancement compared to pure Mel. DSC and IR outcome showed no chemical alteration in the recrystallized drug. DSC and PXRD studies showed that crystallinity of Mel was retained in all of the prepared SA (although slightly reduced compared to pure Mel). The anti-nociceptive effect of F2 (QESD) and F29 (NT) (showing highest dissolution in simulated gastric fluid) was assessed in mice using acetic acid induced abdominal writhing in comparison to pure drug. The selected formulae showed significantly higher analgesic activity in comparison to the pure drug and the control.
Keywords: Meloxicam – Spherical Agglomeration ; Solubility ; Dissolution Rate ; Anti-Nociceptive Effect.

Dept. of Pharmacognosy

1004. Interstrand DNA-DNA Cross-Link Formation Between Adenine Residue And Abasic Sites in Duplex DNA

Nathan E. Price, Kevin M. Johnson, Jin Wang, Mostafa I. Fekry, Yinsheng Wang and Kent S. Gates


The loss of a coding nucleobase from the structure of DNA is a common event that generates an abasic (Ap) site (1). Ap sites exist as an equilibrating mixture of a cyclic hemiacetal and a ring-opened aldehyde. Aldehydes are electrophilic functional groups that can form covalent adducts with nucleophilic sites in DNA. Thus, Ap sites present a potentially reactive aldehyde as part of the internal structure of DNA. Here we report evidence that the aldehyde group of Ap sites in duplex DNA can form an oval adduct with the N6-amino group of adenine residues on the opposing strand. The resulting interstrand DNA-DNA cross-link occurs at 5'-ApT/5'-AA sequences in remarkably high yields (15-70%) under physiologically relevant conditions. This naturally occurring DNA-templated reaction has the potential to generate cross-links in the genetic material of living cells.

Keywords: Dna;Cross-Link;Abasic Sites.

1005. Enantioselective Divergent Syntheses of Several Polyhalogenated Plocamium Monoterpenes and Evaluation of Their Selectivity for Solid Tumors

Carl V. Voge, Halina Pietraszkiewicz, Omar M. Sabry, William H. Gerwick, Frederick A. Valeriote and Christopher D. Vanderwa


The family of polyhalogenated monoterpenes from Plocamium counts over a hundred known members. Using gyceraldehyde acetonide as a chiral pool precursor, an enantioselective and divergent strategy was developed that provides a blueprint for the synthesis of many of the small yet complex acyclic members of this family. The broad applicability of this approach is demonstrated with the short, eight-step synthesis of four natural products and three analogues. These syntheses are the first of any members of the acyl phloroglucinol Plocamium monoterpenes and permitted the evaluation of their selectivity against a range of tumor cell lines.

Keywords: Antitumor Agents; Chlorination; Olefination; Stereocontrol; Total Synthesis

1006. Structural and Biochemical Impact of C8-Aryl-Guanine Adducts Within the NarI Recognition DNA Sequence: Influence of Aryl Ring Size on Targeted Andsemi-Targeted Mutagenicity

Michael Sproviero, Anne M.R. Verwey, Katherine M. Rankin, Aaron A. Witham, Dmitriy V. Soldatov, Richard A. Manderville, Mostafa I. Fekry Shana J. Sturla Purshotam Sharma and Stacey D. Wetmore


Chemical mutagens with an aromatic ring system may be enzymatically transformed to afford aryl radical species that preferentially react at the C8-site of 2'-deoxyguanosine (dG). The resulting carbon-linked C8-aryl-dG adduct possesses altered biophysical and genetic coding properties compared to the precursor nucleoside. Described herein are structural and in vitro mutagenicity studies of a series of fluorescent C8-aryl-dG analogues that differ in aryl ring size and are representative of authentic DNA adducts. These structural mimics have been inserted into a hotspot sequence for frame shift mutations, namely, the reiterated G3-position of the NarI sequence within 12mer (NarI(12)) and 22mer (NarI(22)) oligonucleotides. In the NarI(12) duplexes, the C8-aryl-dG adducts display a preference for adopting an anti-conformation opposite C, despite the strong syn preference of the free nucleoside. Using the NarI(22) sequence as a template for DNA synthesis in vitro, mutagenicity of the C8-aryl-dG adducts was assayed with representative high-fidelity replicative versus lesion bypass Y-family DNA polymerases, namely, Escherichia coli pol I Klenow fragment exo-(KF-) and Sulfolobus solfataricus P2 DNA polymerase IV (Dpo4). Our experiments provide a basis for a model involving a two-base slippage and subsequent realignment process to relate the miscoding properties of C-linked C8-aryl-dG adducts with their chemical structures.

Keywords: DNA; C8; Aryl; Guanine; Mutagenicity.

1007. Cytotoxic Activity of Acyl Phloroglucinols Isolated From the Leaves of Eucalyptus Cinerea F. Mull. Ex Benth. Cultivated in Egypt

Fathy M. Soliman, Magda M. Fathy, Maha M. Salama, Ahmed M. Al-Abd, Fatema R. Saber and Ali M. El-Halawany

Scientific Reports, 1: 1-6 (2014) IF: 5.078

Two acyl phloroglucinol compounds namely; Sideroxylonal B (1) and Macrocarpal A (2) were isolated from the Sideroxylon-Rich Extract (SRE) of the juvenile leaves of Eucalyptus cinerea; F. Mull. ex Benth cultivated in Egypt. Identification of the isolated compounds was established on the basis of physico-chemical properties and spectral analysis (1D & 2D NMR).

The two compounds were isolated for the first time from this species.

The SRE alongside with the isolated compounds were tested against three human cancer cell lines; MCF7 (breast carcinoma cell line), HEP2 (laryngeal carcinoma), CaCo (colon adenocarcinoma) and one type of normal human cell line;10 FS (fibroblast cells). The SRE, (1) and (2) showed cytotoxic activity with IC50 13.6 ± 0.62, 7.2 ± 0.5, 14.8 ± 0.55 μg mL−1 against HEK2 respectively, 11.6 ± 0.47, 4 ± 0.36, 11.4 ± 0.45 μg mL−1 against CaCo, respectively, and 8.6 ± 0.29, 4.4 ± 0.25, and 7.8 ± 0.3 μg mL−1 against MCF7, respectively. Meanwhile, the (SRE) together with the isolated compounds were tested against MCF7, with IC50 55.4 ± 1.4, 43 ± 0.8 and 50.1 ± 1.12 μg mL−1, respectively.

The antiproliferative activity of the tested compounds was evaluated. The cell cycle profile of cells treated with Sideroxylonal-B and Macrocarpal-A indicates possible S-phase specific effects.

Keywords: Eucalyptus cinerea; Sideroxylonal B; Macrocarpal A; Cytotoxicity.
1008. Protective Effect of Aframomum Melegueta Phenolics Against CCl₄-Induced Rat Hepatocyte Damage; Role of Apoptosis and Pro-Inflammatory Cytokines Inhibition

Ali M. El-Halawany, Riham Salah El Dine, Nesrine S. El Sayed and Masao Hattori

*Scientific Reports, 4: 1-9* (2014) IF: 5.078

*Aframomum melegueta* is a commonly used African spice. Through a hepatoprotective bioassay-guided isolation, the chloroform fraction of *A.melegueta* seeds yielded one new diarylheptanoid named 3-(5-acetyl-1-(4′-hydroxy-3′, 5′-di methoxyphenyl)-7-(3′,4′, 5′-trihydroxyphenyl)heptan (1), and two new hydroxysterolalkanones, [8]-dehydrogingerdiene (2) and [6]-dehydropadadiol (3), in addition to six known compounds (4-9). The hepatoprotective effect of *A. melegueta* methanol extract, sub-fractions and isolated compounds was investigated using carbon tetrachloride (CCl₄)-induced liver injury in a rat hepatocytes model. The methanol, chloroform extracts and compounds 1, 5, 8 and 9 of *A. melegueta* significantly inhibited the elevated serum alanine aminotransferase (ALT), thiobarbituric acid reactive substances (TBARS), tumor necrosis factor (TNFα), interleukin-1beta (II-1β), caspase3 and 9 and enhanced the reduced liver glutathione (GSH) level caused by CCl₄ intoxication. These results indicate that *A. melegueta* extracts, and isolated compounds play a protective role in CCl₄ induced acute liver injury which might be due to elevated antioxidative defense potentials, suppressed inflammatory responses and apoptosis of liver tissue.

**Keywords:** Hepatoprotective; Tbars; Alt; Aframomum; Hydroxysterolalkanones.

1009. Classification of Commercial Cultivars of Humulus Lupulus L. (Hop) by Chemometric Pixel Analysis of Two Dimensional Nuclear Magnetic Resonance Spectra

Mohamed A. Farag and Engy A. Mahrous


The development of fast and effective spectroscopic methods that can detect most compounds in an untargeted manner is of increasing interest in plant extracts fingerprinting or profiling projects. Metabolite fingerprinting by nuclear magnetic resonance (NMR) is a fast growing field which is increasingly applied for quality control of herbal products, mostly via 1D H-1 NMR coupled to multivariate data analysis. Nevertheless, signal overlap is a common problem in H-1 NMR profiles that hinders metabolites identification and results in incomplete data interpretation. Herein, we introduce a novel approach in coupling 2D NMR datasets with principal component analysis (PCA) exemplified for hop resin classification. Heteronuclear multiple bond correlation (HMBC) profile maps of hop resins (Humulus lupulus) were generated for a comparative study of 13 hop cultivars. The method described herein combines reproducible metabolite fingerprints with a minimal sample preparation effort and an experimental time of ca. 28 min per sample, comparable to that of a standard HPLC run. Moreover, HMBC spectra provide not only unequivocal assignment of hop major secondary metabolites, but also allow to identify several isomerization and degradation products of hop bitter acids including the sedative principal of hop (2-methylbut-3-en-2-ol). We do believe that combining 2D NMR datasets to chemometrics, i.e. PCA, has great potential for application in other plant metabolome projects of (commercially relevant) nutraceuticals and or herbal drugs.

**Keywords:** Humulus Lupulus L. Hop; 2D Nmr Metabolomics; Bitter Acids; Principal component Analysis; Quality control; Hmbc; Pixel Analysis.

1010. Metabolite Profiling and Fingerprinting of Hypericum Species: A Comparison of Ms and Nmr Metabolomics

Andrea Porzel and Mohamed A. Farag

*Metabolomics, 10: 574-588* (2014) IF: 3.965

Hypericum perforatum, commonly known as St. John’s wort, is a popular herbal supplement used for the treatment of mild to moderate depression. The major secondary metabolites of St. John’s wort extracts include phenylpropanoids, flavonoids, xanthones, phloroglucinols, and naphthodianthrones. There are over 400 species in the genus Hypericum world-wide, most of which are little or not characterized in terms of phytochemical or pharmacological properties. Metabolomics techniques were used to investigate the natural product diversity within the genus Hypericum (Hypericaceae) and its correlation to bioactivity, exemplified by cytotoxic properties. Utilizing nuclear magnetic resonance (NMR) fingerprinting and mass spectrometry (MS) metabolic profiling techniques, MS and NMR spectra of extracts from H. perforatum, H. polyphyllum, H. tetrapetrum, H. androsaemum, H. inodorum, H. undulatum and H. kouytchense were evaluated and submitted to statistical multivariate analyses. Although comparable score plots in principal component analysis were derived from both MS and NMR datasets, loading plots reveal, that different set of metabolites contribute for species segregation in each dataset. Major peaks in H-1 NMR and MS spectra contributing to species discrimination were assigned as those of hyperforins, lipids, chlorogenic and shikimic acid. Shikimic acid and its downstream phenylpropanoids were more enriched in H. perforatum, H. androsaemum, H. kouytchense and H. inodorum extracts; whereas a novel hyperforin was found exclusively in H. polyphyllum. Next to H. perforatum, H. polyphyllum and H. tetrapetrum show the highest levels of hypericins, and H. perforatum and H. polyphyllum are highest in phloroglucinols, suggesting that the latter species might be used as an alternative to St. John’s wort. However, the major hyperforin-type compound in H. polyphyllum possesses a novel constitution of yet unknown bioactivity. Anti-cancer in vitro assays to evaluate the ability of extracts from Hypericum species in inhibiting prostate and colon cancer growth suggest that such bioactivity might be predicted by gross metabolic profiling.

**Keywords:** H. Perforatum; H. Polyphyllum; H-1 Nmr-Based Metabolomics; Lc-MS; Hyperforin; Anticancer activity prediction.

1011. Isolation of Antiosteoporotic Compounds from Seeds of Sophora Japonica

Hossam M. Abdallah, Ahmed M. Al-Abd, Gihan F. Asaad and Ashraf B. Abdel-Nain


Chemical investigation of Sophora japonica seeds resulted in the isolation of seven metabolites identified as: genistin (1), sophoricoside (2), sophorabioside (3), sophoragalflavonoloside (4),
genistein, 7,4'-di-O-b-D-glucopyranoside (5), kaempferol-3-O-a-L-rhamnopyranosyl (1R6) b-D-glucopyranosyl (1R2)b-D-glucopyranoside (6) and rutin (7). Compounds 1, 2 and 5 showed significant estrogenic proliferative effect in MCF-7 cell in subcytotoxic concentration range. Compounds 1 and 2 showed minimal cell membrane damaging effect using LDH leakage assay. Accordingly, compound 2 (sophoricoside, SPH) was selected for further in-vivo studies as a potential anti-osteoporosis agent. The anti-osteoprotic effect of SPH was assessed in ovariectomized (OVX) rats after oral administration (15 mg/kg and 30 mg/kg) for 45 days compared to estradiol (10 mg/kg) as a positive control. Only in a dose of 30 mg/kg, SPH regained the original mechanical bone hardness compared to normal non-osteoporotic group. However, SPH (15 mg/kg) significantly increased the level of alkaline phosphatase (ALP) to normal level. Treatment with SPH (30 mg/kg) increased the level of ALP to be higher than normal group. SPH (15 mg/kg) did not significantly increase the serum level of osteocalcin (OC) compared to OVX group. On the other hand, treatment with SPH (30 mg/kg) significantly increased the level of OC to 78% higher than normal non-ovarectomized animals group. In addition, SPH (15 mg/kg) decreased the bone resorption marker, acid phosphatase (ACP) to normal level and SPH (30 mg/kg) further diminished the level of serum ACP. Histopathologically, sophoricoside ameliorated the ovariectomy induced osteoporosis in a dose dependent manner. The drug showed thicker bony trabeculae, more osteoid, and more osteoblastic rimming compared to OVX group.

**Keywords**: Sophoricoside; Osteoporosis.

1012. Developmental Changes in Leaf Phenolics Composition From Three Artichoke cvs. (Cynara Scolymus) As Determined Via UHPLC-Ms and Chemometrics

Amira S. El Senousy, Mohamed A. Farag, Dalia A. Al-Mahdy, Ludger A. Wessjohann

*Phytochemistry, 108: 67-76 (2014) IF: 3.35*

The metabolomic differences in phenolics from leaves derived from 3 artichoke cultivars (Cynara scolymus): American Green Globe, French Hyrious and Egyptian Baladi, collected at different developmental stages, were assessed using UHPLC-MS coupled to chemometrics. Ontogenic changes were considered as leaves were collected at four different time intervals and positions (top and basal) during artichoke development. Unsupervised principal component analysis (PCA) and supervised orthogonal projection to latent structures-discriminant analysis (O2PLS-DA) were used for comparing and classification of samples harvested from different cultivars at different time points and positions. A clear separation among the three investigated cultivars was revealed, with the American Green Globe samples found most enriched in caffeic acid conjugates and flavonoids vs. other cultivars. Furthermore, these metabolites also showed a marked effect on the discrimination between leaf samples from cultivars harvested at different positions, regardless of the plant age. Metabolite absolute quantifications further confirmed that discrimination was mostly influenced by phenolic compounds, namely caffeoylquinic acids and flavonoids. This study demonstrates an effect of artichoke leaf position, regardless of plant age, on its secondary metabolites composition. To the best of our knowledge, this is the first report for compositional differences among artichoke leaves based on their positions, via a metabolomic approach and suggesting that top positioned artichoke leaves present a better source of caffeoylquinic acids, compared to basal ones.

**Keywords**: Cynara Scolymus L. (Asteraceae); UHPLC-MS; Principal Component Analysis (PCA); Orthogonal Projection To Latent Structures-Discriminant Analysis (O2PLS-DA); Developmental Stages.

1013. Metabolomics Driven Analysis of Six Nigella Species Seeds Via UPLC-qTOF-MS and GC-MS Coupled To Chemometrics

Mohamed A. Farag, Haidy A. Gad, Andreas G. Heiss and Ludger A. Wessjohann

*Food Chemistry, 151: 333-342 (2014) IF: 3.259*

Nigella sativa, commonly known as black cumin seed, is a popular herbal supplement that contains numerous phytochemicals including terpenoids, saponins, flavonoids, and alkaloids. Only a few of the ca. 15 species in the genus Nigella have been characterized in terms of phytochemical or pharmacological properties. Here, large scale metabolic profiling including UPLC-PDA-MS and GC-MS with further multivariate analysis was utilized to classify 6 Nigella species. Under optimized conditions, we were able to annotate 52 metabolites including 8 saponins, 10 flavonoids, 10 alkaloids, and 18 fatty acids. Major peaks in UPLC-MS spectra contributing to the discrimination among species were assigned as kaempferol glycosidic conjugates, with kaempferol-3-O-[glucopyranosyl-(1→2)-galactopyranosyl-(1→2)-glucopyranoside, identified as a potential taxonomic marker for N. sativa. Compared with GC-MS, UPLC-MS was found much more efficient in Nigella sample classification based on genetic and geographical origin. Nevertheless, both GC-MS and UPLC-MS support the remote position of Nigella nigellastrum in relation to the other taxa. (C) 2013 Elsevier Ltd. All rights reserved.

**Keywords**: Black Cumin; Metabolomics; Natural Products; GC-MS; UPLC-MS; Principal Component Analysis; N. Arvensis; N. Damascena; N. Hispanica; N. Nigellastrum; N. Orientalis; N. Sativa.

1014. Metabolomic Fingerprints of 21 Date Palm Fruit Varieties From Egypt Using UPLC/PDA/ESI-qTOF-MS and GC-MS Analyzed By Chemometrics

Mohamed A. Farag, Mahmoud Mohsen, Ramona Heinke, Ludger A. Wessjohann

*Food Research International, 64: 218-226 (2014) IF: 3.05*

Date palm fruits of the species Phoenix dactylifera exhibit a great diversity in sensory attributes including skin color, smell and taste. This study attempts to elucidate the primary and secondary metabolite profiles of 21 date varieties from Egypt. A major difficulty is sugar rich matrix and skin-fibers embedding the secondary metabolites. A total of 49 metabolites extracted from the fruit skin were evaluated in a UPLC/PDA/ESI-qTOF-MS based metabolomics study. The total phenolic contents of the varieties varied from 233 to 1897 mg/100 g (2.3-19 g/kg) dry weight. The predominant flavones were glycosides of luteolin and apigenin, quercetin conjugates were the principal flavonoids, whereas caffeoyl shikimic acid was the main hydroxyxynamic acid conjugate. Aside from these major phenolic classes, a group of sphyngolipids, fatty and other organic acids was also identified. The total non-fatty organic acid content correlates with reported
shelf lives. GC-MS was further utilized to localize primary metabolites in fruits (i.e. sugars and organic acids) with glucose and fructose accounting for up to 95% of TIC among most varieties. Principal component and clustering analyses reveal that flavonols and sugars, both contribute the most to variety classification. This study provides the most complete map for polyphenol & sugar distribution in Egyptian date fruit varieties. By describing the metabolite profiles in a diverse dataset of P. dactylifera, this study provides the basis for future investigations of date fruit nutritional value beyond providing energy and its potential for nutraceutical enhancement or storability. (C) 2014 Elsevier Ltd. All rights reserved.

Keywords: Phoenix Dactylifera; Metabolite Profiling; Uple/Pda/Esi-Qtof-Ms; Ge-Ms; Flavonoids; Principal Component Analysis.

1015. Immunomodulatory Effect of Red Onion (Allium Cepa Linn) Scale Extract on Experimentally Induced Atypical Prostatic Hyperplasia in Wistar Rats

Essam Abdel-Hamid Abdel-Sattar

Mediators of Inflammation, 0: 1-13 (2014) IF: 2.417

Red onion scales (ROS) contain large amounts of flavonoids that are responsible for the reported antioxidant activity, immune enhancement, and anticancer property. Atypical prostatic hyperplasia (APH) was induced in adult castrated Wistar rats by both s.c. injection of testosterone (0.5 mg/rat/day) and by smearing citral on shaved skin once every 3 days for 30 days. Saw palmetto (100 mg/kg) as a positive control and ROS suspension at doses of 75, 150, and 300 mg/kg/day were given orally every day for 30 days. All medications were started 7 days after castration and along with testosterone and citral.

The HPLC profile of ROS methanolic extract displayed two major peaks identified as quercetin and quercetin-4′-β-D-glucoside. Histopathological examination of APH-induced prostatic rats revealed evidence of hyperplasia and inflammation with cellular proliferation and reduced apoptosis. Immunohistochemistry showed increased tissue expressions of IL-6, IL-8, TNF-α, IGF-1, and claudin, while TGF-β1 was decreased, which correlates with the presence of inflammation. Both saw palmetto and RO scale treatment have ameliorated these changes. These ameliorative effects were more evident in RO scale groups and were dose dependent. In conclusion, methanolic extract of ROS showed a protective effect against APH induced rats that may be attributed to potential anti-inflammatory and immunomodulatory effects.

