

## EDITORIAL

**AN OVERVIEW OF THE HISTORY, APPLICATIONS, ADVANTAGES, DISADVANTAGES AND PROSPECTS OF GENE THERAPY**

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Gene therapy has become a significant issue in science-related news. The principal concept of gene therapy is an experimental technique that uses genes to treat or prevent disease. Although gene therapy was originally conceived as a way to treat life-threatening disorders (inborn defects, cancers) refractory to conventional treatment, it is now considered for many non-life-threatening conditions, such as those adversely impacting a patient's quality of life. An extensive range of efficacious vectors, delivery techniques, and approaches for developing gene-based interventions for diseases have evolved in the last decade. The lack of suitable treatment has become a rational basis for extending the scope of gene therapy. The aim of this review is to investigate the general methods by which genes are transferred and to give an overview to clinical applications. Maximizing the potential benefits of gene therapy requires efficient and sustained therapeutic gene expression in target cells, low toxicity, and a high safety profile. Gene therapy has made substantial progress albeit much slower than was initially predicted. This review also describes the basic science associated with many gene therapy vectors and the present progress of gene therapy carried out for various surface disorders and diseases. The conclusion is that, with increased pathobiological understanding and biotechnological improvements, gene therapy will become a standard part of clinical practice.

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## EDITORIAL

**EXTRACORPOREAL SHOCKWAVES AS REGENERATIVE THERAPY IN  
ORTHOPEDIC TRAUMATOLOGY: A NARRATIVE REVIEW FROM BASIC  
RESEARCH TO CLINICAL PRACTICE**

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**Extracorporeal Shock Wave Therapy (ESWT), after its first medical application in the urological field for lithotripsy, nowadays represents a valid therapeutical tool also for many musculoskeletal diseases, as well as for regenerative medicine applications. This is possible thanks to its mechanisms of action, which in the non-urological field are not related to mechanical disruption (as for renal stones), but rather to the capacity, by mechanotransduction, to induce neoangiogenesis, osteogenesis and to improve local tissue trophism, regeneration and remodeling, through stem cell stimulation. On the basis of these biological assumptions, it becomes clear that ESWT can represent a valid therapeutic tool also for all those pathological conditions that derive from musculoskeletal trauma, and are characterized by tissue loss and/or delayed healing and regeneration (mainly bone and skin, but not only). As a safe, repeatable and non-invasive therapy, in many cases it can represent a first-line therapeutic option, as an alternative to surgery (for example, in bone and skin healing disorders), or in combination with some other treatment options. It is hoped that with its use in daily practice also the muscle-skeletal field will grow, not only for standard indications, but also in post-traumatic sequelae, in order to improve recovery and shorten healing time, with undoubted advantages for the patients and lower health service expenses.**

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## EDITORIAL

**HEADACHE, MIGRAINE AND OBESITY: AN OVERVIEW ON PLAUSIBLE LINKS**

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**Headache can represent different disorders with different etiologies; including cardiac, cerebral, vascular, psychiatric, metabolic, neurologic diseases. Recent studies have highlighted that obesity is significantly associated with headache and disability in adults. This rule also applies to children. This review focuses on literature data studying any eventual relationship between headache, migraine and obesity [shown in Body Mass Index (BMI)] in children. Research data have highlighted that there is a relationship between headache physiopathology and central and peripheral mechanisms responsible for food assumption. In this regard, neurotransmitters such as serotonin, and peptides such as orexin and adipocytokines (adiponectin and leptin) seem to play a key role both in food assumption and in headache pathogenesis. These data further emphasize the potential association between headache and BMI. Therefore, those therapeutic strategies aiming to decrease BMI may represent a model of useful treatment to understand whether weight loss reduces the incidence and the severity of headache in obese children. In conclusion, considering the effects of obesity and weight loss on the natural history of headache, important changes are expected in therapeutic management of paediatric headaches.**

## EDITORIAL

**ENDOCRINOLOGY OF THE SKIN: INTRADERMAL NEUROIMMUNE NETWORK,  
A NEW FRONTIER**

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**Endocrinology systems exert an important effect on vascular function and have direct actions on blood vessels. Estrogens provoke an increase in skin elasticity, epidermal hydration, skin thickness, reduce skin wrinkles and augment the content of collagen and the level of vascularisation. Therefore, there is an intricate cross-talk between skin conditions and stress. In stress,  $\beta$ 2-adrenoreceptor ( $\beta$ 2AR) pathway, cortisol, epinephrine and norepinephrine increase DNA damage and interfere with the regulation of the cell cycle, contributing to aging and skin diseases. Substance P is a neuropeptide released in the skin from the peripheral nerve and is related to stress and inflammation. SP provokes infiltration of inflammatory cells in the skin and induces a variety of cytokines/chemokines. Corticotropin-releasing hormone (CRH), produced by mast cells, is a neuropeptide also expressed in skin and responds to stress. CRH initiates diverse intracellular signaling pathways, including cAMP, protein kinase C, and mitogen-activated protein kinases (MAPK). Under stress, CRH, glucocorticoids, epinephrine and cytokines are generated. Moreover, the release of ACTH binds the receptor MC2-R and stimulates the generation of glucocorticoids such as corticosterone and cortisol, which interact with the transcription factors AP-1 and NF- $\kappa$ B. In skin keratinocytes, ACTH promotes the generation of pro-inflammatory cytokines, which enhances T-cell activity. Cortisol is immunosuppressive by inhibiting Th1 and Th2 cell response, antigen presentation, antibody and cytokine/chemokine production. However, glucocorticoids are certainly helpful in Th1-mediated autoimmune disorders. On the other hand, cytokines, such as TNF, IL-1 and IL-6, stimulate the generation of CRH and activate HPA axis in inflammatory states. Here, we describe for the first time a cross-talk between endocrinology and skin, including pro-inflammatory cytokines and neurogenic inflammatory pathways.**