Keywords: Red Onion Scales (Ros).

1016. Protective Effect of Calligonum Comosum on Haloperidol-Induced Oxidative Stress in Rat

Essam A Abdel-Sattar, Samar M Mouneir, Gihan F Asaad and Hossam M Abdallah

Toxicology And Industrial Health, 30: 147-153 (2014) IF: 1.71

The aequorin and methanolic extracts of Calligonum comosum were investigated for their antioxidant and dopaminergic effects on haloperidol (HL)-induced neuro- and hepatotoxicities in male albino rat model.

The total phenolics, flavonoid content and free radical-scavenging activity of the extracts were determined. The results showed that the antioxidant activity of the methanol extract was higher than the aqueous one. HL significantly reduced GSH and increased MDA in brain and liver tissues. These values were nearly normalized, in the examined tissues, on concomitant administration of C. comosum methanolic extract with HL. Superoxide dismutase activity in the examined tissues was significantly decreased by HL administration that was normalized by the coadministration of the methanolic extract and, to a less extent, the water extract. Determination of the brain neurotransmitter contents revealed a marked decrease in norepinephrine, dopamine and serotonin, which were restored to near normal values by concomitant administration of both C. comosum extracts with HL. The results of this study showed that C. comosum methanolic and aqueous extracts ameliorated HL-induced neuro- and hepatotoxicities in rats.

Keywords: Calligonum Comosum; Antioxidant; Neurotoxicity; Hepatotoxicity; Haloperidol; Neurotransmitters; Dopaminergic.

1017. Chemical Composition of The Essential Oil and Botanical Study of the Flowers of Mentha suaveolens

El-Sayed A. El-Kashouyr, Hisham I. El-Askary, Zeinab A. Kandil, and Mohamed A. Salem

Pharmaceutical Biology, 52: 688-697 (2014) IF: 1.337

Context: Herbal medicines play a paramount role in the treatment of wide range of diseases, so there is a growing need for their quality control and standardization. Traditionally, histological and morphological inspections have been the usual methods to authenticate herbs intended for medicinal applications. Mentha suaveolens Ehrl. (Lamiaceae) is native to Africa Temperate Asia and Europe and it’s cultivated in Egypt.

Objective: The macro- and micromorphology of the flowers of M. suaveolens Ehrl. cultivated in Egypt were studied to find the diagnostic characters of this species. In addition, the chemical composition of the essential oil of the flowers was also studied to define the chemotype of the plant.

Materials and Methods: Photographs of macro- and micromorphology were taken using Casio and Leica DFC500 digital cameras, respectively. In addition, the essential oil was prepared by hydrodistillation followed by gas chromatographic/mass spectrometric (GC/MS) analysis for identification of its components.

Results: The macro- and micromorphological characteristics of M. suaveolens were determined. The yield of the essential oil obtained by hydrodistillation from M. suaveolens flowers was 1.7% calculated on dry weight basis. GC/MS analysis of the oil resulted in identification of 29 components, which amounted to 99.77% of the total oil composition. The major component was carvone (30.59%) followed by limonene (31.25%).

Discussion and conclusion: The results obtained herein revealed for the macro, micromorphological and chemical composition characteristics of the flowers. The results of GC/MS analysis of the essential oil supported that M. suaveolens cultivated in Egypt could be categorized as carvone-rich chemotype since this compound pertained its high relative percentile.

Keywords: Apple mint; Botanical study; Carvone; Inflorescence; Taxonomy.
1018. Chemical Composition and Bioactivity of the Volatile Oil From Leaves and Stems of Eucalyptus Cinerea

Fathy M. Soliman, Magda M. Fathy, Maha M. Salama, and Fatema R. Saber


Context: Eucalyptus cinerea F. Mull. ex Benth. (Myrtaceae) is a medium-sized tree cultivated in Egypt. The volatile oil was prepared by hydrodistillation and then identified by GC/MS analysis. Broth microdilution and agar dilution methods were applied for determining the MIC. The antioxidant activity of the oil was studied by determination of glutathione level in blood of alloxan induced diabetic rats.

Results: The yield of the volatile oil hydrodistilled from the juvenile leaves and stems of E. cinerea was 4.5 and 0.5%, respectively. 1,8-Cineole was the major identified oxygenated monoterpenoid (84.55% and 60.15% in the juvenile leaves and stems, respectively). The antibacterial activity of the oil of the juvenile leaves was more potent against all the tested organisms than that of the stems. The (MIC) of volatile oil of the juvenile leaves against Escherichia coli, Pseudomonas aeruginosa, Streptococcus faecalis, Candida albicans, and Aspergillus flavus were 5.2, 5.6, 4, 4.8, and 12.8 mg/mL, respectively. The juvenile leaves’ oil was more active as an antioxidant than that of the stems. They restored glutathione level by 33.7 ± 1.1 and 29.6 ± 0.7 mg/dL, respectively, compared with vitamin E (35.9 ± 1.2 mg/dL) which was used as a reference.

Discussion and Conclusion: Results suggest that the volatile oil is 1,8-cineole chemotype. Moreover, the oil of the juvenile leaves of E. cinerea might find usefulness as a therapeutic agent following further development.

Keywords: 1,8-Cineole, Antimicrobial, Antioxidant, Chemotype, Eucalyptus Cinerea F. Mull. Ex Benth., Go/Ms, Glutathione, Mic, Myrtaceae.

1019. A New α-Glucosidase Inhibitor From Achillea Fragrantissima (Forsk.) Sch. Bip. Growing in Egypt

Ezzat SM and Salama MM.

Natural Product Research, 28: 812-818 (2014) IF: 1.225

α-Glucosidase inhibitors (AGIs) represent a class of oral antidiabetic drugs that delay the absorption of ingested carbohydrates, reducing the postprandial glucose and insulin peaks to reach normoglycaemia. In this study, a bioassay-guided fractionation of the ethanolic extract of the aerial parts of Achillea fragrantissima (Forsk.) Sch. Bip. growing in Egypt led to the isolation of a new potent AGI; acacetin-6-C-6’-acetyl-β-D-glucopyranoside)-8-C-α-L-arabinopyranoside (5) alongside with four known compounds: chondrillasterol (1), quercetin-3,6,7-trimethyl ether (chrysosplenol-D) (2), isovitexin-4’-methyl ether (3) and isovitexin (4). The structure of the new compound (5) was elucidated on the basis of its spectral data, including HR-FAB-MS, UV, (1)H NMR, (13)C NMR, (1)H-(1)H COSY, HSQC and HMBC. The new compound (5) exhibited the most significant α-glucosidase inhibitory activity (IC₅₀ 1.5 ± 0.09 μg/mL). Under the assay conditions, all the tested compounds were more potent than the positive control acarbose (IC₅₀ 224 ± 2.31 μg/mL).

Keywords: A. Fragrantissima; A-Glucosidase Inhibitors; Chondrillasterol; Chrysosplenol- D; Isovitexin; Acacetin-6-C-(600-Acetyl-B-D-Glucopyranoside)-8-C-A-L-Arabinopyranoside.

1020. A New Flavonol Glycoside and Biological Activities of Adenanthera Pavonina L. Leaves

R.S. Mohammed, A.H. Abou Zeid, E.A. Elk-Kashoury, A.A. Sleem and D.A. Waly


Adenanthera pavonina is a plant belonging to family Fabaceae. The 95% ethanol extract (EtOH) of the dried powdered leaves of the plant and successive extracts with solvents of increasing polarities were prepared. Fractionation of the successive aqueous EtOH extract on polyamide column and purification of the isolated compounds on Sephadex LH20 led to the isolation of a new methoxy flavonol glycoside named as quercetin 3-O-arabinopyranosyl(1"→2")-1,8"-b-glucopyranoside-40-methoxy (1), as well as kaempferol-3-O-a-dirhamnopyranosyl-(1"→2")-1,8"-b-glucopyranoside (2), isovitexin (3), quercetin-3-O-rhamnopyranosyl(1"→4")-b-glucopyranoside (4), quercetin-3-O-b-glucopyranoside-40-O-rhamnopyranoside (5), kaempferol-1-3-O-arhamnopyranosyl(1"→2")-b-glucopyranoside (6), quercetin-3-O-rhamnopyranosyl(1"→2")-b-glucopyranoside (7), quercetin-3-O-b-glucopyranoside (8), kaempferol (9) and quercetin (10). Structures of the isolated compounds were established by spectroscopic analysis. Antioxidant activities of EtOH extract, successive extracts and compounds 1 and 2 were evaluated. The ethyl acetate (EtOAc) extract and EtOH extract showed 62.67% and 49.30% free radical scavenging activity, respectively. Cytotoxic activities of the EtOH extract and compounds (1) and (2) were evaluated. The EtOH extract showed a significant cytotoxic activity against Hep G-2 (IC₅₀ 4.250 mg/mL) as compared with cisplatin (IC₅₀ > 10 mg).

Keywords: Adenanthera pavonina; Methoxy flavanol glycoside; Antioxidant; Cytotoxic.

1021. Anti-Influenza A Virus Activity of A New Dihydrochalcone Diglycoside Isolated From the Egyptian Seagrass Thalassodendron Ciliatum (Forsk.) Den Hartog

Nabaweya Mostafa ALi El-fiky


One new dihydrochalcone diglycoside has been isolated from the EtOAc fraction of the Egyptian seagrass Thalassodendrin ciliatum (Forsk.) Den Hartog, and was identified as 6′-O-rhamnosyl-(1″→4″)-glucopyranosyl asebogenin for which a trivial name Thalassodendrin was established. Furthermore, five known phenolics were isolated and identified as asebotin, quercetin 3,7-diglucoside, protocatechuic acid, ferulic acid and p-hydroxybenzoic acid.

The structures of all the isolated compounds were established based on 1D and 2D NMR spectroscopy and high-resolution mass spectrometer. High-resolution electrospray ionization mass spectra (HR-ESI-MS) were obtained using a JEOL JMS-T100TD spectrometer (JEOL Ltd., Tokyo, Japan). The anti-influenza A
virus activity of the isolated new compound and asebotin was evaluated, and the obtained results revealed that the inhibition dose concentration of asebotin was more than that of Thalassodendrone with IC50 = 2.00 and 1.96 µg/mL, respectively, and with cytotoxic concentration (CC50) of 3.36 and 3.14 µg/mL, respectively.

Keywords: Thalassodendron Ciliatum (Forsk.) Den Hartog, Cymodoceaceae, Dihydrochalcones, Phenolics, Antiviral; Structure–Activity Relationship Studies.

1022. Profiling the Chemical Content of Ficus Lyrae Extracts Via UPLC-PDA-qTOF-MS and Chemometrics
Mohamed A. Faraga, Mohamed S. Abdel fattahb, Sherif E.A. Badrc and Ludger A. Wessjohannd

This study attempts to elucidate the secondary metabolite profiles of Ficus lyrae leaves and fruits grown in Egypt. Non-targeted metabolite profiling via ultra performance liquid chromatography (UPLC-qTOF-MS) was used to identify various chemical classes in F. lyrae fruits and leaves (i.e. flavonoids, phenolic acids and fatty acids) analysed by chemometrics. A total of 72 metabolites were evaluated via a UPLC-qTOF-MS-based metabolic study. Seventeen flavonoids were characterised and tentatively identified with the main constituents being catechins/procyanidins, O- and C-linked flavonoid glycosides. The major procyanidins were dimers and trimers comprising (epi)catechin and (epi)azaelchin units, whereas the predominant flavones were C-glycosides of luteolin and apigenin. Aside from these major flavonoid classes, a group of benzoic acids, caffeoylquinic acids, fatty acid and spingolipids were also annotated. This study provides the most complete map for the flavonoid distribution in F. lyrae leaves and fruits and the basis for future investigation of its fruits nutritional value or possible nutraceutical uses.

Keywords: Phoenix Dactylifera; Metabolite Profiling; Uplc/Pda/Qtof Ms; Gc-Ms; Flavonoids; Principal Component Analysis.

1023. Triterpenes as Uncompetitive Inhibitors of A-Glucosidase from Flowers of Punica Granatum L.
Riham Salah El Dine, Qiong Ma, Zeinab A. Kandil and Ali M. El-Halawanya

The a-glucosidase and maltase inhibitory effects of Punica granatum L. flowers (PGFMe) were investigated. The methanol extract (PGFBMe), n-hexane extract (PGFHH), chloroform extract (PGFC) and the remaining water fraction (PGFW) were assayed for their a-glucosidase and maltase inhibitory effects. PGFW showed potent aglucosidase inhibition with IC50 of 0.8mg/mL followed by PGFBMe (IC50 of 4.0mg/mL) then PGFC (IC50 of 5.21mg/mL) in comparison to acarbose (0.9nmM). Due to its selectivity towards a-glucosidase, PGFC was subjected to bioactivity-guided isolation of its main active constituents. Five known compounds (1-5) were identified as bsitosterol (1), oleanolic acid (2), ursolic acid (3), p-coumaric acid (4) and apigenin (5). Ursolic and oleanolic acids showed potent a-glucosidase inhibition (IC50 of 39.0 and 35.0nm, respectively), while they did not show significant maltase inhibition. Kinetic study using the double Lineweaver–Burk plot revealed that urusolic acid uncompetitively inhibited a-glucosidase in comparison with acarbose as a competitive inhibitor.

Keywords: Punica Granatum Flower; A-Glucosidase; Ursolic Acid; Uncompetitive.

1024. Cholinesterase Inhibiting Activity and A New Piperidine Alkaloid From Lobelia Laxiflora L. Roots (Campanulaceae)
Abdel Rahman, Enas H.; Abdel Monem and Azza R.

The total alkaloidal fraction of Lobelia laxiflora L. roots was tested for cholinesterase inhibiting activity using spectrophotometric method. The IC50 value of the alkaloidal fraction recorded was close to that of eserine (286.3 µg/mL and 270 µg/mL, respectively). This biologically active alkaloidal fraction was subjected to a phytochemical study to isolate and identify its major constituents. Two piperidine alkaloids, N-methyl-2'-methoxybutyl),6(2'-hydroxybutyl)-1',3'-piperidine (1) and N-methyl-2'-hydroxybutyl,6(2'-hydroxybutyl)-1',3'-piperidine (2), were isolated. The structures of the two compounds were established based on their spectral data, including MS, 1H- and 13C-NMR, COSY, HMOC and HMBC spectral experiments. Compound (1) is a new natural compound while compound (2) was previously isolated from the aerial parts of the same plant.

Keywords: Lobelia Laxiflora; Piperidine Alkaloids; Cholinesterase Inhibiting Activity.

1025. Anti-Infl Ammatory Activity of Selected Plants From Saudi Arabia
Hossam M. Abdallah, Ashraf B. Abdel-Naim, Osama M. Ashour, Ibrahim A. Shehata, and Essam A. Abdel-Sattar.

Zeitschrift Für Naturforschung C, 69C: 1-9 (2014) IF: 0.569

For possible anti-infl ammatory activity using the carrageein-induced paw edema model in rats. The methanolic extracts of Vernonnia schimperi, Trichodesma trichodesmoides var. tomentosum, and Anabasis articulata exhibited the highest anti-infl ammatory activity. The active extracts were further subjected to fractionation with chloroform, ethyl acetate, and n-butanol and tested together with their mother liquor for their anti-infl ammatory activity in the same rat model. The most potent fractions were the n-butanol fractions of Anabasis articulata and Vernonnia schimperi and the aqueous mother liquor of Trichodesma trichodesmoides. Nevertheless, the three potent methanolic extracts showed higher anti-infl ammatory activities than their individual fractions. The antioxidant properties were assessed by their in vitro 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical scavenging activities. It was concluded that the anti-infl ammatory activity is dependent, at least in part, on the reduction of prostaglandin (PG)E2 and tumour necrosis factor-a (TNF-a) levels and cyclooxygenase-2 (COX-2) activity.

Keywords: Anti-Infl Ammatory, Saudi Arabian Plants, Cox.

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1026. Effect of Seasonal Variation on the Composition of the Essential Oil of Solidago Canadensis Cultivated in Egypt

Moshera El-Sherel, Amal Khaleel, Amira Abdel Motaal and Passent Abd-Elbaki

Journal Of Essential Oil Bearing Plants, 17: 891-898 (2014) IF: 0.187

The hydrodistilled essential oils of the fresh flowers and the remaining green aerial parts of Solidago canadensis L., family Asteraceae, recently introduced into Egypt were investigated by GC-MS analysis. A comparative study on the composition of the essential oils obtained in the four seasons of the year was carried out to assess the effect of seasonal variation on the collected oil samples. The major compounds detected in the oil samples of all seasons were germacrene D (9.86-29.47 %), α-pinene (3.38-29.17%), γ-cadinene (0.39-20.36 %), myrcene (2.98-13.74 %) and limonene (4.81-11.47 %). Summer samples contained the highest percentage of monoterpenic hydrocarbons, while winter samples showed the highest percentage of sesquiterpene hydrocarbons. Oil samples collected in summer and winter showed potential cytotoxic activity against human liver, breast and cervix carcinoma; HepG2, MCF7 and Hela respectively. Winter samples showed a relatively higher cytotoxic activity compared to the summer samples. Keywords: Solidago Canadensis L., Essential Oil Seasonal Variations, Cytotoxic Activity.

1027. Antihyperglycemic and Antihyperlipidemic Effects of the Methanolic Extracts of Cleome Ramosissima Parl., Barleria Bispinosa (Forssk.) Vahl. and Tribulus Macropterus Boiss.

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The antihyperglycemic and antihyperlipidemic effects of the methanolic extracts of the aerial parts of Cleome ramosissima Parl. (Cleomaceae), Barleria bispinosa (Forssk.) Vahl. (Acanthaceae) and Tribulus macropterus Boiss. (Zygophyllaceae) were evaluated in streptozotocin (STZ) induced diabetic rats at a dose of 500 mg/kg bw. The reduction in fasting blood glucose level (BGL) was observed in the following order C. ramosissima, B. bispinosa and T. macropterus also showed significant increase in plasma insulin by 100.6% and 189.9%, respectively. The studied plant extracts induced an increase in plasma insulin by 100.6% and 189.9%, respectively. B. bispinosa decreased the lipoprotein cholesterol (LDL-C) (42.6% and 37.2%, respectively) and low density lipoprotein cholesterol (TC) (48.0% and 42.1%, respectively) and the increase of high density lipoprotein cholesterol (HDL-C) by 81.0% and 91.9%, respectively. B. bispinosa decreased the blood levels of LDL-C and increased the levels of HDL-C, while it did not affect the TC blood levels. The present data suggest that C. ramosissima and T. macropterus have both antihyperglycemic and antihyperlipidemic effects with high insulin-secreting activity. Keywords: Antidiabetic; Hypolipidemic; Insulin Restoring; Cleome Ramosissima; Barleria Bispinosa; Tribulus Macropterus.

1028. Natural Anti-Obesity Agents

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Bulletin of Faculty of Pharmacy, Cairo University, 52: 269-284 (2014)

Obesity is a complex disease caused by the interaction of a myriad of genetic, dietary, lifestyle, and environmental factors, which favors a chronic positive energy balance, and leads to increased body fat mass. The incidence of obesity is rising at an alarming rate and is becoming a major public health concern with incalculable social costs. Indeed, obesity facilitates the development of metabolic disorders such as diabetes, hypertension, and cardiovascular diseases in addition to chronic diseases such as stroke, osteoarthritis, sleep apnea, some cancers, and inflammation-based pathologies. Recent researches demonstrated the potential of natural products to counteract obesity. Multiple-natural product combinations may result in a synergistic activity that increases their bioavailability and action on multiple molecular targets, offering advantages over chemical treatments. In this review, we discuss the anti-obesity potential of natural products and analyze their mechanisms. Keywords: Obesity; Tools; Plants; Flavonoids; Triterpenes.

Dept. of Pharmacology and Toxicology

1029. Activation of Poly(Adp-Ribose) Polymerase-1 Delays Wound Healing By Regulating Keratinocyte Migration and Production of Inflammatory Mediators

Tarek El-Hamoly, Csaba Hegedüs, Petra Lakatos, Katalin Kovács, Péter Bai, Mona A El-Ghazaly, Ezzeddin S El-Denshary, Éva Szabó, and László Virág


Poly (ADP-ribosyl) ation (PARylation) is a protein modification reaction regulating various diverse cellular functions ranging from metabolism, DNA repair and transcription to cell death. We set out to investigate the role of PARylation in wound healing, a highly complex process involving various cellular and humoral factors. We found that topically applied poly[ADP-ribosyl] polymerase (PARP) inhibitors 3-aminobenzamide and PJ-34 accelerated wound closure in a mouse model of excision wounding. Moreover, wounds also closed faster in PARP-1 knockout mice as compared with wild-type littermates. Immunofluorescent staining for poly(ADP-ribose) (PAR) indicated increased PAR synthesis in scattered cells of the wound bed. Expression of interleukin (IL)-6, tumor necrosis factor (TNF)-α, inducible nitric oxide synthase and matrix metalloproteinase-9 was lower in the wounds of PARP-1 knockout mice as compared with control, and expression of IL-1β, cyclooxygenase-2, TIMP-1 and -2 also were affected. The level of nitrotyrosine (a marker of nitrating stress) was lower in the wounds of PARP-1 knockout animals as compared with controls. In vitro scratch assays revealed significantly faster migration of keratinocytes treated with 3-aminobenzamide or PJ34 as compared with control cells. These data suggest that PARylation by PARP-1 slows down the wound healing process.
by increasing the production of inflammatory mediators and nitrating stress and by slowing the migration of keratinocytes.

**Keywords:** Keratinocyte; Inflammatory Mediators; Wound Healing.

1030. Cilostazol Renoprotective Effect: Modulation of PPAR-γ, NGAL, KIM-1 and IL-18 Underlies its Novel Effect in A Model of Ischemia-Reperfusion
Diaa Ragab, Dalaal M. Abdallah and Hanan S. El-Abhar

Cilostazol, a phosphodiesterase-III inhibitor, reportedly exhibits positive effects against ischemia/reperfusion (I/R)-induced injury in several models. However, its potential role against the renal I/R insult has not been elucidated. To test whether the PPAR-γ (of peroxisome proliferator activated receptor gamma) pathway is involved in the cilostazol effect, rats were randomized into sham, I/R, cilostazol (50 and 100 mg/kg per day, orally), pioglitazone (3 and 10 mg/kg per day, orally) and their combination at the low dose levels. Drugs regimens were administered for 14 days prior to the I/R induction. Pretreatment with cilostazol or pioglitazone provided significant protection against the I/R-induced renal injury as manifested by the attenuated serum levels of creatinine, blood urea nitrogen and cystatin C. Both drugs have also opposed the I/R-induced elevation in tissue contents/activity of neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (Kim-1), nuclear factor-κB, interleukin-18, caspase-1, as well as malondialdehyde, iNOS, myeloperoxidase, ICAM-1 and VCAM-1. Nevertheless, the drugs increased both the PPAR-γ transcriptional activity and the content of glutathione. Furthermore, combining the two low doses of both drugs produced effects comparable to that of the high dose level of either drug, advocating the fortification of pioglitazone renoprotective effect when given concomitantly with cilostazol. In conclusion, cilostazol purveyed conceivable novel renoprotective mechanisms and alleviated incidents associated with acute renal injury either alone or in combination with pioglitazone partially via the elevation of PPAR-γ besides the amendment of the aforementioned biomarkers.

**Keywords:** Cilostazol; Kidney; Pioglitazone; NGAL; kim-1.

1031. Novel CoQ10 Antidiabetic Mechanisms Underlie Its Positive Effect: Modulation of Insulin and Adiponectin Receptors, Tyrosine Kinase, Pi3k, Glucose Transporters, Sragge and Visfatin in Insulin Resistant/Diabetic Rats
Mohamed M. Amin, Gihan F. Asaad, Rania M. Abdel Salam, Hanan S. El-Abhar and Mahmoud S. Arbid

As a nutritional supplement, coenzyme Q10 (CoQ10) was tested previously in several models of diabetes and/or insulin resistance (IR); however, its exact mechanisms have not been profoundly explicated. Hence, the objective of this work is to verify some of the possible mechanisms that underlie its therapeutic efficacy. Moreover, the study aimed to assess the potential modulatory effect of CoQ10 on the antidiabetic action of glimebide. An insulin resistance/type 2 diabetic model was adopted, in which rats were fed high fat/high fructose diet (HFFD) for 6 weeks followed by a single sub-diabetogenic dose of streptozotocin (35 mg/kg, i.p.). At the end of the 7(th) week animals were treated with CoQ10 (20 mg/kg, p.o) and/or glimebide (0.5 mg/kg, p.o) for 2 weeks. CoQ10 alone opposed the HFFD effect and increased the hepatic/muscular content/activity of tyrosine kinase (TK), phosphatidylinositol kinase (PI3K), and adiponectin receptors. Conversely, it decreased the content/activity of insulin receptor isoforms, myeloperoxidase and glucose transporters (GLUT4; 2). Besides, it lowered significantly the serum levels of glucose, insulin, fructosamine and HOMA index, improved the serum lipid panel and elevated the levels of glutathione, sRAGE and adiponectin. On the other hand, CoQ10 lowered the serum levels of malondialdehyde, visfatin, ALT and AST. Surprisingly, CoQ10 effect surpassed that of glimebide in almost all the assessed parameters, except for glucose, fructosamine, TK, PI3K, and GLUT4. Combining CoQ10 with glimebide enhanced the effect of the latter on the aforementioned parameters.

**Keywords:** CoQ10; Diabetes; Pi3k; Glut4; Tk.

1032. Telmisartan Attenuates Colon Inflammation, Oxidative Perturbations and Apoptosis In A Rat Model of Experimental Inflammatory Bowel Disease
Hany H. Arab, Muhammad Y. Al-Shorbagy, Dalaal M. Abdallah and Noha N. Nassar

Telmisartan (TLM) is an angiotensin II receptor antagonist with marked anti-inflammatory and antioxidant actions that mediated its cardio-, reno- and hepatoprotective actions. However, its impact on IBD has not been previously explored. Thus, we aimed to investigate the potential alleviating effects of TLM in tri-nitrobenzene sulphonic acid (TNBS)-induced colitis in rats. Pretreatment with TLM (10 mg/kg p.o.) attenuated the severity of colitis as evidenced by decrease of disease activity index (DAI), colon weight/length ratio, macroscopic damage, histopathological findings and leukocyte migration. TLM suppressed the inflammatory response via attenuation of tumor necrosis factor-α (TNF-α), prostaglandin E2 (PGE2) and myeloperoxidase (MPO) activity as a marker of neutrophil infiltration besides restoration of interleukin-10 (IL-10). TLM also suppressed mRNA and protein expression of nuclear factor kappa B (NF-κB) p65 and mRNA of cyclo-oxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) proinflammatory genes with concomitant upregulation of PPAR-γ. The alleviation of TLM to colon injury was also associated with inhibition of oxidative stress as evidenced by suppression of lipid peroxides and nitric oxide (NO) besides boosting glutathione (GSH), total anti-oxidant capacity (TAC) and the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx). With respect to apoptosis, TLM downregulated the increased mRNA, protein expression and activity of caspase-3. It also suppressed the elevation of cytochrome c and Bax mRNA besides the upregulation of Bcl-2. Together, these findings highlight evidences for the beneficial effects of TLM in IBD which are mediated through modulation of colonic inflammation, oxidative stress and apoptosis.

**Keywords:** Telmisartan; Tnbs; Colitis; Apoptosis; Oxidative Stress.
**1033. Tempol, A Superoxide Dismutase Mimetic Agent, Ameliorates Cisplatin-Induced Nephrotoxicity Through Alleviation of Mitochondrial Dysfunction in Mice**

Lamiaa A. Ahmed, Nagwa I. Shehata, Noha F. Abdelkader and Mahmoud M. Khattab

*Plos One, 9 (10): (2014) IF: 3.534*

**Background:** Mitochondrial dysfunction is a crucial mechanism by which cisplatin, a potent chemotherapeutic agent, causes nephrotoxicity where mitochondrial electron transport complexes are shifted mostly toward imbalanced reactive oxygen species versus energy production. In the present study, the protective role of tempol, a membrane-permeable superoxide dismutase mimetic agent, was evaluated on mitochondrial dysfunction and the subsequent damage induced by cisplatin nephrotoxicity in mice.

**Methods and Findings:** Nephrotoxicity was assessed 72 h after a single i.p. injection of cisplatin (25 mg/kg) with or without oral administration of tempol (100 mg/kg/day). Serum creatinine and urea as well as glucosuria and proteinuria were evaluated. Both kidneys were isolated for estimation of oxidative stress markers, adenosine triphosphate (ATP) content and caspase-3 activity. Moreover, mitochondrial oxidative phosphorylation capacity, complexes I-IV activities and mitochondrial nitric oxide synthase (mNOS) protein expression were measured along with histological examinations of renal tubular damage and mitochondrial ultrastructural changes. Tempol was effective against cisplatin-induced elevation of serum creatinine and urea as well as glucosuria and proteinuria. Moreover, pretreatment with tempol notably inhibited cisplatin-induced oxidative stress and disruption of mitochondrial function by restoring mitochondrial oxidative phosphorylation, complexes I and III activities, mNOS protein expression and ATP content. Tempol also provided significant protection against apoptosis, tubular damage and mitochondrial ultrastructural changes. Interestingly, tempol did not interfere with the cytotoxic effect of cisplatin against the growth of solid Ehrlich carcinoma.

**Conclusion:** This study highlights the potential role of tempol in inhibiting cisplatin-induced nephrotoxicity without affecting its antitumor activity via amelioration of oxidative stress and mitochondrial dysfunction.

**Keywords:** Cisplatin; Mitochondria; Nephrotoxicity; Tempol.

**1034. Naringenin Adds To The Protective Effect Of L-Arginine In Monocrotaline-Induced Pulmonary Hypertension in Rats: Favorable Modulation of Oxidative Stress, Inflammation and Nitric Oxide**

Lamiaa A. Ahmed, Al Arqam Z. Obaid, Hala F. Zaki and Azza M. Agha


The present study was directed to investigate the possible modulatory effect of naringenin when co-administered with L-arginine in monocrotaline-induced pulmonary hypertension in rats. Pulmonary hypertension was induced by a single subcutaneous injection of monocrotaline (60 mg/kg). L-arginine (500 mg/kg) and naringenin (50 mg/kg) were orally administered daily, alone and in combination, for 3 weeks. Mean arterial blood pressure, electrocardiography and echocardiography were then recorded and rats were sacrificed and serum was separated for determination of total nitrate/nitrite level. Right ventricles and lungs were isolated for estimation of oxidative stress markers, tumor necrosis factor-alpha, total nitrate/nitrite and transforming growth factor-beta. Myeloperoxidase and caspase-3 activities in addition to endothelial and inducible nitric oxide synthase protein expression were also determined. Moreover, histological analysis of pulmonary arteries and cardiomyocyte cross-sectional area was performed. Combined therapy provided a significant improvement in L-arginine protective effect toward preserving hemodynamic changes and ameliorating oxidative stress, inflammatory and apoptotic markers induced by monocrotaline treatment. Furthermore, combined therapy prevented monocrotaline-induced changes in endothelial and inducible nitric oxide synthase protein expression as well as histological analysis compared with either treatment alone. In conclusion, naringenin significantly adds to the protective effect of L-arginine in pulmonary hypertension induced by monocrotaline in rats.

**Keywords:** Monocrotaline; Naringenin; Pulmonary hypertension; L-Arginine.

**1035. Enhanced Efficacy and Reduced Side Effects of Diazepam By Kava Combination**

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*Journal Of Advanced Research, 5: 587-594 (2014) IF: 3*

The long term use of antiepileptic drugs poses many unwanted effects; thus, new safe combinations are urgently mandated. Hence, the present study aimed to investigate the anticonvulsant effect of kava alone or in combination with a synthetic anticonvulsant drug, diazepam (DZ). To this end, female Wistar rats were divided into two subsets, each comprising 6 groups as follows: group (i) received 1% Tween 80 p.o. and served as control, while groups (ii) and (iii) received kava at two dose levels (100 and 200 mg/kg, p.o.). The remaining three groups received (iv) DZ alone (10 mg/kg p.o.) or kava in combination with DZ (v) (5 mg/kg, p.o.) or (vi) (10 mg/kg, p.o.). Results of the present study revealed that kava increased the maximal electroshock seizure threshold (MEST) and enhanced the anticonvulsant effect of diazepam following both acute and chronic treatment. Moreover, neither kava nor its combination with DZ impaired motor co-ordination either acutely or chronically. Furthermore, kava ameliorated both the reduction in locomotor activity as well as changes in liver function tests induced by chronic administration of DZ. Moreover, no elevation was shown in the creatinine concentration vs. control group following chronic administration of kava or DZ either alone or in combination with kava. In conclusion, the present study suggests the possibility of combining a low dose DZ with kava to reduce harmful effects and might be recommended for clinical use in patients chronically treated with this synthetic anticonvulsant drug.

**Keywords:** Kava; Diazepam; Anticonvulsant; Locomotor Activity; MEST.

**1036. Exploring the Protective Role of Apocynin, A Specific NADPH Oxidase Inhibitor, in Cisplatin-Induced Cardiotoxicity in Rats**

Maha M. El-Sawalhi and Lamiaa A. Ahmed


Medicine Sciences Sector
Despite the clinical reports, few studies have focused on reducing the cardiotoxicity of cisplatin. In the present study, cardiotoxicity was examined after a single ip injection of cisplatin (7mg/kg) in rats. Apocynin was given in drinking water (600mg/L) for five successive days before and after cisplatin injection. At the end of the experiment, hemodynamic parameters were recorded, animals were sacrificed and serum creatine kinase-MB activity was determined. The whole ventricle was isolated for estimation of tumor necrosis factor-alpha (TNF-α) content, NADPH oxidase, myeloperoxidase and caspase-3 activities in addition to nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1) and nuclear factor koppa B (NF-κB) gene expressions. Furthermore, oxidative stress markers and antioxidant enzymes were measured in postmitochondrial and mitochondrial fractions. Mitochondrial membrane potential, nuclear DNA fragmentation and cardiomycocyte cross-sectional area were also evaluated. Apocynin was effective against cisplatin-induced decrement in heart rate and blood pressure. Moreover, pretreatment with apocynin notably ameliorated the state of oxidative stress, mitigated inflammation and preserved mitochondrial membrane potential. Apocynin provided also a significant cardioprotection as revealed by alleviating the overexpression of Nrf2, HO-1 and NF-κB, the elevation of caspase-3 activity, the prominent nuclear DNA fragmentation and the decreased cardiomycyte cross-sectional area. This study highlights the potential role of apocynin in inhibiting cisplatin-induced hemodynamic changes, postmitochondrial and mitochondrial damage as indicated by improvement in the state of oxidative stress, inflammation and apoptosis.

**Keywords:** Apocynin; Cardiotoxicity; Cisplatin; Inflammation; Oxidative stress.

### 1037. Overexpression of NMDAR 2B in an Inflammatory Model of Alzheimer’s Disease: Modulation By Nos Inhibitors

**Maher A. El-Sayed NS, Breitinger HG and Gad MZ**


**Background:** Alzheimer's disease (AD) is a common form of age-related dementia, characterized by deposition of amyloid β plaques, neuroinflammation and neurodegeneration. N-methyl-D-aspartate receptors (NMDAR) are postsynaptic glutamate receptors that play a role in memory formation and are targets for memantine, an anti-AD drug. Nitric oxide (NO) signaling has been involved in both memory development through neuronal NO synthase (nNOS), and neuroinflammation through inducible NO synthase (iNOS) which mediates CNS inflammatory processes.

**Aim:** To study the expression of the NMDAR2B subunit in an inflammatory model of AD before and after treatment with NO modulators.

**Materials and Methods:** AD was induced in mice by a single dose of lipopolysaccharide (LPS). Behavioral tests for spatial and non-spatial memories and locomotor activity were performed to assess disease severity and progression. The effects of L-NAME (general NOS inhibitor), 1400W (iNOS inhibitor), diflunisal (systemic anti-inflammatory drug that does not cross the blood brain barrier), and L-arginine, the substrate for NOS was determined. Immunohistochemistry was done to confirm AD and brain lysates were tested for Aβ formation, levels of NMDAR2B subunits, and brain NO levels.

**Results:** Systemic LPS induced AD, as shown by cognitive impairment; increased levels of Aβ and concomitant increase in the brain NO concentrations. This was associated with overexpression of NMDAR2B. All tested drugs improved behavioral dysfunction, prevented Aβ formation and NMDAR overexpression, and lead to decrease in NO concentration in the brain. L-Arginine alone, however, did not produce similar improvements.

**Conclusion:** NMDAR2B subunits are overexpressed in an inflammatory model of AD and NO inhibitors ameliorate this expression.

**Keywords:** Alzheimer-Nitric Oxide- Nmdar- Nos Inhibitors- Diflunisal- Lps.

### 1038. Pyrrolidine Dithiocarbamate Protects Against Scopolamine-Induced Cognitive Impairment in Rats

**Mai A. Abd-El-Fattah, Noha F. Abdelakader and Hala F. Zaki**


Alzheimer's disease (AD) is a chronic neurodegenerative disorder that leads to disturbances of cognitive functions. Although the primary cause of AD remains unclear, brain acetylcholine deficiency, oxidative stress and neuroinflammation may be considered the principal pathogenic factors. The present study was constructed to investigate the anti-annemic effect of pyrrolidine dithiocarbamate (PDTC) on scopolamine-induced behavioral, neurochemical and biochemical changes in rats. PDTC (50 and 100mg/kg) and donepezil (2.5mg/kg) were orally administered for 14 successive days. Dementia was induced at the end of the treatment period by a single injection of scopolamine (20mg/kg; i.p.), and Y-maze test was conducted 30min thereafter. Rats were then sacrificed and homogenates of cortical and hippocampal tissues were used for the estimation of noradrenaline, dopamine, serotonin and heat shock protein 70 contents along with acetylcholinesterase activity. In addition, certain oxidative stress markers, pro-inflammatory and anti-inflammatory cytokines were assessed. Histological examination of cortical and hippocampal tissues was also performed. Scopolamine resulted in memory impairment that was coupled by alterations in the estimated neurotransmitters, heat shock protein 70, acetylcholinesterase activity, oxidative stress as well as inflammatory biomarkers. Histological analysis revealed serious damaging effects of scopolamine on the structure of cerebral cortex and hippocampus. Pretreatment of rats with PDTC in both doses mitigated scopolamine-induced behavioral, biochemical, neurochemical and histological changes in a manner comparable to donepezil. The observed anti-annemic effect of PDTC makes it a promising candidate for clinical trials in patients with cognitive impairment.

**Keywords:** Acetylcholinesterase; Dementia; Heat shock protein 70; Neuroinflammation; Oxidative stress; Pyrrolidine dithiocarbamate.

### 1039. Role of Oxidative Stress, Inflammation, Nitric Oxide and Transforming Growth Factor-Beta in the Protective Effect of Diosgenin in Monocrotaline-Induced Pulmonary Hypertension in Rats

**Lamiaa A. Ahmed, AlArqam Z.Obaid, Hala F.Zaki and Azza M. Agha**


**Background:** Diosgenin, a steroidal saponin isolated from Dioscorea species, has been reported to exert diverse pharmacological effects, including anti-inflammatory and antioxidant activities. The protective effect of diosgenin against monocrotaline (MCT)-induced pulmonary hypertension (PH) was reported previously. The mechanism underlying the protective effect of diosgenin against MCT-induced PH remains unknown. Recent advances have highlighted the importance of the redox balance and the inflammatory state in the pathogenesis of PH.

**Aim:** To evaluate the role of oxidative stress, inflammation, nitric oxide (NO), and transforming growth factor-beta (TGF-β) in the protective effect of diosgenin against MCT-induced PH.

**Materials and Methods:** Male Wistar rats were subjected to MCT-induced PH and treated with diosgenin (200 mg/kg) or L-NAME (20 mg/kg) and/or indomethacin (10 mg/kg) or their combination. The protective effect of diosgenin against MCT-induced PH was assessed by measuring pulmonary arterial pressure, right ventricular systolic pressure, and right ventricular systolic area. Furthermore, the effects of diosgenin on pulmonary arterial remodeling were evaluated by measuring pulmonary arterial wall thickness and media thickness. The role of oxidative stress, inflammation, and TGF-β in the protective effect of diosgenin against MCT-induced PH was assessed by measuring levels of malondialdehyde (MDA), nitric oxide (NO), and transforming growth factor-beta (TGF-β) in the pulmonary arteries.

**Results:** Treatment with diosgenin significantly attenuated MCT-induced PH, pulmonary arterial remodeling, and oxidative stress, inflammation, and TGF-β levels in the pulmonary arteries compared to MCT-treated rats. The combination of diosgenin and L-NAME or diosgenin and indomethacin further enhanced the protective effect of diosgenin against MCT-induced PH.

**Conclusion:** The protective effect of diosgenin against MCT-induced PH is mediated by its anti-inflammatory and antioxidant activities, and downregulation of TGF-β.

**Keywords:** Diosgenin; Pulmonary hypertension; Monocrotaline; Oxidative stress; Inflammation; Transforming growth factor-beta.

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Pulmonary hypertension is a progressive disease of various origins that is associated with right ventricular dysfunction. In the present study, the protective effect of diosgenin was investigated in monocrotaline-induced pulmonary hypertension in rats. Pulmonary hypertension was induced by a single subcutaneous injection of monocrotaline (60 mg/kg). Diosgenin (100 mg/kg) was given by oral administration once daily for 3 weeks. At the end of the experiment, mean arterial blood pressure, electrocardiography and echocardiography were recorded. Rats were then sacrificed and serum was separated for determination of total nitrate/nitrite level. Right ventricles and lungs were isolated for estimation of oxidative stress markers, tumor necrosis factor-alpha, total nitrate/nitrite and transforming growth factor-beta contents. Myeloperoxidase and caspase-3 activities in addition to endothelial and inducible nitric oxide synthase protein expression were also determined. Moreover, histological analysis of pulmonary arteries and cardiomyocyte cross-sectional area was performed. Diosgenin treatment provided a significant improvement toward preserving hemodynamic changes and alleviating oxidative stress, inflammatory and apoptotic markers induced by monocrotaline in rats. Furthermore, diosgenin therapy prevented monocrotaline-induced changes in nitric oxide production, endothelial and inducible nitric oxide synthase protein expression as well as histological analysis. These findings support the beneficial effect of diosgenin in pulmonary hypertension induced by monocrotaline in rats.