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## REGULATORY EFFECT OF miRNA ON MULTI-DIRECTIONAL DIFFERENTIATION ABILITY OF MESENCHYMAL STEM CELL IN TREATMENT OF OSTEOPOROSIS

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This study was designed to evaluate the effect of miRNA acting in regulating multi-directional differentiation ability of mesenchymal stem cell in treatment of osteoporosis (OP), with the aim of finding a new idea and approach for clinical treatment of OP. Estrogen deficiency-induced OP mice model was established by means of ovariectomy (OVX). Additionally, a sham group was set up for control. Bone Marrow Mesenchymal Stem Cells (BMMSCs) of OVX group (O/BMMSCs) and BMMSCs of sham group (S/BMMSCs) were separately cultured. Then surface markers of BMMSCs were detected. Multi-directional differentiation ability was identified in the two groups by giving cells targeted induced stimulation. It was found that the bone trabecula, bone density and bone volume fraction of distal femoral metaphysis in the OVX group were much lower than those of the sham group. Moreover, trabecular bone space in the OVX group became larger; O/BMMSCs and S/BMMSCs both had normal expression of surface markers as well as potentials of osteogenic and adipogenic differentiation; O/BMMSCs had a weaker osteogenic capability but a stronger adipogenic capability than S/BMMSCs. All the findings suggest that the regulatory effect of miRNA on multi-directional differentiation ability plays a vital role in the treatment of OP, and there is a close correlation between them; deficiency or functional defect of BMMSCs can result in the occurrence of OP.

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## TARGETING LEUKEMIC SIDE POPULATION CELLS BY ISATIN DERIVATIVES OF NICOTINIC ACID AMIDE

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Side population (SP) cells mediate chemoresistance in leukemia. However, chemical inhibition approach to target SP cells has been poorly studied. Herein, we report the discovery of isatin derivatives of nicotinic acid amide as potent side population cell inhibitors. The selected derivatives showed superior potency over the reference drug verapamil. Furthermore, the treatment increased chemosensitivity and inhibited the cell proliferation on three different leukemic cell lines, K562, THP-1 and U937, suggesting that both SP and the bulk of leukemic cells are affected. Moreover, treatment with the most potent compound Nic9 reduced the expression of ABCG2, demonstrating that side population inhibition effect of the target derivatives is at least via ABCG2 inhibition. Importantly, the target derivatives induced erythrocyte/dendritic differentiation to leukemic cells mainly through Musashi/Numb pathway modulation.

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## INVASION AND METASTASIS ABILITY OF RENAL CANCER CELL STRAINS 786-0: UNDER THE INFLUENCE OF miR-141

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**This study aimed to explore the invasion and metastasis ability of miR-141 in 786-0 renal cancer tissue cells, as well as identify the key function of endogenous miR-141 in adjustment and control of malignant activities of renal cancer. The renal cancer cell strain with overexpression of miR-141 and its control renal cancer cell line were constructed; methyl thiazolyl tetrazolium (MTT) assay was adopted to measure proliferation of renal cancer cells; Transwell assay was performed to measure the invasion and metastasis ability of cells; MTT assay and fluorescence activated cell sorting (FACS) were used for measurement of cell apoptosis and drug susceptibility. Results indicated that the expression of miR-141 in 786-0 cells could be significantly increased 400-fold by slow viruses that contained miR-141; moreover, comprehensive functions showed that miR-141 inhibited the invasion and metastasis ability of renal cancer cells to a great extent ( $p < 0.001$ ), partially inhibited cell growth ( $p < 0.05$ ) and also induced cell cycle to be arrested in G0/G1 as well as reducing the number of cells in S phase (DNA replicative phase). Moreover, miR-141 could not induce morphologic changes of renal cancer cells, had no direct stimulating effect on cell apoptosis and could not improve the drug susceptibility of renal cancer cells to drugs such as cis-Dichlorodiamineplatinum (DDP), 5-fluorouracil (5-FU) and tumor-related apoptosis-inducing ligand (TRAIL). In conclusion, miR-141 can be considered an important cancer suppressor gene of renal cancer by inhibiting proliferation and metastasis of renal cancer cells.**

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## CO-SUPPRESSION OF VITAMIN C COMPOSITE NANO-DRUG CARRIER AND ITS DRUG DELIVERY TO NIDUS IN TUMOR CELLS

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**This study aimed to discuss the co-suppression of vitamin C-contained composite nano-drug carrier and its drug delivery to nidus in tumor cells. Amphiphilic polymers PLA-block-PAAA and block polymer PLA-PEG4000-Maleimide, PLA-block-PAAA and PLA-PEG4000-Maleimide composite nano-micelles were prepared, and, PLA-block-PAAA polymer-coated Nile red nano-micelle, PLA-block-PAA and PLA-PEG4000-Maleimide composite nano-micelles as well as paclitaxel-carrying composite nano-micelle in different molar ratios were given stability tests. Lastly, PLA-block-PAAA and PLA-PEG4000-Maleimide composite nano-micelle cancer cells and paclitaxel-carrying composite nano-micelle cancer cells were given toxicity tests. Stability tests showed that self stability of PLA-block-PAAA (63/8) nano-micelle was not sufficient; the stability was good when the molar ratio of PLA-block-PAAA and PLA-PEG4000-Maleimide composite nano-micelle was 3:1; paclitaxel-carrying composite nano-micelle had good stability within 48 hours; PAAA segment had an inhibiting effect on C6 cancer cells and paclitaxel-carrying composite nano-micelle had a strong inhibiting effect also on tumors. After 24 hours, with the continuous release of paclitaxel, the tumor inhibiting effect of paclitaxel-carrying composite nano-micelle enhanced gradually, and the controlled-release of drugs had continuous inhibiting effect on tumor cells. Therefore, PAAA segment and paclitaxel had time-postponed synergistic effect. In conclusion, vitamin C-contained composite nanometer drug carrier materials can deliver anti-cancer drugs to nidus and thus inhibit tumor cells.**