**Keywords:** Diosgenin; Monocrotaline; Nitric Oxide; Oxidative Stress; Pulmonary hypertension.

### 1040. Sulforaphane Increases the Survival Rate in Rats With Fulminant Hepatic Failure Induced by D-Galactosamine and Lipopolysaccharide

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*Nutrition Research, 34: 982-989 (2014) IF: 2.585*

Fulminant hepatic failure (FHF) is a life-threatening clinical syndrome, with liver transplantation being the only effective therapy. Sulforaphane (SFN) is a natural compound that is extracted from cruciferous vegetables and possesses potent anti-inflammatory, antioxidant, and anticancer activities. This study was designed to test the hypothesis that SFN (3 mg/kg) may protect against FHF induced in rats by administering a combination of D-galactosamine (GalN: 300 mg/kg) and lipopolysaccharide (LPS; 30 μg/kg). The rats were given a single intraperitoneal injection of SFN, 1 hour before the FHF induction. Sulforaphane reduced the mortality and alleviated the pathological liver injury. In addition, SFN significantly reduced the increase in serum aminotransferase activities and lipid peroxidation. The glutathione content decreased in the GalN/LPS group, and this decrease was attenuated by SFN. Increases in serum tumor necrosis factor α, interleukin-6, and interleukin-10, which were observed in GalN/LPS-treated rats, were significantly reduced after using SFN. The GalN/LPS treatment increased the expression of superoxide dismutase-1, glutathione peroxidase 2, catalase, and heme oxygenase-1 genes. Sulforaphane inhibited the induction of reactive oxygen species scavenging proteins. Moreover, SFN inhibited GalN/LPS-induced caspase-3 activation and suppressed FAS and FASL expression. These findings suggest that SFN alleviates GalN/LPS-induced liver injury, possibly by exerting antioxidant, anti-inflammatory, and antiapoptotic effects and modulating certain antioxidant defense enzymes.

**Keywords:** Sulforaphane; Rats; Fulminant Hepatic Failure; D-Galactosamine; Lipopolysaccharide.

### 1041. Synergistic Apoptotic Effect of Doxil and Aminolevulinic Acid-Based Photodynamic Therapy on Human Breast Adenocarcinoma Cells

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*Photodiagnosis and Photodynamic Therapy, 11: 227-238 (2014) IF: 2.524*

**Background:** 5-Aminolevulinic acid (ALA) is a natural heme precursor metabolized into protoporphyrin IX (PpIX). PpIX preferentially accumulates in tumor cells resulting in the formation of singlet oxygen upon exposure to visible light. Doxil®), an active agent against breast and ovarian cancer, is a nano-formulation of doxorubicin. This study aimed to investigate in vitro synergistic cytotoxic effect of low doses of combined chemotherapy and ALA/PDT to human breast adenocarcinoma cells (MCF-7) compared to high doses of each individual therapy.

**Methods:** MCF-7 cells were pretreated with Doxil® (48 h) followed by ALA/PDT (4h). The cell viability was evaluated by trypan blue assay and PpIX production was measured spectrophotometrically. Alkaline phosphatase was determined as a marker for cellular differentiation. Apoptosis and necrosis were evaluated by fluorescence stains. The apoptosis cell death pathways were investigated: detection of mitochondrial membrane potential (ΔΨm) and percent of DNA fragmentation, malondialdehyde, histone deacetylase (HDAC) activity, caspase-3 and death receptors (DR4 and DR5). Vascular endothelial growth factor (VEGF) was determined by ELISA, as an angiogenic mediator.

**Results:** There was a higher reduction in cell viability in Doxil®+ALA/PDT-treated cells compared with their individual effect. The combined therapy showed enhanced apoptosis with a significant increase in the loss of ΔΨm, DNA fragmentation %, caspase-3, DR4, DR5 and lipid peroxides and inhibited HDAC. Pretreatment with Doxil® resulted in a twofold increase in the intracellular PpIX, by increasing the PDT killing of MCF-7 cells.

**Conclusion:** The combined therapy using 50% of IC50 of ALA/PDT and Doxil® possessed a synergistic apoptotic effect on MCF-7 cells compared to 100% of IC50 of each therapy through enhancing both intrinsic and extrinsic apoptotic pathways, thus may minimize side effects of Doxil® and ALA.

**Keywords:** Breast Cancer; 5-Aminolevulinic acid; Protoporphyrin IX; Doxil; Apoptosis; Death receptors.

### 1042. Anti-Depressant Effect of Hesperidin in Diabetic Rats

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*Canadian Journal of Physiology and Pharmacology, 92: 945-952 (2014) IF: 1.546*

This study aimed to investigate the anti-depressant effect of hesperidin (Hsp) in streptozotocin (STZ)-induced diabetic rats. Additionally, the effect of Hsp on hyperglycaemia, oxidative stress, inflammation, brain-derived neurotrophic factor (BDNF),
and brain monoamines in diabetic rats was also assessed. The Wistar rats in the experimental groups were rendered hyperglycaemic with a single dose of STZ (52.5 mg/kg body mass)-1, by intraperitoneal injection. The normal group received the vehicle only. Hyperglycaemic rats were treated with Hsp (25.0, 50.0, or 100.0 mg*(kg body mass)-1*day-1, per oral) and fluoxetine (Flu) (5.0 mg*(kg body mass)-1*day-1, per oral) 48 h after the STZ injection, for 21 consecutive days. The normal and STZ control groups received the vehicle (distilled water). Behavioral and biochemical parameters were then assessed. When Hsp was administered to the STZ-treated rats, this reversed the STZ-induced increase in immobility duration in the forced swimming test (FST) and attenuated hyperglycaemia, decreased malondialdehyde (MDA), increased reduced glutathione (GSH) decreased interleukin-6 (IL-6), and increased BDNF levels in the brain. Treatment with Hsp attenuated STZ-induced neurochemical alterations, as indicated by increased levels of monoamines in the brain, namely, norepinephrine (NE), dopamine (DA), and serotonin (5-hydroxytryptamine; 5-HT). All of these effects of Hsp were similar to those observed with the established anti-depressant Flu. This study shows that Hsp exerted anti-depressant effect in diabetic rats, which may have been partly mediated by its amelioration of hyperglycaemia as well as its anti-oxidant and anti-inflammatory activities, the enhancement of neurogenesis, and changes in the levels of monoamines in the brain.

Keywords: Hesperidin; Anti-depressant; Forced swimming Test; Streptozotocin; Fluoxetine.

1043. Red Yeast Rice and Coenzyme Q10 As Safe Alternatives To Surmount Atorvastatin-Induced Myopathy in Hyperlipidemic Rats

Marwan Abdelbaset, Marwa M. Safar, Sawsan S. Mahmoud, Seham A. Negm, and Azza M. Agha


Statins are the first line treatment for the management of hyperlipidemia. However, the primary adverse effect limiting their use is myopathy. This study examines the efficacy and safety of red yeast rice (RYR), a source of natural statins, as compared with atorvastatin, which is the most widely used synthetic statin. Statin interference with the endogenous synthesis of coenzyme Q10 (CoQ10) prompted the hypothesis that its deficiency may be implicated in the pathogenesis of statin-associated myopathy. Hence, the effects of combination of CoQ10 with either statin have been evaluated. Rats were rendered hyperlipidemic through feeding them a high-fat diet for 90 days, during the last 30 days of the diet they were treated daily with either atorvastatin, RYR, CoQ10, or combined regimens. Lipid profile, liver function tests, and creatine kinase were monitored after 15 and 30 days of drug treatments. Heart contents of CoQ9 and CoQ10 were assessed and histopathological examination of the liver and aortic wall was performed. RYR and CoQ10 had the advantage over atorvastatin in that they lower cholesterol without elevating creatine kinase, a hallmark of myopathy. RYR maintained normal levels of heart ubiquinones, which are essential components for energy production in muscles. In conclusion, RYR and CoQ10 may offer alternatives to overcome atorvastatin-associated myopathy.

Keywords: Atorvastatin; Red Yeast Rice; Coenzyme Q10; Hyperlipidemia; Myopathy; Ubiquinones.

1044. Ellagic Acid Antiinflammatory and Antiapoptotic Potential Mediate Renoprotection in Cisplatin Nephrotoxic Rats

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Journal of Biochemical and Molecular Toxicology, 28(10): 472-479 (2014) IF: 1.317

Ellagic acid (EA) renoprotective effect against cisplatin (CIS)-induced nephrotoxicity remains elusive. Therefore, male Sprague-Dawley rats received CIS alone or EA (10 and 30 mg/kg, p.o.) for 5 days before and after CIS injection. CIS increased serum levels of blood urea nitrogen, creatinine, y-glutamyl transferase, and reduced those of albumin and total protein. It also raised serum endothelin-1, as well as serum and renal nitric oxide, tumor necrosis factor-α, and monocyte chemoattractant protein-1. CIS enhanced the renal capase-3, heme oxygenase (HO)-1, nuclear factor-κB, and inducible nitric oxide. EA hampered CIS-induced nephrotoxicity manifested by an enhancement of the glomerular filtration rate which was associated by the reduction of inflammatory mediators and the apoptotic marker in the serum and/or kidney. The present study discloses that EA suppresses HO-1 and, its renoprotection is also linked to its anti-inflammatory and antiapoptotic properties, as well as the reduction of nitric oxide and endothelin-1

Keywords: Apoptosis; Cisplatin; Ellagic acid; Inflammation; Nephrotoxicity.

1045. Evaluation of Plant Phenolic Metabolites as A Source of Alzheimer’s Drug Leads

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Biomedical Research International, 2014: 1-10 (2014) IF: 0.1

Epidemiological studies have proven an association between consumption of polyphenols and prevention of Alzheimer’s disease, the most common form of dementia characterized by extracellular deposition of amyloid beta plaques. The aim of this study is pharmacological screening of the aqueous alcohol extract of Markhamia platycalyx leaves, Schotia brachypetala leaves and stalks, and piceatannol compared to aqueous alcohol extract of Camellia sinensis leaves as potential Alzheimer’s disease drugs. LC-HRESI (-ve)-MSn was performed to identify phenolics’ profile of Schotia brachypetala stalks aqueous alcohol extract and revealed ten phenolic compounds as first report: daidzein, naringin, procyanidin isomers, procyanidin dimer gallate, quercetin 3-glucuronide, quercetin hexose gallic acid, quercetin hexose protocatechuic acid, and ellagic acid. Alzheimer’s disease was induced by a single intraperitoneal injection of LPS. Adult male Swiss albino mice were divided into groups of 8–10 mice each receiving treatment for six days. In vivo behavioral tests (Ymaze and object recognition) and in vitro estimation of amyloid beta 42 by ELISA showed significant differences between results of treated and nontreated animals.

Keywords: Alzheimer; Beta Amyloid; Green Tea; Schotia; Camellia.
1046. Modulatory Role of Chelating Agents in Diet-Induced Hypercholesterolemia in Rats

Heba M. Mahmoud, Hala F. Zaki, Gamal A. El Sherbiny and Hekma A. Abd El-Latif

Bulletin of Faculty of Pharmacy, Cairo University, 52: 27-35 (2014)

Introduction: Hypercholesterolemia is a major risk factor for the development of atherosclerosis and endothelial dysfunction. Chelating agents may play a modulatory role in atherosclerosis by removal of calcium from atherosclerotic plaques.

Aim: The present study aimed to explore the effects of calcium disodium ethylenediaminetetraacetic acid (CaNa2EDTA) and meso-2,3-dimercaptosuccinic acid (DMSA) on diet-induced hypercholesterolemia in rats using simvastatin as a reference standard.

Methods: Hypercholesterolemia was induced by feeding rats with cholesterol-rich diet for six weeks. Rats were divided into five groups (n= 8): normal control, hypercholesterolemic control, simvastatin (20 mg/kg; p.o.), CaNa2EDTA (100 mg/kg; i.p.) and DMSA (100 mg/kg; i.p.). Treatments continued daily for the six weeks of diet feeding.

Results: Diet-induced hypercholesterolemia resulted in alterations in the lipid profile markers and a state of oxidative stress coupled by compensatory increase in serum nitric oxide (NO) level and decreased aortic endothelial nitric oxide synthase (eNOS) activity parallel to increased inducible nitric oxide synthase (iNOS) activity, aortic calcium content and aortic wall thickness. Treatment with simvastatin, CaNa2EDTA and DMSA improved lipid profile and oxidative stress markers. In addition, they attenuated hypercholesterolemia-induced changes in serum NO level, aortic eNOS and iNOS activities, calcium content and aortic wall thickness.

Keywords: CaNa2edta; Dmsa; Hypercholesterolemia; Oxidative Stress; Lipid Profile; Nitric Oxide Synthases.

1047. Naringenin Protects Against Scopolamine-Induced Dementia in Rats

Hala F. Zaki, May A. Abd-El-Fattah and Amina S. Attia

Bulletin of Faculty of Pharmacy, Cairo University, 52: 15-25 (2014)

Background: Alzheimer’s disease (AD), the most common cause of progressive dementia in the elderly population, is a chronic neurodegenerative disorder that leads to disturbances of cognitive functions. Although the primary cause of AD remains unclear, brain acetylcholine deficiency and oxidative stress are principal pathogenic factors.

Aim of the study: The present study was constructed to investigate the anti-annestic effect of naringenin on scopolamine-induced behavioral and neurochemical changes in rats.

Methods: Naringenin (50 and 100 mg/kg) and donepezil (2.5 mg/kg) were orally administered for 7 successive days. Dementia was induced at the end of the treatment period by a single injection of scopolamine (20 mg/kg; i.p.). Conditioned avoidance and Y-maze tests were conducted 30 min thereafter then rats were sacrificed and brain homogenates were used for the estimation of noradrenaline, dopamine, serotonin and c-amino butyric acid contents along with acetylcholinesterase activity. In addition, certain inflammatory and oxidative stress markers as well as histopathologic studies were performed.

Results: Scopolamine resulted in memory impairment that was coupled by alterations in the estimated neurotransmitters and acetylcholinesterase activity as well as increased brain oxidative stress. Pretreatment of rats with naringenin in both doses mitigated scopolamine-induced behavioral, neurochemical and histological changes in a manner comparable to donepezil.

Conclusions: The observed anti-annmetic effect of naringenin makes it a promising candidate for clinical trials in patients with cognitive impairment.

Keywords: Dementia; Scopolamine; Naringenin; Oxidative Stress; Acetylcholinesterase.
The National Cancer Institute
Dept. of Clinical Pathology

1048. The Induction of the P53 Tumor Suppressor Protein Bridges the Apoptotic and Autophagic Signaling Pathways to Regulate Cell Death in Prostate Cancer Cells


The p53 tumor suppressor protein plays a crucial role in influencing cell fate decisions in response to cellular stress. As p53 elicits cell cycle arrest, senescence or apoptosis, the integrity of the p53 pathway is considered a key determinant of anti-tumor responses. p53 can also promote autophagy, however the role of p53-dependent autophagy in chemosensitivity is poorly understood. VMY-1-103 (VMY), a dansylated analog of purvalanol B, displays rapid and potent anti-tumor activities, however the pathways by which VMY works are not fully defined. Using established prostate cancer cell lines and novel conditionally reprogrammed cells (CRCs) derived from prostate cancer patients; we have defined the mechanisms of VMY-induced prostate cancer cell death. Herein, we show that the cytotoxic effects of VMY required a p53-dependent induction of autophagy, and that inhibition of autophagy abrogated VMY-induced cell death. Cancer cell lines harboring p53 missense mutations evaded VMY toxicity and treatment with a small molecule compound that restores p53 activity re-established VMY-induced cell death. The elucidation of the molecular mechanisms governing VMY-dependent cell death in cell lines, and importantly in CRCs, provides the rationale for clinical studies of VMY, alone or in combination with p53 reactivating compounds, in human prostate cancer.

Keywords: P53; Apoptosis; Autophagy; Primary cells; Prostate.

Dept. of Clinical Pathology

1049. High-Dose Methotrexate in Egyptian Pediatric Acute Lymphoblastic Leukemia: the Impact of ABCG2 C421a Genetic Polymorphism on Plasma Levels, What is Next?

Hala O. El Mesallamy, Wafa M. Rashed, Nadia M. Hamdy and Nayera Hamdy


Purpose High-dose methotrexate (HD-MTX) is a cornerstone antineoplastic drug in most treatment protocols of pediatric acute lymphoblastic leukemia (AL). Among the membrane efflux transporters of MTX, the human breast cancer resistant protein is the second member of the G subfamily of AT P-binding cassette (ABC) efflux pump (ABCG2). A single-nucleotide polymorphism (SNP) in ABCG2, the exchange of C to A at position 421, represents 13 % in the Middle Eastern population. We studied the effect of this SNP on the plasma levels of HD-MTX in Egyptian pediatric ALL. Methods Twenty hundred AL patients were recruited from Children’s Cancer Hospital Egypt-57357, and all were treated according to the St Jude Total XV protocol. Determination of plasma MTX levels was done at 23, 42 and 68 h. Genotyping of C421A of ABCG2 was done by polymerase chain reaction-restriction fragment length polymorphism. Results We found 14.5 % of the variant allele of the ABCG2 C421A SNP. The statistical association between ABCG2 421C>A SNP and the cutoff toxic plasma level of 24 h HD-MTX infusion at different time points tested was not statistically significant. There was no statistical significance between steady-state plasma concentration in patients with and without this SNP. Conclusions To date, this is the largest study on Egyptian AL patients for this SNP. This study shows that there is no effect of ABCG2 421C>A on plasma concentrations of HD-MTX. Replacing candidate gene association studies with genome-wide studies of HD-MTX is now mandatory and is part of our research blueprint.

Keywords: High-Dose Methotrexate; Egyptian Pediatric Acute Lymphoblastic Leukemia; Abcg2 C421a Genetic Polymorphism; Plasma Level.

1050. Evaluation of Serum PIVKA-II and Mif as Diagnostic Markers for HCV/HBV Induced Hepatocellular Carcinoma

Mahmoud M. Kamel, Mohamed F. Saad, Amal A. Mahmoud, Awatief A. Edries and Ahmed S. Abdel-Moneim

Microbial Pathogenesis, 77: 31-35 (2014) IF: 2

Viral hepatitis is the most significant predisposing factor for hepatocellular carcinoma (HCC). Liver cancer grows silently with mild or no symptoms until the disease is advanced and with little hope of cure. Early recognition of the onset of HCC would help to select more effective therapies for patients leading to a better prognosis and life span. The current study aims to evaluate two diagnostic and prognostic markers – Prothrombin induced by vitamin K absence-II (PIVKA-II) and macrophage migration inhibitory factor (MIF) in the serum of patients with HCC and those with a high risk of developing hepatic cancers. Serum samples from hepatocellular carcinoma, hepatitis C and normal subjects were subjected to quantitative determinations of different parameters including alpha-fetoprotein (AFP), PIVKA-II and MIF. Significant differences between the various groups were recorded. PIVKA-II and AFP showed a higher specificity and sensitivity compared to MIF, and there was considerable correlation between AFP and both PIVKA and MIF. It is concluded that analysis of PIVKA-II and AFP can serve as useful non-invasive markers for the early detection of HCC with good sensitivity and specificity.

Keywords: AFP; HBV; HCV; HCC; MIF; PIVKA II.

1051. P Selectin and T Cell Profiles Provide Verification To Understand the Pathogenesis of Liver Cirrhosis in HCV and Schistosoma Mansoni Infections

Mahmoud M. Kamel, Salah A. Romyeya, Mohamed M. Ali, Heisham A. Aziz and Ahmed S. Abdel-Moneim

Microbial Pathogenesis, 73: 19-24 (2014) IF: 2

Hepatitis C virus (HCV) and Schistosoma mansoni are two major causes of chronic liver disease (CLD). Both immune alteration and thrombocytopenia are common complications in the majority of cirrhotic patients. The current study aimed to monitor the effect
of T cell profile and platelets activation on the pathogenesis of liver cirrhosis in patients suffered from single or concomitant schistosomiasis and HCV infections. The subjects were divided into 4 groups: Group I, patients infected with schistosomiasis; Group II, patients infected with HCV; Group III, patients with combined liver diseases and Group IV: healthy individuals. All groups were subjected to full clinical evaluation as well as laboratory examination including ELISA anti-HCV antibodies screening, parasitological examination, and complete blood picture as well as flow cytometry for CD41, CD42, CD62P (P selectin), CD63, CD4 and CD8. The platelets count was significantly decreased in HCV and/or schistosoma infected patients compared to controls. The percentage of the total T-lymphocytes and T-helper was significantly reduced in all infected groups, while the percentage of T-lytotoxic was increased. The patients possessed a significantly higher percentage of the platelets activation markers than control group. There were considerable correlations between the platelets counts and P selectin and MPI. Thrombocytopenia was a common finding in patients with CLD. Patients with CLD showed increased platelets activation which may contribute to the occurrence of thrombocytopenia and play a role in the pathogenesis of CLD. Infected patient showed reduction in the cell-mediated-immunity as evidenced by low T efhelper cells.