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## REGULATORY EFFECT OF ESTROGEN RECEPTOR- $\alpha$ -MEDIATED Wnt/ $\beta$ -CATENIN SIGNALING PATHWAY ON OSTEOBLAST PROLIFERATION

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This study was designed to investigate the regulatory effect of estrogen receptor- $\alpha$  (ER $\alpha$ )-mediated Wnt/ $\beta$ -catenin signaling pathway on osteoblast proliferation. Mc3T3-E1 cells were infected by ER $\alpha$  and ER $\beta$  small interfering ribose nucleic acid (siRNA) viruses and treated with estradiol 2 (E2) for 120 min after 24-h infection. Western blot was used to detect expressions of  $\beta$ -catenin, Gsk 3 $\beta$ , p-Gsk3 $\beta$  (Ser9) and CyclinD1; and methyl thiazolyl tetrazolium (MTT) was applied to detect osteoblast proliferation after interference by different ERs. Western blot results indicated that the expressions of  $\beta$ -catenin, p-Gsk3 $\beta$  (Ser9) and CyclinD1 decreased after ER $\beta$  interference and ER $\alpha$  + ER $\beta$  joint interference, and a more obvious decrease was found after the joint interference. After ER $\beta$  interference,  $\beta$ -catenin, p-Gsk3 $\beta$  (Ser9) and CyclinD1 were strongly expressed compared with expressions in the blank control group. MTT results demonstrated that the proliferation rate of osteoblast was lower after the joint interference than after ER $\beta$  interference, while a slight increase was found in the proliferation rate after ER $\beta$  interference in comparison with the blank control group. It can be concluded that estradiol is able to promote the proliferation of osteoblasts in mice by ER $\alpha$ -mediated Wnt/ $\beta$ -catenin signaling pathway.

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**ACTIVATION OF PROTEIN PHOSPHATASE 2A IS RESPONSIBLE FOR INCREASED CONTENT AND INACTIVATION OF RESPIRATORY CHAIN COMPLEX I INDUCED BY ALL-TRANS RETINOIC ACID IN HUMAN KERATINOCYTES**

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**This study presents the effect of all-trans retinoic acid (ATRA) on cell growth and respiratory chain complex I in human keratinocyte cultures. Keratinocyte treatment results in increased level of GRIM-19 and other subunits of complex I, in particular of their carbonylated forms, associated with inhibition of its enzymatic activity. The results show that in keratinocytes ATRA-promoted phosphatase activity controls the proteostasis and activity of comp**

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## Wnt SIGNALING PATHWAY INHIBITORS AS PROMISING DIAGNOSTIC SERUM MARKERS OF OSTEOLYTIC BONE METASTASIS

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Despite the clinical importance of bone metastases, we still know little about their onset and progression and current diagnostic tools lack the sensitivity and specificity required for clear early diagnosis. We therefore need to continue studying the pathogenesis of bone metastatic invasion in order to improve diagnosis. The Wnt pathway has been described as having an important role in bone carcinogenesis and metastatic progression. This study investigated the diagnostic potential of the two main Wnt inhibitors, sclerostin and DKK-1, to improve the detection of osteolytic bone metastases. We measured sclerostin and DKK-1, MMP-2 and MMP-9, the bone resorption marker TRAP5b and the metastatic marker survivin in a control group of healthy patients, in patients with primary tumors and in a group with metastasis. Sclerostin and DKK-1 were clearly high in primary tumor patients and even higher in metastatic patients, compared to controls. The close correlations with metastatic markers and bone resorption markers make sclerostin and DKK-1 promising as new biomarkers in the diagnosis of bone osteolytic metastases.

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## HYALURONAN SCAFFOLD SUPPORTS OSTEOGENIC DIFFERENTIATION OF BONE MARROW CONCENTRATE CELLS

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Osteochondral lesions are considered a challenge for orthopedic surgeons. Currently, the treatments available are often unsatisfactory and unable to stimulate tissue regeneration. Tissue engineering offers a new therapeutic strategy, taking into account the role exerted by cells, biomaterial and growth factors in restoring tissue damage. In this light, Mesenchymal Stem Cells (MSCs) have been indicated as a fascinating tool for regenerative medicine thanks to their ability to differentiate into bone, cartilage and adipose tissue. However, in vitro-cultivation of MSCs could be associated with some risks such as de-differentiation/reprogramming, infection and contaminations of the cells. To overcome these shortcomings, a new approach is represented by the use of Bone Marrow Concentrate (BMC), that could allow the delivery of cells surrounded by their microenvironment in injured tissue. For this purpose, cells require a tridimensional scaffold that can support their adhesion, proliferation and differentiation. This study is focused on the potentiality of BMC seeded onto a hyaluronan-based scaffold (Hyaff-11) to differentiate into osteogenic lineage. This process depends on the specific interaction between cells derived from bone marrow (surrounded by their niche) and scaffold, that create an environment able to support the regeneration of damaged tissue. The data obtained from the present study demonstrate that BMC grown onto Hyaff-11 are able to differentiate toward osteogenic sense, producing specific osteogenic genes and matrix proteins.