**Keywords:** HCV; Hepatitis; P Selectin; Schistosoma Mansoni; Viral Immunity.

### 1052. Impact of Vitamin D Receptor Gene Polymorphisms in Pathogenesis of Type-I Diabetes Mellitus

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**Background:** Type I diabetes mellitus (TIDM) results from an immune-mediated destruction of insulin-producing-cells in the pancreatic islets of Langerhans. There are clear differences in immunogenetic predisposition to type1 diabetes among countries. Studies have indicated that vitamin D supplementation in early childhood decreases the risk of TIDM. Vitamin D exerts its action via the nuclear vitamin D receptor (VDR), which shows an extensive polymorphism. VDR gene polymorphisms have been associated with altered gene expression or gene function. Four single nucleotide polymorphisms (SNPs) in the VDR gene produce variation in four recognition sites. These recognition sites variants include Fok I, Bsm I, Apa I and Taq I.

**Aim of the study:** TO investigate the relationship between VDR gene polymorphisms (at positions Taq I and Apa I) and the incidence of TIDM in Egyptian peoples. Subjects and methods: This study included 74 patients with type 1 DM in addition to 28 healthy age and sex matched control subjects. All of them were subjected to full history taking and clinical examination. Three ml of venous blood were withdrawn from each patient at fasting and postprandial times and used for genomic DNA extraction, estimation of Hb A1C, as well as, fasting and postprandial C-peptide and blood glucose levels.

**Results:** Apa I recognition site was found in low frequency in diabetic patients (14/74) 18.9% while, its frequency was high (16/28) 57.1% among normal subjects. Taq I has two recognition sites. The first was found at nucleotide number 293 that was found in a frequency of (2/28) 7.1% in normal non-diabetic individuals while it was detected in (14/74) 18.9% in diabetic patients. The second Taq I recognition site was found at nucleotide number 494 without any differences between diabetic and normal individuals.

**Conclusion:** This study indicates that there is an association between VDR genetic polymorphism and incidence of TIDM in Egyptian patients.

**Keywords:** Vitamin D Receptor (VDR); Polymorphism; Type I Diabetes Mellitus (TIDM).

#### 1053. Comparing Prothrombin Induced By Vitamin K Absence-II (PIVKA-II) With the Oncofetal Proteins Glypican-3, ALPHA Feto Protein and Carcinoembryonic Antigen in Diagnosing Hepatocellular Carcinoma Among Egyptian Patients

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*Journal of the Egyptian National Cancer Institute, 26: 79-85 (2014)*

**Background:** Hepatocellular carcinoma (HCC) is usually asymptomatic in the early stage and does not show elevated alpha-feto protein (AFP). AFP shows 60–80% sensitivity in diagnosing HCC. Glypicans-3 (GPC-3) is an oncoprotein that is only detected in HCC cells but not in benign liver tissues, while Carcinoembryonic antigen (CEA) is expressed in various neoplasms including HCC. Although, it is not specific for HCC, Prothrombin induced by vitamin K absence-II (PIVKA-II) is an abnormal prothrombin protein that is increased in the serum of HCC patients. It has higher sensitivity and specificity compared to AFP. The aim of this study is to compare the clinical utility of PIVKA-II with GPC-3, AFP and CEA in diagnosing HCC.

**Keywords:** HCC; Pivka-II; Oncofetal Antigens.

### Dept. of Medical & Cancer Epidemics Statistics

#### 1054. Dexmedetomidine as an Adjunctive Analgesic With Bupivacaine in Paravertebral Analgesia for Breast Cancer Surgery

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*Pain Physician, 17 (5): E589-98 (2014) IF: 4.766*

**Background:** There is little systematic research on the efficacy and tolerability of the addition of adjunctive analgesics agents in paravertebral analgesia. The addition of adjunctive analgesics, such as fentanyl and clonidine, to local anesthetics has been shown to enhance the quality and duration of sensory neural blockades, and decrease the dose of local anesthetic and supplemental analgesia.

**Objectives:** Investigation of the safety and the analgesic efficacy of adding 1 μg/kg dexmedetomidine to bupivacaine 0.25% in thoracic paravertebral blocks (PVB) in patients undergoing modified radical mastectomy.

**Study Design:** A randomized, double-blind trial.

**Setting:** Academic medical center.

**Methods:** Sixty American Society of Anesthesiologists physical status –I – III patients were randomly assigned to receive thoracicPVB with either 20 mL of bupivacaine 0.25% (Group B, n = 30), or 20 mL of bupivacaine 0.25% + 1 μg/kg dexmedetomidine (Group BD, n= 30). Assessment parameters
included hemodynamics, sedation score, pain severity, time of first analgesics request, total analgesic consumption, and side effects in the first 48 hours.

**Results:** There was a significant reduction in pulse rate and diastolic blood pressure starting at 30 minutes in both groups, but more evidenced in group BD (P < 0.001). Intraoperative Systolic blood pressure showed a significant reduction at 30 minutes in both groups (P < 0.001) then returned to baseline level at 120 minutes in both groups. There was a significant increase in pulse rate starting 2 hours postoperative until 48 hours postoperatively in group B but only after 12 hours until 48 hours in group BD (P < 0.001). The time of the first rescue analgesic requirement was significantly prolonged in the group BD (8.16 ± 42 hours) in comparison to group B (6.48 ± 5.24 hours) (P = 0.04). The mean total consumption of intravenous tramadol rescue analgesia in the postanesthesia care unit in the firtst 48 hours postoperatively was significantly decreased in group BD (150.19 ± 76.98 mg) (P = 0.03). No significant serious adverse effects were recorded during the study.

**Conclusion:** This study is limited by its sample size.

**Limitations:** This study is limited by its small sample size.

**Keywords:** Dexmedetomidine, Caudal Block, Pediatric Cancer Surgery.

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**1055. Efficacy and Safety of Dexmedetomidine Added to Caudal Bupivacaine in Pediatric Major Abdominal Cancer Surgery**

Nelly Hassan Mohamed Alieldin, Khaled Mohamed Fares and Ahmed H. Othman

**Background:** Caudal analgesia has been prolonged by the addition of various adjuvants. Dexmedetomidine is a highly selective alpha-2 agonist with sedative and analgesic properties.

**Objective:** To investigate the effect of addition of dexmedetomidine to 0.25% bupivacaine for caudal analgesia in children undergoing major abdominal cancer surgery.

**Study Design:** A randomized double-blind trial.

**Setting:** Academic medical center.

**Methods:** Forty pediatric patients, aged 3 - 12 years, weighting 10 - 40 kg, and of American Society of Anesthesiologists (ASA) physical status I and II scheduled for major abdominal cancer surgeries under general anesthesia combined with caudal analgesia were enrolled. They were randomly allocated into 2 groups: Group I (BD): (n = 20) received 1 mL/kg bupivacaine 0.25% with dexmedetomidine 1 µg/kg and group II (B): (n = 20) received 1 mL/kg bupivacaine 0.25%. Heart rate (HR), mean arterial pressure (MAP), and oxygen saturation (SPO2) were recorded for 120 minutes. Pain was assessed immediately postoperative and at hours 2, 4, 6, 12, 18, and 24 of postoperative period by Face, Legs, Activity, Cry and Consolability (FLACC) score. Time to first request for analgesia and total analgesic consumption in the first 24 hours were recorded. The level of sedation was recorded using Ramsay's sedation scale [Intravenous acetaminophen 15mg/kg (perfalgan, Squibb)]. Adverse effects were recorded and treated.

**Results:** There was significant reduction in FLACC score in group BD at 2, 4, 6, and 12 hours postoperatively compared to group B. At the eighteenth and twenty-fourth hour there was no significant difference. Time of the first rescue analgesic requirement was significantly prolonged in group BD compared to group B. The mean total consumption of rescue analgesia in the 24 hours of the postoperative period was significantly decreased in group BD (405.00 ± 215.03 mg) when compared with group B (810.35 ± 200.93 mg).

**Limitations:** This study is limited by its small sample size.

**Conclusion:** Addition of dexmedetomidine (1 µg/kg) to caudal bupivacaine 0.25% (1 mL/kg) in pediatric major abdominal cancer surgeries achieved significant postoperative pain relief for up to 19 hours, with less use of postoperative analgesics, and prolonged duration of arousable sedation. Hemodynamic changes were statistically significant, yet of no clinical significance.

**Keywords:** Dexmedetomidine, Caudal Block, Pediatric Cancer Surgery.

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**1056. Age At Diagnosis In Women With Non-Metastatic Breast Cancer: Is It Related to Prognosis?**

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**Journal of the Egyptian National Cancer Institute, 26: 23-30 (2014)**

**Objective:** Primary objective was to verify whether breast cancer patients aged less than 40 years at diagnosis have poorer prognosis than older patients. Secondary to assess prognostic factors influencing disease free survival.

**Methods:** 941 women were diagnosed with non-metastatic breast cancer at NCI, Cairo in 2003. Epidemiologic, clinico-pathological characteristics, treatment modalities and disease free survival were compared among the two age groups. Prognostic factors were evaluated for association with disease-free survival.

**Results:** One hundred-eighty-one patients (19.2%) were younger than 40 years and 760 (80.8%) were older. Older women presented with higher rates of comorbidities and younger women presented with more hormone non-responsive tumors. Young women presented with larger tumors pT4 = 13.8% compared to 8.6% in older women, yet not significant. Young women were treated with more conservative surgery, more adjuvant chemotherapy and radiotherapy while older women with more radical mastectomies and more hormonal treatment. Recurrence rates were significantly higher among young women 44.2% compared to 34.5% in older women. Five year disease free survival in young women was 38.9% ± 4.6% compared to 48.6% ± 2.5% with adjusted hazard ratio of 1.22 (95% CI (0.91–1.64), p = 0.19. Multivariate analyses identified positive axillary lymph nodes (pN2-pN3), larger tumor size (pT3-pT4), hypertension, lobular carcinoma type and lack of adjuvant systemic treatment as independent factors associated with poor DFS.

**Conclusion:** Young women were not found to have poorer prognosis, yet they presented with more ER negative tumors. Most of women presented with advanced stage and young women had higher recurrence rates.

**Keywords:** Breast Cancer; Young Age; Disease-Free Survival; Prognostic Factors.
1057. Anastrozole For Prevention of Breast Cancer In High-Risk Postmenopausal Women (IBIS-II): An International, Double-Blind, Randomised Placebo-Controlled Trial

Hussein Mostafa Mosa Khaled

Background: Aromatase inhibitors effectively prevent breast cancer recurrence and development of new contralateral tumours in postmenopausal women. We assessed the efficacy and safety of the aromatase inhibitor anastrozole for prevention of breast cancer in postmenopausal women who are at high risk of the disease.

Methods: Between Feb 2, 2003, and Jan 31, 2012, we recruited postmenopausal women aged 40–70 years from 18 countries into an international, double-blind, randomised placebo-controlled trial. To be eligible, women had to have at increased risk of breast cancer (judged on the basis of specific criteria). Eligible women were randomly assigned (1:1) by central computer allocation to receive 1 mg oral anastrozole or matching placebo every day for 5 years. Randomisation was stratified by country and was done with blocks (size six, eight, or ten). All trial personnel, participants, and clinicians were masked to treatment allocation; only the trial statistician was unmasked. The primary endpoint was histologically confirmed breast cancer (invasive cancers or non-invasive ductal carcinoma in situ). Analyses were done by intention to treat. This trial is registered, number ISRCTN31488319.

Findings: 1920 women were randomly assigned to receive anastrozole and 1944 to placebo. After a median follow-up of 5·0 years (IQR 3·0–7·1), 40 women in the anastrozole group (2%) and 85 in the placebo group (4%) had developed breast cancer (hazard ratio 0·47, 95% CI 0·32–0·65, p<0·0001). The predicted cumulative incidence of all breast cancers after 7 years was 3·6% in the placebo group and 2·8% in the anastrozole group. 18 deaths were reported in the anastrozole group and 17 in the placebo group, and no specific causes were more common in one group than the other (p=0.836).

Interpretation: Anastrozole effectively reduces incidence of breast cancer in high-risk postmenopausal women. This finding, along with the fact that most of the side-effects associated with oestrogen deprivation were not attributable to treatment, provides support for the use of anastrozole in postmenopausal women at high risk of breast cancer.

Keywords: Anastrozole Breast Cancer.


Response criteria have always been difficult to apply to malignant pleural mesothelioma (MPM), due to its unique pattern of growth. We developed some models to show that progression free survival rate (PFSR) could be a better predictor of overall survival (OS) than the response rate (RR) in MPM patients. The results were validated independently in the European Organisation for Research and Treatment of Cancer (EORTC) 08052, a phase II study in MPM.

Methods: Individual patient data from 10 EORTC-Lung Cancer Group (LCG) studies of first-line chemotherapy in MPM were pooled. Response to therapy was assessed according to World Health Organisation (WHO) criteria in all except the two most recent trials, which used Response Evaluation Criteria in Solid Tumours (RECIST). Landmarks analyses (LA) at 9 weeks and 18 weeks after registration/randomisation were performed to assess the association between PFSR and OS. Independent validation of the results was conducted in EORTC 08052 study (82 patients) employing the same LA.

Results: All 10 studies (N=523 patients) were included in the LA of PFSR at 9 and 18 weeks (PFSR-9 and PFSR-18). PFSR-9 and PFSR-18 were confirmed as predictors of OS, with hazard ratio (HR) of 0.37 (95% confidence interval (CI), 0.30–0.47) and 0.50 (0.38–0.65) and C-index of 0.62 and 0.58, respectively. In the validation study, 28.4% achieved CR/PR and 77.8% had disease control (CR/PR/SD) as their best overall response. PFSR-9 and PFSR-18 weeks were both strongly correlated with OS (HR of 0.35 [80% CI, 0.25–0.49] and 0.46 (0.32–0.67) and C-index of 0.66 and 0.60, respectively).

Conclusion: PFSR-18 was strongly correlated and discriminated patients with better OS from the poorer prognosis patients. An earlier end-point, PFSR-9 was also strongly correlated to OS with better discriminating capacity. The results were independently validated.

Keywords: Malignant Pleural Mesothelioma (Mpm); Overall Survival (Os) Prediction; Progression Free Survival Rates At 9 And 18Weeks (Pfsr-9 And 18); Response Rates.

1059. The Biochemical Value of Urinary Metalloproteinases 3 and 9 in Diagnosis and Prognosis of Bladder Cancer in Egypt

Fathia El-Sharkawi, Mahmoud El Sabah, Zeinab Hassan and Hussein Khaled

Background: Matrix metalloproteinases (MMPs) have long been associated with cancer-cell invasion and metastasis. Few studies are available that describe this association with bladder cancer either related or unrelated to schistosoma infection. Evaluating the urinary levels of MMP3 and MMP9 as diagnostic and prognostic biomarkers in different stages of schistosomal and non schistosomal bladder cancer was the aim of the present study. Urine samples were collected from 70 patients with schistosomal and non schistosomal bladder cancer at early and advanced stages and also from12 healthy volunteers as controls. Urinary levels of MMP-3 and MMP-9 was measured by ELISA technique. Sensitivity and specificity of both markers were determined.

Results: Urinary levels of both MMP-3 and MMP-9 were significantly elevated in all bladder cancer patients compared with controls. MMP-3 started to elevate in early stages of schistosomal bladder cancer ( 0.173 ng/ml) and non-schistosomal bladder cancer patients (0.308 ng/ml) compared to control (0.016 ng/ml) and remained elevated in advanced stages (0.166, 0.235 ng/ml) of both types of bladder cancer patients. In contrast, MMP-9 showed a significant elevation in advanced stages only of both
1060. Gemcitabine And Cisplatin as Neoadjuvant Chemotherapy for Invasive Transitional and Squamous Cell Carcinoma of The Bladder: Effect on Survival and Bladder Preservation


**Background:** Despite aggressive local therapy, patients with locally advanced bladder cancer have a significant risk of distant metastases. This study evaluated the role of neoadjuvant combination chemotherapy with gemcitabine/cisplatin (GC) in improving the outcome of this group of patients over radical cystectomy alone.

**Patients and Methods:** A total of 114 patients with newly diagnosed bladder cancer (T3-T4, N0-2, M0) were randomized to radical cystectomy alone or initial 3 cycles of GC, then managed according to response. Patients who achieved complete response completed 6 cycles of GC followed by local radiation therapy (RT) only. If tumors were downstaged to T1, complete transurethral resection was done, followed by 3 cycles of GC and then RT. Patients with partial response underwent radical cystectomy followed by 3 cycles of GC. Patients with stable disease or disease progression underwent further radical cystectomy.

**Results:** The overall response rate to GC was 55.1%, and complete response was achieved in 28.6%. The 3-year overall survival (OS) was 51.9% versus 51.2% in the chemotherapy and surgery arms, respectively (P = .399). The 3-year disease-free survival was 31.8% in the chemotherapy arm and 45.1% in the surgery arm (P = .06). Bladder preservation was achieved in 22.5% of patients in the neoadjuvant arm. OS was 78% in responding patients and 100% in patients with complete response.

**Conclusion:** Neoadjuvant GC did not improve survival in locally advanced bladder cancer over radical cystectomy alone. However, bladder preservation was feasible, and OS in responding patients was impressive. Therefore, predictive models to select patients are needed. This is the largest prospective study of squamous cell carcinoma and transitional cell carcinoma using neoadjuvant GC.

**Keywords:** Bladder Cancer; Bladder Preservation; Bladder Squamous Cell Carcinoma; Muscle Invasive; Neoadjuvant GC.

1061. Plasma Vascular Endothelial Growth Factor 165 in Advanced Non-Small Cell Lung Cancer

Abdallah A, Belal M, El Bastawisy A and Gaafar R

**Oncology Letters, 7(6): 2121-2129 (2014) IF: 0.987**

Currently, there is no serum marker that is routinely recommended for lung cancer. Therefore, the aim of the present study was to demonstrate that plasma vascular endothelial growth factor 165 (VEGF 165) may be a potential marker for advanced lung cancer. Lung cancer is the leading cause of cancer-related mortality worldwide, therefore, it is important to develop novel diagnostic techniques. The present prospective case control study included two groups of patients; a control group of healthy volunteers and a second group of patients with advanced non-small cell lung cancer (NSCLC). The plasma VEGF 165 levels were measured at baseline by ELISA prior to the first-line gemcitabine-cisplatin regimen. The high VEGF 165 expression level cut-off was >703 pg/ml, and the primary endpoint was used to compare the plasma VEGF 165 levels between the NSCLC patients and the control group subjects. The secondary endpoint was used to identify the correlations between high VEGF 165 levels and clinical response (CR), progression-free survival (PFS) and overall survival (OS) in the advanced NSCLC patients. In total, patients with advanced NSCLC (n=35) were compared with a control group of age- and gender-matched healthy subjects (n=34). The follow-up period was between Oct 2009 and Oct 2012, with a median follow-up time of 10.5 months. The median plasma VEGF 165 level was 707 pg/ml in the NSCLC patients versus 48 pg/ml in the healthy control subjects (P<0.001). However, no significant correlation was found between the plasma VEGF 165 levels and CR (P>0.5), median PFS (P=1.00) or OS (P=0.70). Therefore, it was concluded that plasma VEGF 165 may serve as a potential diagnostic marker for advanced NSCLC.

**Keywords:** Non-Small Cell Lung Cancer; Vascular Endothelial Growth Factor.
DFS was 4 months in the elderly compared to 20 months in the non-elderly (p=0.004). The median PFS was 2 months in the elderly compared to 3 months in the non-elderly (p=0.685). In multivariate analysis, poor performance status was an independent predictor of poor OS, DFS and PFS. Non-curative or no surgery and lack of chemotherapy use were independent predictors of poor OS. Age was an independent predictor of poor DFS.

**Conclusions:** Compared to the non-elderly, GC in the elderly has similar clinicopathological characteristics and exhibits comparable outcomes with the same treatment options. Treatments should be tailored to each patient.

**Keywords:** Egypt; Elderly; Gastric Neoplasms; Gharbiah; Survival; Treatment.

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**1063. Review of 40-Year Md Theses in Medical Oncology**

Zeenneldin A, Diyaa A, Moneer M, Elgammal M and Buhoush W

*Journal of the Egyptian National Cancer Institute, 26: 109-118 (2014)*

**Background and Objective:** It is almost 40 years since the foundation of the Medical Oncology (MO) Department. We aimed to appraise the clinical research to fulfill the Medical Doctorate (MD) degree in MO at the National Cancer Institute, Cairo University (NCI, CU). **Methods:** This review included 62 MD theses containing 66 studies. They were reviewed regarding aims, type of study, clinical trial phase, design and methodology, statistical tests, results, limitations, consent and IRB approval. Theses were grouped into 3 periods: 1970-1989, 1990-1999 and 2000-2008. **Results:** Almost 76% of the studies were intervention and 24% were observational. Informed consent and Institutional Review Board approval were mentioned in 18 and 2 studies, respectively. While all studies mentioned the aims, none, clearly mentioned the research question. Outcomes were mainly efficacy followed by safety. Study design was inadequately considered, especially in 70’s-80’s period (p=0.038). Median sample size and study duration were almost stable during the three periods (p=0.441, 0.354, respectively). Most of the studies used both descriptive and analytical statistical methods. In a descending order, researched cancers were lymphoma, breast, leukemia, liver, urinary bladder, lung and colorectal. The commonest stages researched were IV and III. The number of studies focused on assessing biomarkers, biomarkers plus drugs/procedures, drugs and procedures are 20, 20, 16 and 6, respectively. **Conclusion:** With time, research within MD theses in MO increased quantitatively and qualitatively. Improvements were noticeable in documentation of study design. **Keywords:** Clinical Trials; Md Theses; Medical Oncology Department; National Cancer Institute, Cairo University; Study Design.