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## VASCULAR ENDOTHELIAL GROWTH FACTOR AND NITRIC OXIDE SYNTHASE EXPRESSION IN HUMAN TOOTH GERM DEVELOPMENT

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Vascular Endothelial Growth Factor (VEGF) and Nitric Oxide Synthase (NOS) expression, were evaluated in human tooth germs at two different stages of embryogenesis, to clarify the role of angiogenesis during tooth tissue differentiation and growth. Seventy-two third molar germ specimens were selected during oral surgery. Thirty-six were in the early stage and 36 in the later stage of tooth development. The samples were evaluated with Semi-quantitative Reverse Transcription-Polymerase chain Reaction analyses (RT-PcR), Western blot analysis (WB) and immunohistochemical analysis. Western blot and immunohistochemical analysis showed a VEGF and NOS 1-2-3 positive reaction in all samples analysed. VEGF high positive decrease reaction was observed in stellate reticulum cells, ameloblast and odontoblast clusters in early stage compared to later stage of tooth germ development. Comparable VEGF expression was observed in endothelial cells of early and advanced stage growth. NOS1 and NOS3 expressions showed a high increased value in stellate reticulum cells, and ameloblast and odontoblast clusters in advanced stage compared to early stage of development. The absence or only moderate positive reaction of NOS2 was detected in all the different tissues. Positive NOS2 expression showed in advanced stage of tissue development compared to early stage. The action of VEGF and NOS molecules are important mediators of angiogenesis during dental tissue development. VEGF high positive expression in stellate reticulum cells in the early stage of tooth development compared to the later stage and the other cell types, suggests a critical role of the stellate reticulum during dental embryomorphogenesis.

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LETTER TO THE EDITOR

**THE PREVALENCE OF CHLAMYDIA PNEUMONIAE IN THE AORTIC WALL AND IN PERIPHERAL BLOOD OF PATIENTS SCHEDULED FOR CORONARY ARTERY BYPASS GRAFTING**

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Some reports confirm a potential role of *Chlamydia pneumoniae* (ChP) in atherogenesis. In order to explore possible association between ChP and atherosclerosis, investigations were carried out in which the frequency of ChP in the arterial wall and peripheral blood was assessed in a group of patients with chronic coronary artery disease (CAD). Fifty-seven patients were enrolled in the study, 13 women and 44 men aged 61.8±6.5 (47-74), with previously diagnosed CAD, scheduled for planned coronary artery bypass grafting due to clinical indications. Vessel specimens retrieved from the ascending aorta (as a part of routine proximal venous graft development procedure) and peripheral blood mononuclear cells (PBMCs) from venous blood were evaluated for the presence of ChP DNA. Genomic DNA was extracted from PBMCs and vessel specimens. Quantitative real-time polymerase chain reaction (qPCR) was performed to detect ChP DNA. A statistically more frequent occurrence of ChP was observed in aortic tissues compared to blood samples (70.2% vs 56.1%, respectively). Similarly, the number of ChP DNA genomic copies [n/1µg genomic DNA] was significantly higher in tissue specimens compared to blood samples (89±91 vs 41±77, respectively; p=0.0046). In patients without ChP in blood specimens, we observed significantly higher amounts of ChP in tissue specimens compared to patients with ChP in blood specimens (156±71 vs 107±88, respectively; p=0.0453). No correlation was found between the number of ChP DNA copies [n/1µg genomic DNA] in blood and in aortic specimens. The infection of ChP in the aortic wall was connected with hypercholesterolemia (p=0.029) and diabetes (p=0.03). We conclude that *Chlamydia pneumoniae* is a pathogen frequently occurring in the aortic wall of patients with CAD. The occurrence of ChP DNA in the aortic tissue is related to classic CAD risk factors such as diabetes and dyslipidemia.

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

*LETTER TO THE EDITOR***ARTICULAR CAPSULE REPAIR IN INITIAL ARTIFICIAL HIP REPLACEMENT VIA ANTEROLATERAL APPROACH TO THE HIP JOINT**

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**This study was carried out to explore articular capsule repair in first artificial hip replacement (AHR) via anterolateral approach and its influence on postoperative dislocation. A total of 292 patients who received AHR via anterolateral approach and had the articular capsule repaired in People's Hospital of Zhengzhou (Henan, China) from February 2008 to February 2014 were selected and divided into total hip replacement (THR) group (group A1) and artificial femoral head replacement (AFHR) group (group A2). Five hundred and five cases in the control group treated using the same approach but receiving no articular capsule repair were divided into THR group (group B1) and AFHR group (group B2). Condition of postoperative dislocation was compared between the two groups. All cases were followed up for 6 months to 5 years (average: 3.75 years); it was noted that the difference in average age, gender, disease constitution and follow-up time in the two groups was not significant ( $P>0.05$ ). Moreover, groups A1 and B1 were found with 1 case of early hip joint dislocation (0.73%) and 13 cases of hip joint dislocation (5.24%) respectively post-operatively, and the comparison between the two groups was statistically significant ( $P<0.05$ ). One case of hip joint dislocation (0.65%) was found in group A2 and 5 cases (1.95%) in group B2 in early post operation and the difference between two groups had no statistical significance ( $P>0.05$ ). Neither the repair group nor the control group developed late-onset dislocation after the operation. Thus, we can state that articular capsule repair is feasible during the first AHR via anterolateral approach, which decreases the occurrence of early hip joint dislocation after operation and proves that repairing articular capsule during AFHR via anterolateral approach is unnecessary.**

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## LETTER TO THE EDITOR

**PSYCHOLOGICAL STRESS MODERATES THE RELATIONSHIP BETWEEN  
RUNNING VOLUME AND CD4+ T CELL SUBPOPULATIONS**

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**Endurance-based exercise training can lead to alterations in components of the immune system, but it is unknown how psychological stress (another potent immunomodulator) may impact these changes. The purpose of this study was to determine the moderating role of psychological stress on exercise-induced immune changes. Twenty-nine recreational runners were recruited for this study four weeks before completing a marathon. Each subject reported: weekly training volume (miles/wk) for the week prior to the study visit; completed the Perceived Stress Scale (PSS), the state version of the State-Trait Anxiety Inventory (STAI) and the Penn State Worry Questionnaire (PSWQ); and donated blood for assessment of CD4+ T cell subpopulations and mitogen-induced cytokine production. Participants ran an average of 30 ( $\pm 13.4$ ) miles (1 mile=1.6 km) per week. Average values (SD) for immune biomarkers were: regulatory T cells (Treg), 3.2% ( $\pm 1.2\%$ ); type 1 regulatory cells (Tr1), 27.1% ( $\pm 8.3\%$ ); T helper 3 (Th3), 1.8% ( $\pm 0.7\%$ ); interferon gamma (IFN $\gamma$ ), 3.1 pg/ml ( $\pm 1.0$ ); interleukin (IL)-4, 1.4 pg/ml ( $\pm 1.1$ ); IFN $\gamma$ /IL-4, 8.6 ( $\pm 1.2$ ); IL-10, 512 pg/ml ( $\pm 288$ ). There was a significant relationship between running volume and both Treg cell numbers (slope of the regression line ( $\beta$ )=0.05,  $p < 0.001$ ) and IL-10 production ( $\beta$ =-10.6,  $p = 0.002$ ), and there was a trending relationship between running volume and Tr1 cell numbers ( $\beta$ =-0.2%,  $p = 0.064$ ). Perceived stress was a trending moderator of the running volume-Treg relationship, whereas worry was a significant moderator of the running volume-IFN $\gamma$  and running volume-IFN $\gamma$ /IL-4 relationships. These data indicate that various forms of psychological stress can impact endurance exercise-based changes in certain immune biomarkers. These changes may reflect an increased susceptibility to clinical risks in some individuals.**

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## LETTER TO THE EDITOR

**ASSESSMENT OF MAGNESIUM INFLUENCE ON FATTY ACID CONTENT IN ISOLATED RAT HEPATOCYTES SUBJECTED TO INCUBATION**

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Magnesium salts are components of many dietary supplements used in treatment or prevention of magnesium deficiency. Hypomagnesemia usually results from an improper lifestyle, including unbalanced diet. Isolated hepatocytes of animals or humans are the preferred model used to study the *in vitro* effects of exogenous factors on cellular metabolic changes. The aim of this study was to evaluate the content of saturated, monounsaturated and polyunsaturated fatty acids and their esters in isolated rat hepatocytes influenced by different magnesium concentrations. The isolated rat hepatocytes were used as the test material. Hepatocytes were prepared in culture medium (Hepatocyte Medium) + MgCl<sub>2</sub> solution to concentrations of 2 mM/dm<sup>3</sup> MgCl<sub>2</sub>, 4 mM/dm<sup>3</sup> MgCl<sub>2</sub>. After incubation with different concentrations of magnesium ions, changes in the content of fatty acids and their esters were found for the whole hepatocytes and hepatocyte membranes. Despite changes in the fatty acid content in the whole hepatocytes and their membranes, there were no changes in the coefficient of degree of saturation of fatty acids when different concentrations of MgCl<sub>2</sub> were used.

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LETTER TO THE EDITOR

**INSULIN PUMP FOR THE TREATMENT OF DIABETES IN COMBINATION WITH  
ULCERATIVE FOOT INFECTIONS**

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*Received September 1, 2015 – Accepted March 29, 2016*

Ulcerative foot infection is a chronic complication frequently seen in diabetic patients, and can result in disability. To evaluate insulin pump treatment for type 2 diabetes in combination with ulcerative foot infection, we selected 168 diabetic patients who developed foot ulcers and received treatment from April 2012 to April 2014 in the People's Hospital of Zhengzhou, Henan, China. The patients were divided into a treatment group and a control group, 84 in each group. Besides anti-infection treatment, patients in the control group were given multiple subcutaneous insulin injection (MSII), while patients in the treatment group were given continuous subcutaneous insulin infusion (CSII). Ulcer area, fasting plasma glucose (FPG), C-reactive protein (CRP) and count of white blood cells (WBC) were recorded before treatment, one week after treatment, two weeks after treatment and four weeks after treatment; moreover, ulcer healing condition was recorded four weeks after treatment and the related factors were analyzed. Patients in the treatment group showed an obviously narrowed ulcer area two and four weeks after treatment ( $P<0.05$ ) and significantly lowered levels of FPG, CRP and WBC in the 1st, 2nd and 3rd weeks after treatment ( $P<0.05$ ); four weeks after treatment, 88.1% of patients in the treatment group and 66.7% in the control group had healed well, and the difference between two groups was statistically significant ( $\chi^2=5.509$ ,  $P=0.019$ ). Multi-factor logistic regression analysis indicated that levels of FPG, CRP and WBC at baseline and four weeks after treatment had a positive correlation to ulcer healing ( $P<0.05$ ). All the above findings suggest that insulin pump can improve ulcer healing of patients suffering from diabetic foot ulcers as it effectively controls blood glucose level, restrains inflammatory reaction and prevents spreading of infection.