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**1064. Tamoxifen Compared To Best Supportive Care in Advanced Hepatocellular Carcinoma: A Retrospective Matched-Cohort Study**

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*Journal of the Egyptian National Cancer Institute, 26: 1-7 (2014)*

**Background:** Hepatocellular carcinoma (HCC) is a common cancer worldwide as well as in Egypt with hepatitis B and C, alcohol and aflatoxins being the commonest risk factors. Tamoxifen was initially reported to confer a marginal survival benefit in advanced HCC. However, later reports declined any benefit. **Objective:** To study the impact of tamoxifen on overall survival (OS) compared to best supportive care (BSC) in Egyptian patients with advanced HCC. **Methods:** This retrospective matched-cohort study was conducted at Tanta Cancer Center (TCC), Egypt where 116 advanced HCC cases treated with tamoxifen were compared to TNM stage and Child-Pugh class matched 116 HCC cases who received BSC. **Results:** The median OS in the tamoxifen group was 9.3 months (95% confidence interval [CI], 6.7-11.9 months) compared to 8.7 months (95%CI, 6.8-10.6) in the BSC group (p=0.758). With univariate analyses, it was shown that absence of fatigue, Child-Pugh class A, single tumors, less advanced tumors (T2), and absence of metastases (M0), had significantly better OS than their counterparts. Multivariate analysis showed that absence of fatigue, Child-Pugh class A and T2 tumors were independent prognostic factors affecting OS. Tamoxifen produced partial response and clinical stabilization in one% and 16% of cases, respectively. The median PFS with tamoxifen was 7.2 months (95%CI, 5.2-9.5). **Conclusions:** Tamoxifen did not show any OS advantage in Egyptian patients with advanced HCC. Use of this drug is discouraged. **Keywords:** Egypt; Hepatocellular Carcinoma; Matched Cohort; Tamoxifen; Treatment.

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**1065. Treatment Outcomes of Female Germ Cell Tumors: The Egyptian National Cancer Institute Experience**

Magdy M. Saber, Ahmed A. Zeenneldin, Mosaad M. El Gammal, Salem E. Salem, Amira D. Darweesh, Alshaymaa A. Abdelaziz and Manar Monir

*Journal of the Egyptian National Cancer Institute, 26: 103-108 (2014)*

**Introduction:** Female germ cell tumors (GCTs) are rare tumors that carry a good prognosis. **Aim:** To report the experience of the Egyptian National Cancer Institute (ENCI) in managing female GCTs. **Methods:** This retrospective study included 19 females with ovarian GCTs presenting to the ENCI between 2006 and 2010. **Results:** The median age was 23 years. Ovaries were the primary site in all patients. Dysgerminoma and teratoma were the predominant pathologies followed by mixed GCT in females. Unilateral ovariectomy or ovarian tumorectomy were the classic surgical procedures with R0 resection being feasible in most cases. Surveillance was adopted in six patients with stage I disease. Chemotherapy was administered in 63% of ovarian GCTs with BEP being the commonest regimen with reasonable tolerability and good response rates. The median OS and EFS were not reached. The projected 5-year OS rate was 93.8%. Both OS and EFS were better in patients responding to chemotherapy than non-responders (p<0.002). Stage of disease did not significantly affect OS or EFS. **Conclusions:** Female GCTs rarely affect Egyptian females. They have good prognosis. **Keywords:** Chemotherapy; Female Germ-Cell Tumors; Side Effects; Survival; Treatment.

Kallehaage JF, Tandrup K, Duan C, Haack S, Pedersen EM, Lindegaard JC, Fokdal LU, Mohamed SM and Nielsen T


Background: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) offers a unique capability to probe tumour microvasculature. Different analysis of the acquired data will possibly lead to different conclusions. Therefore, the objective of this study was to investigate under which conditions the Tofts (TM), extended Tofts (ETM), compartmental tissue uptake model (C-TU) and 2-compartment exchange model (2CXM) were the optimal tracer kinetic models (TKMs) for the analysis of DCE-MRI in patients with cervical cancer.

Material and Methods: Ten patients with locally advanced cervical cancer (FIGO: IIA/IIA/IIIB/IVA - 1/5/3/1) underwent DCE-MRI prior to radiotherapy. From the two-parameter TM it was possible to extract the forward volume transfer constant (K(trans)) and the extracellular-extravascular volume fraction (ve). From the three-parameter ETM, additionally the plasma volume fraction (vp) could be extracted. From the three-parameter C-TU it was possible to extract information about the blood flow (Fp), permeability-surface area product (PS) and vp. Finally, the four-parameter 2CXM extended the C-TU to include ve. For each voxel, corrected Akaike information criterion (AICc) values were calculated, taking into account both the goodness-of-fit and the number of model parameters. The optimal model was defined as the model with the lowest AICc.

Results: All four TKMs were the optimal model in different contiguous regions of the cervical tumours. For the 24 999 analysed voxels, the TM was optimal in 17.0%, the ETM was optimal in 22.2%, the C-TU in 23.4% and the 2CXM was optimal in 57.3%. Throughout the tumour, a high correlation was found between K(trans)/(TM) and Fp/(2CXM), r = 0.91.

Conclusion: The 2CXM was most often optimal in describing the contrast agent enhancement of pre-treatment cervical cancers, although this model broke down in a subset of the tumour voxels where overfitting resulted in non-physiological parameter estimates. Due to the possible overfitting of the 2CXM, the C-TU was found more robust and when 2CXM was excluded from comparison the C-TU was the preferred model.

Keywords: Cervical Cancer; Dynamic Contrast-Enhanced MRI.

1067. Evaluation of the Frequency and Pattern of Local Recurrence Following Intersphincteric Resection for Ultra-Low Rectal Cancer

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Journal of the Egyptian Cancer Institute, 26: 87-92 (2014)

Introduction: Abdomino-perineal resection has been the standard treatment for rectal tumors located 65 cm from the anal verge. Recently, intersphincteric resection became a valid option which preserves the bowel continuity with better functional outcome.

Aim: Is to evaluate the oncological and functional outcome alongside the associated surgical morbidity in patients with T1-3 rectal cancer, who underwent intersphincteric resection (ISR).

Patients & methods: Between the years 2006 and 2011, 55 patients with invasive rectal adenocarcinoma, T1-3 lesions, located 2–5 cm from the anal verge underwent ISR with total mesorectal excision. When inevitable, complete, optional ISR was performed. Otherwise partial ISR was done. All T3 patients underwent total meso-rectal excision (TME) while some had lateral lymph node dissection (LND) with concomitant pelvic autonomic nerve preservation (PANP). Results: Among the 55 patients, 21 (38.1%) patients were T1-2 and 34 (61.9%) patients were T3. The tumor location range was 0–5 cm from the anal verge (median 2.3 cm). Partial or complete ISR was done for 35 (63.6%) and 20 (36.4%), respectively. Patients were followed for a median of 1.5 years (range 1–4.6 years). The 3 year local recurrence and distant metastasis free rates were 85.2% and 85.6%, respectively. All the 3 local recurrences occurred in T3 patients group, and had positive circumferential resection margins. Overall 3-year disease-free survival was 82.6%; while the overall 3-year survival was 88.7%. Conclusion: Intersphincteric resection with TME does not affect the local recurrence or overall survival rate in early rectal cancer T1-2 & 3, with preservation of bowel continuity and better life quality.

Keywords: Intersphincteric Resection; Local Recurrence; Low Rectal Cancer.

1068. Outcome of Different Oncoplastic Surgical (OPS) Techniques for Centrally Located Breast Cancer (CLBC)

Moustafa A and Fakhr I

Journal Of The Egyptian National Cancer Institute, 26: 203-209 (2014)

Background: Oncoplastic breast surgery is a standard treatment of early breast cancer, offering a balance between good cosmetic outcome and limited risk of locoregional recurrence, by enabling proper resection margins.

Aim of Study: To present multiple techniques of partial breast reconstruction following the resection of centrally located breast cancer (CLBC) resection.

Patients and Methods: From January 2011 to August 2014, 21 patients underwent central quadrantectomy for carcinoma of the central region of the breast. Excisions included the nipple/areola complex, in most of the cases, down to the pectoralis fascia with a wide safety margin, and proper axillary management. Oncoplastic approaches included latissimus dorsi flap, inferior pedicle flap, Melon slice, Grisotti and round block techniques.

Results: Mean age of patients was 49.5 ± 10.61 years. Tumor size ranged from 1.5 to 4.5 cm. Postoperative pathology revealed a tumor mean safety margin of 2.5± 0.83 cm, with positive axillary lymph nodes in 15 (75.0%) patients. Nineteen (95.0%) patients received postoperative breast radiotherapy, while 9/20 (45.0%) and 3/20 (15.0%) received adjuvant chemotherapy or hormonal therapy, respectively, and only 8/20 (40.0%) patients received both therapies. During a median follow-up period of 14.89 months, neither local nor distant metastasis, were detected. The postoperative cosmetic result evaluated by the patients was excellent in 6/20 patients (30.0%), good in 11/20 patients (55.0%), fair in 3/20 (15.0%) with neither poor nor bad results, with an overall mean of 4.0± 0.5 equivalent to 80% satisfaction.

Conclusion: Multiple oncoplastic breast surgery techniques can be used for the resection of CLBC with satisfying cosmetic outcomes.
Keywords: Central Breast Cancer; Oncoplastic Breast Surgery (Obs); Inferior Pedicle Flap; Grisotti Procedure; Melon Slice; Latissimus Dorsi (Ld) Flap; Round Block Technique (Donut Mastopexy Resection).

1069. Pelvic Exenteration and Composite Sacral Resection in the Surgical Treatment of Locally Recurrent Rectal Cancer
Wael Gawad, Medhat Khafagy, Mohamed Gamal, Ibrahim Fakhr, Moustafa Negm, Nadia Mokhtar, Mohamed Lotayef and Osman Mansour

Journal of the Egyptian National Cancer Institute, 26: 167-173 (2014)

Background: The incidence of rectal cancer recurrence after surgery is 5–45%. Extended pelvic resection which entails En-bloc resection of the tumor and adjacent involved organs provides the only true possible curative option for patients with locally recurrent rectal cancer.

Aim: To evaluate the surgical and oncological outcome of such treatment.

Patients and methods: Between 2006 and 2012 a consecutive series of 40 patients with locally recurrent rectal cancer underwent abdominosacral resection (ASR) in 18 patients, total pelvic exenteration with sacral resection in 10 patients and extended pelvic exenteration in 12 patients. Patients with sacral resection were 28, with the level of sacral division at S2–3 interface in 10 patients, at S3–4 in 15 patients and S4–5 in 3 patients.

Results: Forty patients, male to female ratio 1.7:1, median age 45 years (range 25–65 years) underwent extended pelvic resection in the form of pelvic exenteration and abdominosacral resection. Morbidity, re-admission and mortality rates were 55%, 37.5%, and 5%, respectively. Mortality occurred in 2 patients due to perineal flap sepsis and massive myocardial infarction. A R0 and R1 sacral resection were achieved in 62.5% and 37.5%, respectively. The 5-year overall survival rate was 22.6% and the 4-year recurrence free survival was 31.8%.

Conclusion: Extended pelvic resection as pelvic exenteration and sacral resection for locally recurrent rectal cancer are effective procedures with tolerable mortality rate and acceptable outcome. The associated morbidity remains high and deserves vigilant follow up.

Keywords: Recurrent Rectal Cancer; Abdominosacral Resection; Extended Pelvic Exenteration.

1070. When Would We Advocate A Total Thyroidectomy in Cases of Hypopharyngeal Carcinoma?
Zeida Gad, Abdelmaksoud Mohamed and Ibrahim Fakhr

Journal of the Egyptian National Cancer Institute, 26: 93-98 (2014)

Background and Aim: The incidence of invasion of the thyroid gland by hypopharyngeal carcinomas is reported to be up to 57%. Our aim was to analyze the frequency of thyroid gland invasion in hypopharyngeal carcinoma treated by thyroidectomy with total laryngopharyngectomy and to identify patients in whom preservation of the thyroid gland is oncologically feasible and hence reduces post-operative hypothyroidism.

Patients and Methods: This retrospective cohort study included 58 patients with hypopharyngeal squamous cell carcinoma treated by thyroidectomy with total laryngopharyngectomy at the National Cancer Institute, Cairo University between May 1996 and October 2005. Thyroid gland involvement was analyzed through review of charts and pathologic reports. Patients were assessed preoperatively by CT. The correlation between the thyroid gland involvement and the clinical and radiologic CT findings was meticulously examined.

Results: Thyroid gland involvement occurred in 37.9% (22/58) of all patients. T4 hypopharyngeal tumors were present in 29.3% (n = 17/58) of patients, paratracheal LN invasion was present in 37.9% (22/58) of patients, thyroid cartilage invasion was obvious in 19% (11/58) of patients, and previous radiotherapy was present in 5.2% (3/58) of patients. All patients with T4 hypopharyngeal tumors (n = 17/58) and with thyroid cartilage involvement (n = 11/58) had thyroid gland invasion as well. T4 hypopharyngeal tumors, paratracheal LN invasion, and thyroid cartilage invasion were statistically significant factors (P < 0.001, P > 0.009 and P < 0.01 respectively) in independent correlation.

Conclusion: We would advocate a total thyroidectomy in cases of advanced stages of hypopharyngeal carcinoma, bilateral tumors, postrcicoid carcinoma and in all patients with definite radiological evidence of thyroid gland invasion.

Keywords: Hypopharyngeal Cancers; Thyroid Gland; Total Laryngectomy.
Conclusions: We show for the first time that E2-induced hESC proliferation is associated with a shift in glucose metabolism toward aerobic glycolysis, and the molecular basis for this metabolic shift is linked to the effects of E2 on PKM2. In addition, PKM2 acts as a transcriptional coactivator for ERα and small-molecule PKM2 activators inhibit ERα transcriptional activity and reduce E2-induced cell proliferation.

Keywords: Estradiol; Pyruvate Kinase; Estradiol-ALPHA; Pyruvate Kinase; Leiomysoma.

1072. Inhibition of PARP1-Dependent End-Joining Contributes to Olaparib-mediated Radiosensitization in Tumor Cells

Kötter A, Cornils K, Borgmann K, Dahm-Daphi J, Petersen C, Dikomey E and Mansour WY

Molecular Oncology, 8: 1616-1625 (2014) IF: 5.935

Poly-ADP-ribose-polymerase inhibitors (PARPi) are considered to be optimal tools for specifically enhancing radiosensitivity. This effect has been shown to be replication-dependent and more profound in HR-deficient tumors. Here, we present a new mode of PARPi-mediated radiosensitization which was observed in four out of six HR-proficient tumor cell lines (responders) investigated, but not in normal cells. This effect is replication-independent, as the radiosensitization remained unaffected following the inhibition of replication using aphidicolin. We showed that responders are radiosensitized by Olaparib because their DSB-repair is switched to PARP1-dependent end-joining (PARP1-EJ), as evident by (i) the significant increase in the number of residual γH2AX foci following irradiation with 3 Gy and treatment with Olaparib, (ii) the enhanced enrichment of PARP1 at the chromatin after 3 Gy and (iii) the inhibition of end-joining activity measured by a specific reporter substrate upon Olaparib treatment. This is the first study which directly demonstrates the switch to PARP1-EJ in tumor cells and its contribution to the response to Olaparib as a radiosensitizer, findings which could widen the scope of application of PARPi in tumor therapy.

Keywords: Dsb Repair, Parp1-Ej, Olaparib, Radiosensitivity.

1073. Peripheral vein infusion of autologous mesenchymal stem cells in Egyptian HCV-positive patients with end-stage liver disease

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Introduction: We have assessed the utility of autologous mesenchymal stem cell (MSC) peripheral vein infusion as a possible therapeutic modality for patients with end-stage liver diseases.

Methods: Forty patients with post-hepatitis C virus (HCV) end-stage liver disease were randomized into two groups: Group 1 (GI): 20 patients who received granulocyte colony-stimulating factor (G-CSF) for 5 days followed by autologous MSCs peripheral-vein infusion and group 2 (GII): 20 patients who received regular liver-supportive treatment only (control group).

Results: In MSC-infused patients (GI), 54% showed near normalization of liver enzymes and improvement in liver synthetic function. Significant changes were reported in albumin (P = 0.000), bilirubin (P = 0.002), increased international normalized ratio (INR) (P = 0.017), prothrombin concentration (P = 0.029) and alanine transaminase (ALT) levels (P = 0.029), with stabilization of clinical and biochemical status in 13% of cases. None of the patients in GI II showed any significant improvement. Hepatic fibrosis was assessed in GI by detection of procollagen III N peptide level (PIIINP) and procollagen III peptide level (PIIIP). The pretreatment values of s-PIIINP and s-PIIIP were 9.4 ± 4.2 and 440 ± 189, respectively, with a decrease to 8.1 ± 2.6 and 388 ± 102, respectively, 3 months after MSC therapy. However, the difference was statistically nonsignificant (P = 0.7). A significant correlation coefficient was reported from 3 months between the s-PIIINP and prothrombin concentration (P = -0.5) and between s-PIIICP and ascites (P = 0.550).

Conclusions: First, autologous MSC infusion into a peripheral vein is as effective as the previously reported intrahepatic infusion. Second, MSCs have a supportive role in the treatment of end-stage liver disease, with satisfactory tolerability and beneficial effects on liver synthetic functions and hepatic fibrosis. Third, IV infusion of MSCs after G-CSF mobilization improves s-albumin within the first 2 weeks and prothrombin concentration and alanine Taransaminase after 1 month. According to the data from this current study and those previously reported by our group, we recommend further studies on patients’ infusion with pure CD133 and CD34 followed by IV infusion of in vitro-differentiated MSCs within 1 week and another infusion after 3 months.

1074. Hepatitis C Virus Hypervariable Region I Variants Presented on Hepatitis B Virus Capsid-Like Particles Induce Cross-Neutralizing Antibodies

Lange, M; Fiedler, M; Bankwitz, D; Osburn, W; Viazov, S; BrovkO, O; Zekri, AR; Khudyakov, Y; Nassal, M; Pumpens, P; Pietschmann, T; Jimm, J; Roggendorf, M and Walker, A

PLOS ONE, 9 (7): (2014) IF: 3.534

Hepatitis C virus (HCV) infection is still a serious global health burden. Despite improved therapeutic options, a preventative vaccine would be desirable especially in undeveloped countries. Traditionally, highly conserved epitopes are targets for antibody-based prophylactic vaccines. In HCV-infected patients, however, neutralizing antibodies are primarily directed against hypervariable region 1 (HVRI) in the envelope protein E2. HVRI is the most variable region of HCV, and this heterogeneity contributes to viral persistence and has thus far prevented the development of an effective HVRI-based vaccine. The primary goal of an antibody-based HCV vaccine should therefore be the induction of cross-reactive HVRI antibodies. In this study we approached this problem by presenting selected cross-reactive HVRI variants in a highly symmetric repeated array on capsid-like particles (CLPs). SplitCore CLPs, a novel particle antigen presentation system derived from the HBV core protein, were used to deliberately manipulate the orientation of HVRI and therefore enable the presentation of conserved parts of HVRI. These HVRI-CLPs induced high titers of cross-reactive antibodies, including neutralizing antibodies. The combination of only four HVRI CLPs was sufficient to induce antibodies cross-reactive with 81 of 326 (24.8%) naturally occurring HVRI peptides. Most importantly, HVRI CLPs with AS03 as an adjuvant induced antibodies with a 10-fold increase in neutralizing capability. These antibodies were able to neutralize
infectious HCVcc isolates and 4 of 19 (21%) patient-derived HCVpp isolates. Taken together, these results demonstrate that the induction of at least partially cross-neutralizing antibodies is possible. This approach might be useful for the development of a prophylactic HCV vaccine and should also be adaptable to other highly variable viruses.

**Keywords:** Hepadnavirus core proteins; Phase-I trial; Therapeutic vaccines; Cell epitopes; Infection; Display; antigen; Responses; Carrier; Surface.

### 1075. Methylation of Multiple Genes in Hepatitis C Virus Associated Hepatocellular Carcinoma


We studied promoter methylation (PM) of 11 genes in Peripheral Blood Lymphocytes (PBLs) and tissues of hepatitis C virus (HCV) associated hepatocellular carcinoma (HCC) and chronic hepatitis (CH) Egyptian patients. The present study included 31 HCC with their ANT, 38 CH and 13 normal hepatic tissue (NHT) samples. In all groups, PM of APC, FHT, p15, p73, p14, p16, DAPK1, CDH1, RARβ, RASSF1A, O6MGMT was assessed by methylation-specific PCR (MSP). APC and O6-MGMT protein expression was assessed by immunohistochemistry (IHC) in the studied HCC and CH (20 samples each) as well as in a different HCC and CH set for confirmation of MSP results. PM was associated with progression from CH to HCC. Most genes showed high methylation frequency (MF) and the methylation index (MI) increased with disease progression. MF of p14, p73, RASSF1A, CDH1 and O6MGMT was significantly higher in HCC and their ANT. MF of APC was higher in CH. We reported high concordance between MF in HCC and their ANT, MF in PBL and CH tissues as well as between PM and protein expression of APC and O6MGMT. A panel of 4 genes (APC, p73, p14, O6MGMT) classifies the cases independently into HCC and CH with high accuracy (89.9%), specificity (83.9%) and specificity (94.7%). HCV infection may contribute to hepatocarcinogenesis through enhancing PM of multiple genes. PM of APC occurs early in the cascade while PM of p14, p73, RASSF1A, RARB, CDH1 and O6MGMT are late changes. A panel of APC, p73, p14, O6-MGMT could be used in monitoring CH patients for early detection of HCC. Also, we found that, the methylation status is not significantly affected by whether the tissue was from the liver or PBL, indicating the possibility of use PBL as indicator to genetic profile instead of liver tissue regardless the stage of disease.

**Keywords:** Hepatitis C virus-genotype 4; Chronic hepatitis; Hepatocellular carcinoma; Promoter methylation.

### 1076. Chloroquine Synergizes Sunitinib Cytotoxicity Via Modulating Autophagic, Apoptotic and Angiogenic Machineries

Amal Kamal Abdel-Aziz, Samia Shouman, Ebtelhe El-Demerdash, Mohamed Elyendi and Ashraf B. Abdel-Naim

*Chemico-Biological Interactions, 217: 28-40 (2014) IF: 2.982*

Tyrosine kinases play a pivotal role in oncogenesis. Although tyrosine kinase inhibitors as sunitinib malate are used in cancer therapy, emerging studies report compromised cytotoxicity when used as monotherapy and thus combinations with other anti-cancer agents is recommended. Chloroquine is a clinically available anti-malarial agent which has been shown to exhibit anti-cancer activity. In the current study, we questioned whether chloroquine can modulate sunitinib cytotoxicity. We found that chloroquine synergistically augmented sunitinib cytotoxicity on human breast (MCF-7 and T-47D), cervical (Hela), colorectal (Caco-2 and HCT116), hepatocellular (HepG2), laryngeal (Hep2) and prostate (PC3) cancer cell lines as indicated by combination and concentration reduction indices. These results were also consistent with that of Ehrlich ascites carcinoma (EAC) Swiss albino mice models as confirmed by tumor volume, weight, histopathological examination and PCNA expression. Sunitinib induced autophagy via upregulating beclin-1 expression which was blocked by chloroquine as evidenced by accumulated SQSTM1/p62 level. Furthermore, chloroquine augmented sunitinib-induced apoptosis by decreasing survivin level and increasing caspase 3 activity. Chloroquine also enhanced the antiangiogenic capacity of sunitinib as indicated by decreased CD34 expression and peritoneal/skin angiogenesis. Sunitinib when combined with chloroquine also increased reactive nitrogen species production via increasing inducible nitric oxide synthase expression and nitric oxide level whilst reduced reactive oxygen species production by increasing GSH level, activities of glutathione peroxidase and catalase and reducing lipid peroxides compared to sunitinib-only treated group. Taken together, these findings suggest that chloroquine enhanced sunitinib cytotoxicity in a synergetic manner via inducing apoptosis while switching off autophagic and angiogenic machineries. Nevertheless, further studies are required to elucidate the efficacy and safety profile of such combination. (C) 2014 Elsevier Ireland Ltd. All rights reserved.

**Keywords:** Sunitinib; Chloroquine; Autophagy; Apoptosis; Angiogenesis; Oxidative Stress.

### 1077. In Vitro Anti-Proliferative and Anti-Angiogenic Activities of Thalidomide Dithiocarbamate Analogs

El-Aarag BY, Kasai T, Zahran MA, Zakitary NI, Shigeori T, Sekhar SC, Agwa HS, Mizutani A, Murakami H, Kakuta H and Seno M

*Int Immunopharmacol., 21(2): 283-292 (2014) IF: 2.711*

Inhibition of angiogenesis is currently perceived as a promising strategy in the treatment of cancer. The anti-angiogenicity of thalidomide has inspired a second wave of research on this teratogenic drug. The present study aimed to investigate the anti-proliferative and anti-angiogenic activities of two thalidomide dithiocarbamate analogs by studying their anti-proliferative effects on human umbilical vein endothelial cells HUVECs and MDA-MB-231 human breast cancer cell lines. Their action on the expression levels of IL-6, IL-8, TNF-α, VEGF165, and MMP-2 was also assessed. Furthermore, their effect on angiogenesis was evaluated through wound healing, migration, tube formation, and nitric oxide NO assays. Results illustrated that the proliferation of HUVECs and MDA-MB-231 cells was not significantly affected by thalidomide at 6.25-100µM. Thalidomide failed to block angiogenesis at similar concentrations. By contrast, thalidomide dithiocarbamate analogs exhibited significant anti-proliferative action on HUVECs and MDA-MB-231 cells without causing cytotoxicity and also showed powerful anti-angiogenicity in wound healing, migration, tube formation, and NO assays.
Talidomide analogs 1 and 2 demonstrated more potent activity to suppress expression levels of IL-6, IL-8, TNF-a, VEGF165, and MMP-2 than thalidomide. Analog 1 consistently showed the highest potency and efficacy in all the assays. Taken together, our results support further development and evaluation of novel talidomide analogs as anti-tumor and anti-angiogenic agents.

Keywords: Angiogenesis; Migration; No; Thalidomide Dihydrocarbamate Analogs; VEGF.

1078. Expression of microRNA-1234 related signal transducer and activator of transcription 3 in patients with diffuse large B-cell lymphoma of activated B-cell like type from high and low infectious disease areas

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Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous disease, and infectious agents are suspected to be involved in the tumorigenesis of DLBCL. MicroRNAs (miRNAs) are non-coding RNAs modulating protein expression. We compared miRNA expression profiles in lymph node tissues of patients with DLBCL of the activated B-cell (ABC) type from two geographical areas with different background exposures, Sweden and Egypt. We showed previously that DLBCL tissues of the ABC-type in Swedish patients had a higher expression of signal transducer and activator of transcription 3 (STAT3) compared to Egyptian patients. Here, we analyzed the involvement of miRNAs in STAT3 regulation. miR-1234 was significantly up-regulated in Egyptian patients with DLBCL compared to Swedish patients (p < 0.03). The miR-1234 expression level correlated inversely with the expression of STAT3. The Stat3 protein was down-regulated in cells transfected with miR-1234, suggesting that STAT3 might be a potential target for miR-1234. miR-1234 and STAT3 might be involved in the tumorigenesis of DLBCL of ABC type and possibly associated with environmental background exposure.

Keywords: Non-hodgkins-lymphoma; Gene-expression; Cancer; Survival; Targets; Classification; Pathogenesis; Translation; Biogenesis; Pathways.

1079. Circulating tumor and cancer stem cells in hepatitis C virus-associated liver disease

Bahnassy, AA; Zekri, ARN; EI-Bastawisy, A; Fawzy, A; Shetta, M; Hussein, N; Omran, D; Ahmed, AAS and El-Labbady, SS


Aim: To assess the role of circulating tumor cells (CTCs) and cancer stem cells (CSCs) in hepatitis C virus (HCV) associated liver disease.

Methods: Blood and/or tissue samples were obtained from HCV (genotype 4)-associated hepatocellular carcinoma patients (HCC; n = 120), chronic hepatitis C patients (CH; n = 30) and 33 normal control subjects (n = 33). Serum levels of alpha-fetoprotein (AFP), alkaline phosphatase, and alanine and aspartate aminotransferases were measured. Cytoketatin 19 (CK19) monoclonal antibody was used to enumerate CTCs, and CD133 and CD90 were used to enumerate CSCs by flow cytometry. The expression levels of the CSCs markers (CD133 and CD90) as well as telomerase, melanoma antigen encoding gene 1 ( Mage1) and Mage3 were assessed by RTPCR and quantitative real-time polymerase chain reactions. The number of CTCs and/or the expression levels of CK19, CD133, telomerase, Mage1 and Mage3 were correlated to the standard clinicopathologic prognostic factors and disease progression.

Results: Levels of AFP, alkaline phosphatase and aspartate aminotransferase were significantly different among the HCC, CH and control groups (P < 0.001), whereas alanine aminotransferase differed significantly between patient (HCC and CH) and control groups (P < 0.001). At the specified cutoff values determine by flow cytometry, CK19 (49.8), CD90 (400) and CD133 (73) were significantly higher in the blood of HCC patients compared to those in the CH and control groups (P < 0.001). On the other hand, CD133 at a 69.5 cutoff was significantly higher in the CH compared to the control group (P = 0.001). Telomerase, Mage1 and Mage3 RNA were expressed in 55.71%, 60.00% and 62.86% of the HCC patients respectively, but were not detected in patients in the CH or control groups, which were statistically significant (Ps <= 0.001). The expression levels of telomerase, CD90, Mage3, CD133 and CK19 were all significantly associated with high tumor grade and advanced stage in HCC patients (all Ps < 0.05).

Conclusion: CTC counts and AFP, CK19, telomerase, and Mage1/Mage3 expression predict disease progression in patients with HCV, whereas telomerase, Mage3, CD90, CD133 and CK19 are prognostic markers in HCC. (C) 2014 Baishideng Publishing Group Inc. All rights reserved.

Keywords: Cancer stem cells; Circulating tumor cells; Hepatitis C virus genotype-4; Hepatocellular carcinoma.

1080. Differential expression of p53 family proteins in colorectal adenomas and carcinomas: Prognostic and predictive values

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Histology and Histopathology, 29 (2): 207-216 (2014) IF: 2.236

We studied the contribution of p53 family proteins and their isoforms to the development and progression of colorectal carcinoma in relation to VEGF. Methods: p53, p63, p73 and VEGF proteins were assessed in 45 colorectal adenomas (CRAs), 80 carcinomas (CRCs) and 36 normal colonic tissue samples (NCT) by immunohistochemistry. Different p63 and p73 isoforms were assessed by RT-PCR. Aberrant protein and RNA expressions were correlated to patients’ characteristics, disease free and overall survival (DFS& OS).

Results: p53, p63, p73 and VEGF proteins were detected in 22.2%, 73.3%, 33.3%, 46.7% CRAs; in 68.8%, 38.8%, 62.5%, 62.5% CRCs and 16.7%, 83.3%; 13.9%, 27.8% NCT (p<0.05 except for VEGF). Commonest isoforms were TAp63 alpha, Delta Np63, TAp73 alpha in CRA and Delta Np63, TAp63 alpha, Delta Np73, TAp73 beta in CRC. Significant correlations were found between aggressive tumor phenotypes and aberrations in p73, p53, p63, VEGF. DFS correlated with advanced stage, p73 and VEGF aberrations. While advanced stage, positive lymph nodes, p73 and p53 correlated with OS. Prognosis was worse in patients with aberrant p63 & p73 than in those with normal p63 & p73 expression regardless of p53 gene status (p<0.05).

Conclusions: p53 family proteins and VEGF play a pivotal role in colorectal carcinogenesis, p53 prognostic potential is augmented by p73 and p63 aberrations indicating a synergistic
effect between the three family members. Nodal status, stage, p73, VEGF and p53 could be used as predictors of DFS and OS.

**Keywords:** Colorectal carcinoma; Adenoma; p53; VEGF; Prognosis.

**1081. Promoter methylation: Does it affect response to therapy in chronic hepatitis C (G4) or fibrosis?**

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Background and aim. DNA methylation plays a critical role in the control of important cellular processes. The present study assessed the impact of promoter methylation (PM) of some genes on the antiviral response to antiviral therapy and it's relation to the presence of fibrosis in HCV-4 infected patients from Egypt. Material and methods. Clinical, laboratory and histopathological data of 53 HCV-4 infected patients who were subjected to combined antiviral therapy were collected: patients were classified according to their response to treatment and the fibrosis status. The methylation profiles of the studied groups were determined using the following genes: APC, P14ARF, P73, DAPK, RASSF1A, and O6MGMT in patients' plasma. Results. O6MGMT and P73 showed the highest methylation frequencies (64.2 and 50.9%) while P14 showed the lowest frequency (34%). Sustained virological response (SVR) was 54.7% with no significant difference in clinicopathological or laboratory features between the studied groups. PM of O6MGMT was significantly higher in non-responders (p value 0.045) while DAPK showed high methylation levels in responders with no significance (p value: 0.09) and PM of RASSF1A was significantly related to mild fibrosis (p value: 0.019). No significant relations were reported between PM of any of the studied genes and patients' features. Conclusion. PM of some Tumor Suppressor genes increases in chronic active HCV-4. However, only O6MGMT can be used as a predictor of antiviral response and RASSF1A as a marker of marked fibrosis in this small set of patients. An extended study, including more patients is required to validate the results of this preliminary study.

**1082. New insight into HCV E1/E2 region of genotype 4a**

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*Virology Journal, 11: (2014) IF: 2.058*

**Introduction:** Hepatitis C virus (HCV) genome contains two envelope proteins (E1 and E2) responsible for the virus entry into the cell. There is a substantial lack of sequences covering the full length of E1/E2 region for genotype 4. Our study aims at providing new sequences as well as characterizing the genetic divergence of the E1/E2 region of HCV 4a using our new sequences along with all publicly available datasets.

**Methods:** The genomic segments covering the whole E1/E2 region were isolated from Egyptian HCV patients and sequenced. The resulting 36 sequences 36 were analyzed using sequence analysis techniques to study variability within and among hosts in the same time point. Furthermore, previously published HCV E1/E2 sequence datasets for genotype 4a were retrieved and categorized according to the geographical location and date of isolation and were used for further analysis of variability among Egyptian over a period of 15 years, also compared with non-Egyptian sequences to figure out region-specific variability.

**Results:** Phylogenetic analysis of the new sequences has shown variability within the host and among different individuals in the same time point. Analysis of the 36 sequences along with the Egyptian sequences (254 sequences in E1 in the period from 1997 to 2010 and 8 E2 sequences in the period from 2006 to 2010) has shown temporal change over time. Analysis of the new HCV sequences with the non-Egyptian sequences (182 sequences in E1 and 155 sequences in the E2) has shown region specific variability. The molecular clock rate of E1 was estimated to be 5E-3 per site per year for Egyptian and 5.38E-3 for non-Egyptian. The clock rate of E2 was estimated to be 8.48E per site per year for Egyptian and 6.3E-3 for non-Egyptian.

**Conclusion:** The results of this study support the high rate of evolution of the Egyptian HCV genotype 4a. It has also revealed significant level of genetic variability among sequences from different regions in the world.

**Keywords:** HCV; Genotype 4; Variability; Molecular clock.

**1083. Low-Dose Versus Standard-Dose Gemcitabine Infusion And Cisplatin For Patients With Advanced Bladder Cancer: A Randomized Phase II Trial-an Update**


Prolonged infusion of low-dose gemcitabine and cisplatin (GC) proved to be an effective treatment for patients with advanced bladder cancer. One hundred and twenty untreated patients with stage III/IV bladder cancer were randomized to receive either gemcitabine (250 mg/ m2) 6-h infusion on days 1 and 8, and cisplatin (70 mg/m2) on day 2 every 21-day cycle (arm 1) or gemcitabine (1.250 mg/m2) 30-min infusion on days 1 and 8, with the same dose of cisplatin (arm 2). The 92 males and 28 females included in the study had a median age of 62 years (range 40–85 years). Among the 120 patient, complete response was achieved in 11.7 % (760 patients of arm 1) and 5 % (360 patients of arm 2). Eighteen patients in arm 1 (30 %) and 17 patients (28.3 %) in arm 2 had partial response on therapy. Thus, the overall response rate of patients in arm 1 and arm 2 was 41.7 % (25/60 patients) and 33.3 % (20/60 patients), respectively (p = 0.37). No significant difference in median time to disease progression (26 vs. 24 months, p = 0.4), median survival (12 vs. 16 months, p = 0.8), and 1-year survival (49.9 vs. 54.7, p = 0.8) was detected between arms 1 and 2, respectively.

Main toxicities were similar in both arms with no statistically significant differences. Low-dose, prolonged infusion gemcitabine in combination with cisplatin is not inferior to the standard GC regimen with favorable toxicity profile and less financial costs.

**Keywords:** Bladder Cancer; Prolonged Infusion.
1084. Disease progression from chronic hepatitis C to cirrhosis and hepatocellular carcinoma is associated with increasing DNA promoter methylation

Zekri, Abd El-Rahman Nabawy; Nassar, Auhood Abdel-Monem; El-Din El-Rouby, Mahmoud Sour; Shousha, Hend Ibrahim; Barakat, Ahmed Barakat; El-Desouky, Eman Desouky; Zayed, Naglaa Ali; Ahmed, Ola Sayed; El-Din Youssef, Amira Salah; Kaseh, Ahmed Omar; Abd El-Aziz, Ashraf Omar and Bahnassy, Abeer Ahmed

Background: Changes in DNA methylation patterns are believed to be early events in hepatocarcinogenesis. A better understanding of methylation states and how they correlate with disease progression will aid in finding potential strategies for early detection of HCC. The aim of our study was to analyze the methylation frequency of tumor suppressor genes, P14, P15, and P73, and a mismatch repair gene (O6MGMT) in HCV related chronic liver disease and HCC to identify candidate epigenetic biomarkers for HCC prediction.

Materials and Methods: 516 Egyptian patients with HCV-related liver disease were recruited from Kasr Alaini multidisciplinary HCC clinic from April 2010 to January 2012. Subjects were divided into 4 different clinically defined groups - HCC group (n=208), liver cirrhosis group (n=108), chronic hepatitis C group (n=100), and control group (n=100) - to analyze the methylation status of the target genes in patient plasma using EpiTect Methyl qPCR Array technology. Methylation was considered to be hypermethylated if >10% and/or intermediately methylated if >60%.

Results: In our series, a significant difference in the hypermethylation status of all studied genes was noted within the different stages of chronic liver disease and ultimately HCC. Hypermethylation of the P14 gene was detected in 100/208 (48.1%), 52/108 (48.1%), 16/100 (16%) and 8/100 (8%) among HCC, liver cirrhosis, chronic hepatitis and control groups, respectively, with a statistically significant difference between the studied groups (p-value 0.008). We also detected P15 hypermethylation in 92/208 (44.2%), 36/108 (33.3%), 20/100 (20%) and 4/100 (4%) respectively (p-value 0.006). In addition, hypermethylation of PT3 was detected in 136/208 (65.4%), 72/108 (66.7%), 32/100 (32%) and 4/100 (4%) (p-value <0.001). Also, we detected O6MGMT hypermethylation in 84/208 (40.4%), 60/108 (55.3%), 20/100 (20%) and 4/100 (4%) respectively (p-value <0.001).

Conclusions: The epigenetic changes observed in this study indicate that HCC tumors exhibit specific DNA methylation signatures with potential clinical applications in diagnosis and prognosis. In addition, methylation frequency could be used to monitor whether a patient with chronic hepatitis C is likely to progress to liver cirrhosis or even HCC. We can conclude that methylation processes are not just early events in hepatocarcinogenesis but accumulate with progression to cancer.

1085. IL28B rs12979860 Gene Polymorphism in Egyptian Patients with Chronic Liver Disease Infected with HCV

Zekri, ARN; Salama, H; Medhat, E; Bahnassy, AA; Morsy, HM; Lotfy, MM; Ahmed, R; Darwish, T and Marei, MS

Background: Egypt has one of the highest prevalences of hepatitis C virus (HCV) infection worldwide. Although the IL28B gene polymorphism has been shown to modify the course of chronic HCV infection, this has not been properly assessed in the Egyptian population.

Materials and Methods: The IL28B rs12979860 single nucleotide polymorphism (SNP) was therefore examined in 256 HCV-infected Egyptian patients (group II) at different stages of disease progression and in 48 healthy volunteers (group I). Group II was subdivided into GII-A (chronic hepatitis patients, n=119), GII-B (post hepatitis cirrhosis, n=66) and GII-C (HCC on top of cirrhosis, n=71).

Results: The C/T genotype was the commonest in all groups. It was more frequent in GI (52%) than in GII (48%). There was no significant difference in the frequency of C/T and C/C or T/T genotypes between groups and subgroups (p=0.82). Within the subgroups; the C/C genotype was more common in GII-B while C/T and T/T genotypes were more common in GII-C, though with no significant difference (p=0.59 and p=0.80). There was no significant association between IL28B rs12979860 SNP and viral load, ALP, AFP level, METAVIR scores for necro-inflammation and fibrosis, and Child-Pugh classification.

Conclusions: 1) IL28Brs12979860 C/T genotype is the commonest genotype in HCV-associated CH and HCC in Egypt. 2) IL28Brs12979860 polymorphisms are not associated with disease progression or aggression (histological staging, severity of fibrosis in CH or the incidence of post-HCV HCC). 3) Differences in IL28Brs12979860 genotypes could be a consequence of environmental or ethnic variation. Keywords: HCV; IL28B gene (rs12979860) polymorphism; chronic hepatitis; hepatocellular carcinoma.

1086. Assessment of the Prognostic Value of Methylation Status and Expression Levels of FHit, GSTP1 and P16 in Non-Small Cell Lung Cancer in Egyptian Patients

Haroun RA, Zakhary NI, Mohamed MR, Abdelrahman AM, Kandil EI and Shalaby KA.

Background: Methylation of tumor suppressor genes has been investigated in all kinds of cancer. Tumor specific epigenetic alterations can be used as a molecular markers of malignancy, which can lead to better diagnosis, prognosis and therapy. Therefore, the aim of this study was to evaluate the association between gene hypermethylation and expression of fragile histidine triad (FHit), glutathione S-transferase P1 (GSTP1) and p16 genes and various clinicopathologic characteristics in primary non-small cell lung carcinomas (NSCLC).

Materials and Methods: The study included 28 primary non-small cell lung carcinomas, where an additional 28 tissue samples taken from apparently normal safety margin surrounding the tumors served as controls. Methylation-specific polymerase chain reaction (MSP) was performed to analyze the methylation status of FHit, GSTP1 and p16 while their mRNA expression levels were measured using a real-time PCR assay with SYBR Green I.