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## LETTER TO THE EDITOR

**CONTINUOUS PLASMA FILTRATION ADSORPTION IN TREATMENT OF SEVERE INFECTION-INDUCED MULTIPLE ORGAN DYSFUNCTION SYNDROME**

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**Multiple organ dysfunction syndrome (MODS), a high-risk disease, has a fatality rate of 70%. To improve treatment of this disease, in recent years many scholars have explored the pathological and physiological changes of MODS. To observe the curative effect of continuous plasma filtration adsorption (CPFA) in the treatment of MODS, we selected 96 patients who were diagnosed with severe infection-induced MODS and were treated in the First Affiliated Hospital of Zhengzhou University between February 2012 and October 2014 and divided them into an observation group and a control group. Besides conventional treatment, the observation group was also given CPFA in combination with high volume hemofiltration (HVHF), while the control group only received HVHF. Changes of blood routine index, balance of electrolyte and acid-base as well as vital signs were observed before and after treatment. Also, blood, kidney and blood gas were examined. For all patients, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6) and C-reactive protein (CRP) were recorded at the start of treatment (0 h), and 5 h and 10 h after treatment. It was found that both therapies could lower blood urea nitrogen (BUN) and creatinine levels and maintain balance of electrolyte and acid-base, but had no obvious influence on leukocyte, blood platelet and hematocrit. In the observation group, PaO<sub>2</sub>/FiO<sub>2</sub> and mean arterial pressure (MAP) were significantly improved after surgery ( $P < 0.05$ ), while Acute Physiology and Chronic Health Evaluation (APACHE) II score had an obvious decrease ( $P < 0.05$ ). In contrast, the control group was observed with insignificantly changed PaO<sub>2</sub>/FiO<sub>2</sub>, MAP and APACHE II score ( $P > 0.05$ ). TNF- $\alpha$ , IL-6 and CRP levels of the two groups had no statistically significant difference at the start of treatment ( $P > 0.05$ ), but TNF- $\alpha$ , IL-6 and CRP levels of the observation group became remarkably lower than those of the control group 5 h and 10 h after treatment ( $P < 0.05$ ). Therefore, CPFA is proved to be safe and effective in treating patients with severe infection-induced MODS as it can lower the level of proinflammatory cytokines and improve the level of anti-inflammatory cytokines; thus, it is worthy of clinical promotion.**

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## LETTER TO THE EDITOR

**VENA-VENOUS HEMOFILTRATION IN TREATING SEVERE INJURY-INDUCED  
MULTIPLE ORGAN DYSFUNCTION SYNDROME**

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Yu Fang and Lu Zhang contributed equally to this work

**Severe multiple injury (SMI) can induce multiple organ dysfunction syndrome (MODS) and easily result in complications, as well as having a high mortality rate. To explore the curative effect of continuous vena-venous hemofiltration (CVVH) in treating MODS and its effect on serum tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-10 and nitric oxide (NO), we selected 200 patients who suffered from SMI and received treatment in the First Affiliated Hospital of Zhengzhou University between April 2012 and April 2014 as research subjects. All patients were treated with CVVH. Vital signs, blood oxygen pressure (PaO<sub>2</sub>) and oxygenation index (OI) of artery, electrolyte and acid-base balance were observed before and after treatment. Before treatment, 1 h and 12 h after the start of treatment, and at the end of treatment, TNF- $\alpha$  and IL-10 concentrations in serum and ultrafiltrate were tested using enzyme linked immunosorbent assay, and NO concentration in serum and ultrafiltrate was detected using nitrate reduction method. After treatment, heart rate and respiratory rate of patients had significant decline ( $P < 0.05$ ) and average arterial pressure rose remarkably ( $P < 0.05$ ); blood urea nitrogen and creatinine decreased ( $P < 0.05$  or  $0.01$ ); PaO<sub>2</sub> and OI were both significantly increased ( $P < 0.01$ ); hyperkalemia and acidosis were effectively corrected ( $P < 0.01$ ); but differences of Na<sup>+</sup>, Ca<sup>2+</sup> and Cl<sup>-</sup> before and after treatment had no statistical significance ( $P > 0.05$ ). Serum IL-10 concentration had a significant increase after treatment, while TNF- $\alpha$  and NO concentrations had a significant decline after treatment. A small quantity of IL-10, but not of TNF- $\alpha$ , was detected from ultrafiltrate. Concentration of NO in ultrafiltrate was higher. It can be concluded that CVVH can effectively relieve clinical symptoms of MODS patients, improve function of organs, correct electrolyte disturbance and acid-base imbalance and eliminate TNF- $\alpha$  and NO in serum, which is effective in improving the ratio of successful rescue of patients developing MODS.**

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## LETTER TO THE EDITOR

**BLCA-4 AND UBC COMBINED DETECTION FOR EARLY DIAGNOSIS  
OF BLADDER CANCER**

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The objective of the present study was to report the clinical significance of bladder cancer specific nuclear matrix protein 4 (BLCA-4) and urinary bladder cancer (UBC) on early diagnosis of bladder cancers. Enzyme-linked immunosorbent assay (ELISA) was used to detect BLCA-4 and UBC of 56 bladder cancer patients and 26 patients with urinary tract benign diseases, serving as controls. Urine exfoliated cell test was performed, and then the significance of BLCA-4 and UBC on the diagnosis of bladder cancers was analyzed. The sensitivity of BLCA-4 and UBC of the bladder cancer patients was significantly higher than that of the urine exfoliated cell test ( $P < 0.05$ ). The difference of BLCA-4 and UBC was not significant ( $P > 0.05$ ). The difference of BLCA-4 and UBC in the tumors with different gradings and stagings was not significant ( $P > 0.05$ ). Combined detection of BLCA-4 and UBC could improve the diagnosis sensitivity and specificity of bladder cancers with the advantages of high maneuverability, repeatability and objective results.

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*LETTER TO THE EDITOR*

**THROMBIN IN COMBINATION WITH INTENSIVE NURSING IN TREATING UPPER GASTROINTESTINAL BLEEDING IN CHILDREN**

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*Received September 10, 2015 – Accepted April 13, 2016*

**Pediatric upper gastrointestinal bleeding, a commonly seen pediatric emergency, needs timely symptomatic treatment to avoid a worse outcome. To discuss the clinical effect of thrombin treatment in combination with intensive nursing on pediatric upper gastrointestinal bleeding, this study analyzed 128 children who were treated in the second ward of the Children's Internal Medical Department in the First Affiliated Hospital of Zhengzhou University between February 2012 and December 2014. The patients were divided into two groups, an experimental group and a control group. Besides thrombin, the experimental group was given intensive nursing, consisting of regular nursing and targeted nursing, while the control group was given regular nursing only. Clinical indexes of the two groups, such as effective rate, nursing satisfaction and side effect rate, were compared. Relevant clinical indexes such as duration of hospital stay, time to stopping of bleeding and Self-Rating Anxiety Scale (SAS) score, as well as overall satisfaction level of the observation group were all better than those of the control group and differences between the two groups had statistical significance ( $P < 0.05$ ). Furthermore, difference of overall effective rate between the experimental group (90.63%) and the control group (68.75%) was significant. Difference of incidence of side effects between the two groups was statistically significant. Thus thrombin treatment in combination with intensive nursing proved to have a remarkable clinical effect and high safety level in treating pediatric upper gastrointestinal bleeding and, moreover, it shortens treatment time and enhances the patients' quality of life.**

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## LETTER TO THE EDITOR

**ELEVATED EXPRESSION OF RUNT-RELATED TRANSCRIPTION FACTORS IN HUMAN ABDOMINAL AORTIC ANEURYSM**

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*Received July 10, 2015 – Accepted April 20, 2016*

Abdominal aortic aneurysm (AAA) is a multifactorial disease of unknown etiology. AAA is caused by segmental weakening of the aortic walls and progressive aortic dilation leading to the eventual rupture of the aorta, accompanied by intense inflammation. Additionally, studies have indicated a close relationship between the pathogenesis and progression of AAA and cellular immune responses in aneurysm wall tissue. The Runt-related genes (RUNX) encode multifunctional mediators of the of intracellular signal transduction pathways in vascular remodeling, endothelial function, immune response and inflammation. The aim of this study was to evaluate the expression level of RUNX regulatory genes in AAA tissues and to assess the correlations between them. The study was performed on AAA wall-tissue samples obtained from patients with AAA during open aneurysm repair and normal aortic tissues collected from healthy organ donors. There are no proven clinical management strategies or pharmaco-therapeutics to prevent AAA progression once an AAA has been detected. Moreover, so far no biomarkers have been established to indicate the disease status of AAA. Hence, understanding the pathogenesis of AAA has recently become an increasing priority in basic and translational vascular research. We identified significantly higher mRNA and protein level of all of three Runt-related genes in aneurysmal aorta compared to a normal aorta. Increased expression of RUNX2 was demonstrated for the first time in abdominal aortic aneurysm tissue. Additionally, relationships between the activity of RUNX genes in the pathological tissue were identified. The results of elevated expression of RUNX genes and their relationships in the AAA tissues suggest the involvement of conserved Runt-related genes in the pathophysiology of AAA development.

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LETTER TO THE EDITOR

**EFFECT OF EMBOLIC MICROSPHERES IN THE TREATMENT  
OF PRIMARY HEPATIC CARCINOMA**

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The first two authors contributed equally to this work.

**The purpose of this study was to evaluate the clinical effect of embolic microspheres in the treatment of primary hepatic carcinoma. Fifty-eight patients who were confirmed with primary hepatic carcinoma by imaging were retrospectively analyzed. They were firstly perfused with 50 mg of oxaliplatin and 40 mg of epirubicin. Embolic microspheres were then injected into the distal end of targeted blood vessels. After this procedure, dynamic observation was carried out until tumor stain disappeared. Liver function and blood indexes were reexamined on days 5, 6, 7 and 28 after treatment, and moreover, the liver was examined with Magnetic Resonance Imaging (MRI) or computed tomography (CT). Compared to traditional lipiodol embolization, embolic microspheres did not aggregate the damage on liver function and the imaging examination suggested necrosis of some tumor tissues. Embolic microspheres proved to be effective in treating primary hepatic carcinoma. It produces no damage on liver function and can lead to significant shrinkage of hepatic carcinoma and necrosis of some tumor tissues. Embolic microspheres, which merely block distal branches of tumor-feeding artery, can avoid collateral circulation induced by permanent blocking, thus achieve a good treatment effect.**

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## LETTER TO THE EDITOR

**COMPUTED TOMOGRAPHY DIAGNOSIS OF NEONATAL HYPOXIC ISCHEMIC ENCEPHALOPATHY COMBINED WITH INTRACRANIAL HEMORRHAGE AND CLINICAL NURSING TREATMENT**Y. ZHANG<sup>1</sup>, J.L. ZHANG<sup>2</sup> and Y. LI<sup>3</sup>

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Hypoxic ischemic encephalopathy (HIE), one of the common causes of newborn invalidism, is likely to induce nervous system-associated sequelae and even intracranial hemorrhage in severe cases. The incidence rate of HIE has been rising in recent years. In order to study the clinical nursing effect for HIE combined with intracranial hemorrhage, 76 newborns diagnosed with HIE combined with intracranial hemorrhage by spiral computed tomography (CT) from the of Binzhou People's Hospital, Shandong, China were selected. They were divided into a control group and an intervention group. The control group received routine nursing, while the intervention group received comprehensive nursing intervention. The experimental results suggested that the mental developmental index (MDI) value and the psychomotor developmental index (PDI) value of patients in the intervention group were much higher than those of the control group and the difference was significant ( $p<0.05$ ). The curative effect of the intervention group was remarkably better than that of the control group and the difference was also statistically significant ( $p<0.05$ ). Moreover, the intervention group had a lower incidence rate of untoward reactions. All the findings suggest that comprehensive nursing intervention can help newborns diagnosed with HIE combined with intracranial hemorrhage recover more effectively, therefore is worth applying.