Results: The methylation frequencies of the genes tested in NSCLC specimens were 53.6% for FHIT, 25% for GSTP1, and 0% for p16, and the risk of FHit hypermethylation increased among patients with NSCLC by 2.88, while the risk of GSTP1 hypermethylation increased by 2.33. Hypermethylation of FHit
gene showed a highly significant correlation with pathologic stage (p<0.01) and a significant correlation with smoking habit and FHIT mRNA expression level (p<0.05). In contrast, no correlation was observed between the methylation of GSTP1 or p16 and smoking habit or any other parameter investigated (p>0.05).

Conclusions: RESULTS of the present study suggest that methylation of FHIT is a useful biomarker of biologically aggressive disease in patients with NSCLC. FHIT methylation may play a role in lung cancer later metastatic stages while GSTP1 methylation may rather play a role in the early pathogenesis.

1087. Modulatory Effects of L-Carnitine on Tamoxifen Toxicity and Oncolytic Activity: In Vivo Study

Ibrahim AB, Mansour HH, Shouman SA, Eissa AA, Abu El Nour SM

Human and Experimental Toxicology, 33: 968-979 (2014) IF: 1.407

The aim of this study was to investigate the protective effect of L-carnitine (L-CAR) in tamoxifen (TAM)-induced toxicity and antitumor activity. Adult female rats were randomly divided into four groups. Group I was served as control, groups II and III were treated with TAM (10 mg/kg, periorally) and L-CAR (300 mg/kg, intraperitoneally), respectively, while group IV was treated with both compounds. The treatment continued daily for 28 days. Administration of TAM resulted in significant increase in serum lipid profiles, liver enzymes, and bilirubin level. TAM produced a significant increase in lipid peroxides (LPO) level and nonsignificant change in nitrogen oxide (NO(x)) level accompanied with significant decrease in superoxide dismutase (SOD) activity of hepatic and uterus tissues and significant decrease in glutathione (GSH) content of uterus tissue. Administration of L-CAR for 1 h prior to TAM treatment decreased serum lipids and liver enzymes significantly and significantly increased SOD activity in liver and uterus tissues compared with TAM-treated group. Furthermore, it restored LPO and GSH levels and increased NO(x) level in uterus tissue. DNA fragmentation and the apoptotic marker, caspase-3, were not detected in the liver of all treated groups. Histopathologically, alterations in the liver and uterus structures after TAM treatment, which was attenuated after L-CAR administration. The antitumor effect and survival of the combined treatment of Ehrlich ascites carcinoma (EAC)-bearing mice was less than each one alone. L-CAR interestingly increased survival rate of EAC-bearing mice more than TAM-treated group. In conclusion, L-CAR has beneficial effects regarding TAM toxicity; however, it interferes with its antitumor effect.

Keywords: Tamoxifen; L-Carnitine; Organ Toxicity; Antitumor Activity; Antioxidants.

1088. Pharmacokinetics of Vancomycin in Oncology Egyptian Paediatrics: A Dosage Adjustment Trial

MA Mahmoud, A. H. I. M. Ebid, Samia A Shouman and Emad N Ebid

Indian J Pharm Sci, 76: 82-86 (2014) IF: 0.296

The purpose of this study is to determine the pharmacokinetic parameters of vancomycin in Egyptian paediatric oncology patients and to evaluate the factors that influence the variability of the pharmacokinetic parameters in this population. Vancomycin serum concentration at steady state was determined in 51 paediatric cancer patients who were treated with vancomycin multiple intravenous infusions. Also individual vancomycin pharmacokinetic parameters were calculated assuming one compartment model. The mean vancomycin total body clearance and mean vancomycin volume of distribution were significantly higher among the age range of 2 to <12 years as compared with older age. Obese patients showed significant lower values of peak and trough vancomycin concentrations than those of normal and underweight patients. A significant correlation was found between the estimated creatinine clearance (Schwartz formula) and vancomycin total body clearance in the studied patients. Also, a significant direct correlation between vancomycin volume of distribution and ratio between blood urea nitrogen (mg/dl)/weight (kg) was found. As a conclusion, age and obesity were identified as the most important factors influencing vancomycin total body clearance, volume of distribution and serum concentrations in the studied patients.

Keywords: Oncology; Paediatrics; Pharmacokinetics; Vancomycin.

Dept. of Tumor Pathology

1089. Ki-67 is a Powerful Tool for Grading Neuroendocrine Tumors Neuroendocrine Tumors Among Egyptian Patients: A 10-Year Experience

Salama A, Badawy O and Mokhtar N

Journal Of Cancer Research And Clinical Oncology, 140: 653-661 (2014) IF: 3.009

Background: Neuroendocrine tumors (NETs) arise in most organs of the body and share many common pathologic features. However, a variety of organ-specific systems have been developed for nomenclature, grading and staging of NETs, causing much confusion. In collaboration with WHO, the European Neuroendocrine Tumor Society (ENETS) recommended the use of either mitotic rate or Ki-67 labeling index (LI) for grading and classification. We aim to explore the profile of NETs in Egyptian patients and apply the ENETS system.

Materials And Methods: This retrospective study was carried out on all cases of NETs diagnosed at the Pathology Department, National Cancer Institute, Cairo University, during the period from January 2000 to December 2009. Data about age, sex, anatomic site of tumor, tumor size, tumor stage and presence of nodal metastasis were retrieved. Ki-67 immunostaining and grading according to ENETS were done.

Results: There was a trend toward increased mean age and tumor size and grade according to Ki-67, with significant statistical difference (p < 0.001 and 0.036, respectively). Estimation of mitotic count and Ki-67 LI was strongly associated with NET histopathologic types, but this association was stronger regarding Ki-67 LI than mitotic count (p = 0.002 and 0.035, respectively).

Conclusion: Ki-67 LI was strongly associated with NET histopathologic types, but this association was stronger regarding Ki-67 LI than mitotic count (p = 0.002 and 0.035, respectively). On the other hand, there was discordance between grading according to mitotic count and grading according to Ki-67 LI in relation to NET histopathologic subtypes. Concordance between mitotic rate and Ki-67 LI was reported in 18.89% of cases, while discordance occurred in 81.11% of cases and was more prevalent in G3.

Keywords: Neuroendocrine Tumors; Grading; Ki-67.
Faculty of Physical Therapy

Dept. of Physical Therapy for Neurorhabilitation

1090. Aerobic Exercises Enhance Cognitive Functions and Brain Derived Neurotrophic Factor in Ischemic Stroke Patients

El-Tamawy MS, Abd-Allah F, Ahmed SM, Darwish MH and Khalifa HA


Background: Stroke is a leading cause of functional impairments. High percentage of these patients will experience some degree of cognitive affection, ranging from mild cognitive impairment to dementia.

Objective: Demonstrate the role of aerobic exercises enhancing cognitive functions and its effect on Brain Derived Neurotrophic factor (BDNF) in post-ischemic stroke patients in the territory of anterior circulation.

Subjects and Methods: We included thirty Egyptian ischemic stroke patients in the territory of anterior circulation. They were divided into 2 groups; group 1 (G1) were subjected to physiotherapy program without aerobic exercises and group 2 (G2) were subjected to the same previous program followed by aerobic exercises. Both groups were subjected to pre- and post-treatment Addenbrooke's Cognitive Examination- Revised (ACER) and serum level of BDNF.

Results: Our results showed a significant improvement in ACER score in G2 compared to G1 post-treatment (p = 0.017). BDNF serum level significantly increased in G2 post-treatment compared to pre-treatment (p = 0.001) and compared to G1 group (p = 0.0458). ACER improvement was positively correlated to increase in serum level of BDNF (r = 0.53, p = 0.044).

Conclusion: Aerobic exercises improve cognitive functions of ischemic stroke patients. This improvement is related to the increase in serum level of BDNF.

Keywords: Stroke; Aerobic Exercises; Bdnf.

Dept. of Physical Therapy for BioMechanics

1091. Isokinetic Imbalance of Hip Muscles in Soccer Players With Osteitis Pubis

Mohammad WS, Abdelraouf OR, Elhafez SM, Abdel-Aziem AA and Nassif NS.


In this study, we compared the isokinetic torques of hip flexors/extensors and abductors/adductors in soccer players suffering from osteitis pubis (OP), with normal soccer players. Twenty soccer male athletes with OP and 20 normal soccer athletes were included in this study. Peak torque/body weight (PT/BW) was recorded from hip flexor/extensor and abductor/adductor muscles during isokinetic concentric contraction modes at angular velocity of 2.1 rad · s⁻¹, for both groups. The results showed a significant difference between the normal and OP groups for hip flexors (P < 0.05). The normal group had significant, lower PT/BW value than the OP group for their hip flexors (P < 0.05). The hip flexor/extensor PT ratio of OP affected and non-affected limbs was significantly different from that of normal dominant and non-dominant limbs. There were no significant differences between the normal and OP groups for hip extensor, adductor and abductor muscles (P > 0.05). Regarding the hip adductor/abductor PT ratio, there was no significant difference between the normal and OP groups of athletes (P > 0.05). The OP group displayed increase in hip flexor strength that disturbed the hip flexor/extensor torque ratio of OP. Therefore, increasing the hip extensor strength should be part of rehabilitation programmes of patients with OP.

Keywords: Osteitis Pubis; Isokinetic; Hip Muscles.

1092. Chronic Ankle Instability Alters Eccentric Eversion/Inversion and Dorsiflexion/Plantarflexion Ratio

Abdel-aziem AA and Draz AH


Objective: To determine if the eccentric evertor/invertor and dorsiflexor/plantar-flexor ratio are altered in subjects with chronic ankle instability.

Methods: Twenty chronic ankle instability (CAI) subjects as an experimental group, and twenty healthy subjects as a control group, were matched in age, gender, and activity level. CAI subjects have a history of at least one ankle sprain and repeated episodes of giving way were included in CAI group. Subjects with no prior history of ankle injury were included in the control group. Ankle evertor/invertor and dorsiflexor/plantar-flexor muscles eccentric torque ratios were measured using the eccentric muscle contraction at angular velocities 60 and 120°/s.

Results: Analysis of variance revealed that the eccentric contraction eversion/inversion ratio of CAI group was significantly lower than normal group ratio at angular velocities 60 and 120°/s (p = 0.041 and 0.012) respectively. The eccentric contraction dorsiflexion/plantarflexion ratio of CAI group was significantly higher than normal group ratio at both angular velocities (p = 0.036 and 0.013) respectively. Moreover, at angular velocities of 60°/s and 120°/s a deficit in inversion and eversion eccentric torques were identified in CAI group (p = 0.000), plantarflexion torque deficit of CAI group (p = 0.034 and 0.028), respectively, and no deficit was identified for dorsiflexion torque of CAI group (p = 0.595 and 0.696) respectively.

Conclusion: Chronic ankle instability increases the dorsiflexion/plantarflexion muscles torque ratio and decreases the eversion/inversion ratio at angular velocities 60 and 120°/s. Therefore, the restoration of a normal eccentric eversion, eversion, and plantarflexion strength may prevent recurrent lateral ankle ligament sprain.

Keywords: Eccentric Contraction, Chronic Ankle Instability, Ankle Muscles.

1093. Concentric and Eccentric Strength of Trunk Muscles in Osteitis Pubis Soccer Players

Sayed Mohammad W, Ragaa Abdelraouf O, Abdel-aziem AA


Background and Objectives: Osteitis pubis refers to a painful, inflammatory condition involving the pubic bones, pubic symphysis, and adjacent structures. So, the aims of the study were to evaluate the strength of trunk muscles of soccer players suffering from osteitis pubis, and to compare the agonist/antagonist ratio of trunk muscles in osteitis pubis athletes with that of healthy athletes.
Materials and Methods: Twenty-five soccer male athletes with osteitis pubis, and 25 healthy soccer athletes. Peak torque/body weight (PT/BW) was recorded from trunk muscles during isokinetic concentric and eccentric contraction modes at a speed of 120°/s for healthy and osteitis pubis soccer players.

Results: There was a significant decrease in concentric contraction of back muscles in osteitis pubis group (p=0.01). A significant decrease in eccentric contraction of abdominal muscles was also recorded in osteitis pubis group (p=0.008). Concentric abdominal/back muscles ratio was significantly higher in osteitis pubis group (p=0.016), with no significant difference in eccentric abdominal/back muscles ratio between both groups (p=0.05).

Conclusion: Osteitis pubis group displayed concentric weakness of back muscle and eccentric weakness of abdominal muscles that lead to disturbance of the normal concentric abdominal/back ratio.

Keywords: Osteitis Pubis; Isokinetic; Trunk Muscles; Ratio.

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1094. Effect of Ultrasound Combined With Conventional Therapy on Neck Pain, Function, and Disability in Patients With Cervical Spondylosis: A Randomized Placebo-Controlled Trial

Amr Almaz Abdel-aziem, Amira Hussin Draz, Kadrya Hosny Battecha and Dalia Mohammed Mosaad

Journal of Musculoskeletal Pain, 22: 199-205 (2014) IF: 0.316

Objective: The purpose of this study was to evaluate the effect of continuous ultrasound [US] compared with placebo US combined with conventional physiotherapy program for patients with cervical spondylosis.

Methods: This was a randomized placebo-controlled trial. Patients, diagnosed with cervical spondylosis, were randomly assigned to one of two groups in an orthopedic physical therapy clinic: a group that received electrotherapy, exercise, hot packs, and therapeutic US [True US group] and a group that received electrotherapy, exercise, hot packs, and sham US [Sham US group]. Patients were treated, on average, three times per week for 4 weeks. Outcome measurements were collected at baseline and after 4 weeks using the Numeric Pain Rating Scale, Patient-Specific Functional Scale, and Neck Disability Index.

Results: Analysis of variance showed that both groups had improved regarding Numeric Pain Rating Scale, Patient-Specific Functional Scale, and Neck Disability Index [p=0.05]. There was no significant difference between both groups for pretest and post-test values [p=0.05] for all measures.

Conclusions: The addition of US to conventional physiotherapy program of electrotherapy, exercise, and hot packs yields no additional benefit to neck pain, function, or disability in patients with cervical spondylosis.

Keywords: Physical therapy; Cervical spondylosis; Ultrasound.

1095. Three-dimensional analysis of gait in postmenopausal women with low bone mineral density

Abeer M EIDeeb and Amr S Khodair


Background: There's lack in the literature respecting changes in the trunk and hip angles, and power profile of the lower extremities in postmenopausal women with low bone mineral density (BMD). Therefore, this study aimed to examine gait characteristics of that population, and find out which characteristics may be predictors to BMD. This may provide suitable interventions for subjects with osteoporosis.

Methods: Seventeen healthy postmenopausal women and seventeen with low BMD engaged in this study. Dual X-ray Absorbiometry measured BMD at lumbar (L2-4) and femoral neck. Qualysis gait analysis system assessed the gait pattern of each subject.

Results: Compared to healthy peers, women with low BMD showed less trunk rotation (p = 0.02), hip adduction (p = 0.005) and extension moments (p = 0.008). They showed less hip power generation during early stance (H1S) (p = 0.000), and swing phase (H3S) (p = 0.005), and less hip power absorption (H2S) (p = 0.005). They also, showed less knee power absorption during terminal swing (K4S) (p = 0.002), and ankle power generation at push off (A2S) (p = 0.02). The ability of the gait variables to discriminate between subjects with or without osteopenia was (72%, p = 0.016) for trunk rotation, (78%, p = 0.0004) for hip adductor moment, (76%, p = 0.0013) for hip extensor moment, (87%, p < 0.0001) for H1S, (79%, p = 0.0001) for H2S, (77%, p = 0.0008) H3S, (81%, p = 0.0001) for K4S, and (93%, p < 0.0001) for A2S.

Conclusion: Less power generation at the hip and ankle as well as, less power absorption at the hip and knee, may suggest that postmenopausal women with low BMD showed less propulsion, and stability during walking.

Trunk rotation, hip adduction and extension moments, H1S, H2S, H3S, K4S, and A2S are significant predictors for low bone mass in the postmenopausal women.

Keywords: Gait; Moment; Power; Bone mineral density; Menopause.

Dept. of Physical Therapy of Surgery

1096. Efficacy of Shock Wave Therapy on Chronic Diabetic Foot Ulcer: A Single-Blinded Randomized Controlled Clinical Trial

Omar MT, Alghadir A, Al-Wahhabi KK and Al-Askar AB


Objective: This study was conducted to evaluate the efficacy of extracorporeal shock wave therapy (ESWT) on the healing rate, wound surface area and wound bed preparation in chronic diabetic foot ulcers (DFU).

Methods: Thirty eight patients with 45 chronic DFU were randomly assigned into; the ESWT group (19 patients/24 ulcers) and the control group (19 patients/21 ulcers). Blinded therapist measured wound surface area (WSA), the percentage of reduction in the WSA, rate of healing and wound bed preparation at baseline, after the end of the interventions (W8), and at 20-week follow-up (W20). The ESWT group received shock wave therapy twice per week for a total of eight treatments. Each ulcer was followed up at a frequency of 100 pulse/cm², and energy flux density of 0.11 mJ/cm². All patients received standardized wound care consisting of debridement, blood-glucose control agents, and footwear modification for pressure reduction.


Results: The overall clinical results showed completely healed ulcers in 33.3% and 54% in ESWT-groups and 14.28% and 28.5% in the control group after intervention (W8), and at follow-up (W20) respectively. The average healing time was significantly lower (64.5 ± 8.06 days vs 81.17 ± 4.35 days, p < 0.05) in the ESWT-group compared with the control group.

Conclusion: ESWT-treated ulcers had a significant reduction in wound size and median time required for ulcer healing, with no adverse reactions. So, the ESWT is advocated as an adjunctive therapy in chronic diabetic wound.

Keywords: Shock Wave Therapy; Diabetic Foot Ulcers; Wound Bed Preparation.

1097. Effect of Low-Level Laser Therapy in Patients With Chronic Knee Osteoarthritis: A Single-Blinded Randomized Clinical Study

Alghadir A, Omar MT, Al-Askar AB and Al-Muteri NK.


The aim of this study was to investigate the effect of low-level laser therapy (LLLT) on pain relief and functional performance in patients with chronic knee osteoarthritis (OA). Forty patients with knee OA were randomly assigned into active laser group (n = 20) and placebo laser group (n = 20). The LLLT device used was a Ga-As diode laser with a power output of 50 mW, a wavelength of 850 nm, and a diameter beam of 1 mm. Eight points were irradiated and received dosage of 6 J/point for 60 s, with a total dosage of 48 J/cm(2) in each session. The placebo group was identical but treated without emission of energy. LLLT was applied two times per week over the period of 4 weeks. Outcome measurements included pain intensity at rest and at movement on visual analog scale, knee function using Western Ontario McMaster Universities Osteoarthritis Index scale, and ambulation duration. These measurements were collected at baseline and post-intervention. The results showed significant improvements in all assessment parameters in both groups compared to baseline. Active laser group showed significant differences in pain intensity at rest and movement, knee function, and ambulation duration when compared with the placebo group. Therefore, LLLT seemed to be an effective modality for short-term pain relief and function improvement in patients with chronic knee OA.

Keywords: Low-level laser therapy; Knee; Osteoarthritis; Pain.

1098. Effect of Isokinetic Training on Muscle Strength, Size and Gait After Healed Pediatric Burn: A Randomized Controlled Study

Ebid AA, El-Shamy SM and Draz AH

Burns, 40: 97-105 (2014) IF: 1.836

Objective: The aim of this study is to investigate the effects of isokinetic training program on muscle strength, muscle size and gait parameters after healed pediatric burn. Design: Randomized controlled trial.

Subjects: Thirty three pediatric burned patients with circumferential lower extremity burn with total body surface area (TBSA) ranged from 36-45%, their age ranged from 10-15 years participated in the study and were randomized into isokinetic group and a control group. Non-burned healthy pediatric subjects were assessed similarly to burned subjects and served as matched healthy controls.
Osteoarthritis (OA) is the most common form of arthritis and a leading cause of disability in older adults. Conservative non-pharmacological strategies, particularly exercise, are recommended by clinical guidelines for its management. The aim of this study was to assess the effectiveness of acupressure versus isometric exercise on pain, stiffness, and physical function in knee OA female patients. This quasi experimental study was conducted at the inpatient and outpatient sections at Al-kasr Al-Aini hospital, Cairo University. It involved three groups of 30 patients each: isometric exercise, acupressure, and control. Data were collected by an interview form and the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) scale. The study revealed high initial scores of pain, stiffness, and impaired physical functioning. After the intervention, pain decreased in the two intervention groups compared to the control group (p < 0.001), while the scores of stiffness and impaired physical function were significantly lower in the isometric group (p < 0.001) compared to the other two groups. The decrease in the total WOMAC score was sharper in the two study groups compared to the control group. In multiple linear regression, the duration of illness was a positive predictor of WOMAC score, whereas the intervention is associated with a reduction in the score. In conclusion, isometric exercise and acupressure provide an improvement of pain, stiffness, and physical function in patients with knee OA. Since isometric exercise leads to more improvement of stiffness and physical function, while acupressure acts better on pain, a combination of both is recommended. The findings need further confirmation through a randomized clinical trial.

Keywords: Knee osteoarthritis; Acupressure; Isometric exercise; Pain; Stiffness; Physical function.
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## Authors’ Index

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