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LETTER TO THE EDITOR

**CHANGES IN PHAGOCYTOSIS AND EXPRESSION OF MICROGLIAL CELLS IN CRANIOCEREBRAL INJURY MICE MODELS**

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The objective of this study was to investigate the changes in phagocytic function and expression quantities of CD11b and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) among microglia cells of craniocerebral injury mice. Modified Feeney method was used to establish the craniocerebral injury mice models. Twenty-one male SPF mice were divided into a control group and a trauma group. The scalp was incised and a bone window was opened in the control group without cerebral injury. In the trauma group, the mice were sacrificed after the craniocerebral injury at 1, 3, 6, 12, 24 and 48 h to make frozen sections of cerebral tissues. The phagocytic rate of microglia cells was observed by using fluorescent microsphere. The changes in the expression quantities of CD11b and TNF- $\alpha$  were detected by enzyme-linked immuno sorbent assay (ELISA). The phagocytic ability of the microglia cells after the craniocerebral injury increased at 1 h after injury compared with that of the control group ( $P < 0.01$ ). The expression of surface antigen CD11b of the microglia cells and the expression of TNF- $\alpha$  increased at 1, 3, 6, 12, 24 and 48 h after the injury compared with those of the control group ( $P < 0.01$ ). The phagocytic ability of the microglia cells increased. The expressions of CD11b and TNF- $\alpha$  were also gradually enhanced in the acute phase after craniocerebral injury, and then gradually decreased to the normal level. The expressions of CD11b and TNF- $\alpha$  indicated a high consistency with the changing trend of the phagocytic ability, suggesting that the microglia cells may participate in the regulation of the inflammatory process of the central nervous system through absorbing apoptotic cells and increasing and secreting inflammatory and anti-inflammatory factors.

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## LETTER TO THE EDITOR

**LACTULOSE ORAL SOLUTION FOR THE TREATMENT OF POSTPARTUM CONSTIPATION**P. HUANG<sup>1</sup>, WL. GOU<sup>1</sup>, XT. WANG<sup>2</sup>, YL. DING<sup>3</sup>, J. HE<sup>4</sup> and CH. WANG<sup>5</sup>

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The purpose of this study is to explore the effectiveness and safety of lactulose oral solution in treating puerperal constipation. The lactulose group was given lactulose, 15 ml once a day, and then given a maintenance dose of 5 ~ 15 ml/time according to defecation condition of patients. Maintenance treatment lasted for one week if the symptoms were relieved; but once symptoms recurred, the medication was restored. Patients in the control group were blank controls. The treatment lasted for six weeks. The conditions of patients, adverse events and combined medication were recorded every day. Patients were evaluated with SF-36 scale before and after treatment. Two hundred and eleven patients with postpartum constipation were selected from five research institutes and they were divided into lactulose group (n=106) and control group (n=105). The curative effect and the improvement of symptoms of the lactulose group were much better than those of the control group ( $p < 0.01$ ). Constipation in the lactulose group relieved faster compared to the control group ( $p < 0.05$ ). Number of days without constipation in the lactulose group was much more than that of the control group ( $p < 0.05$ ). Defecation time in the lactulose group was shorter than that of the control group ( $p < 0.05$ ). Dose of lactulose in the lactulose group reduced week by week. Differences of general physical conditions in SF-36 scale between two groups were statistically significant ( $p < 0.05$ ). Various vital signs of the two groups had no significant changes after treatment. It can be concluded that, lactulose is an effective and safe drug for treating postpartum constipation.

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LETTER TO THE EDITOR

**EFFECT OF OPCML GENE ON THE BIOLOGICAL BEHAVIOR OF GASTRIC  
CANCER CELL LINE AGS**

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*Received December 18, 2015 – Accepted April 4, 2016*

The objective of this investigation was to explore the association of OPCML with gastric cancer and its clinical significance. The expression of OPCML was detected by immunohistochemistry in 118 cases of gastric carcinoma. The OPCML expression in the normal tissues and 7 kinds of gastric cells was assessed by RT-PCR. The recombinant plasmid pcDNA3.1-OPCML was constructed and transfected into AGS cells. CCK8 and colony formation assay were employed to analyze the effect of OPCML on AGS. Immunohistochemistry results showed that the expression of OPCML in gastric cancer was 68.6%, and the expression of OPCML was negatively correlated with the depth of tumor invasion and tumor differentiation degree ( $P < 0.05$ ); OPCML expression, depth of tumor invasion, lymph node metastasis and distant metastasis were important factors affecting the prognosis of the survival of the patients ( $P < 0.05$ ). OPCML m-RNA expression in the gastric cancer cells was significantly lower than that in the normal gastric mucosa. RT-PCR showed that the expression of OPCML was aberrantly increased in the cells transfected with pcDNA3.1-OPCML. CCK8 and colony formation assay showed that OPCML significantly inhibited the growth, proliferation, and colony formation of the AGS cells. OPCML plays an important role in gastric cancer, and may be a new prognostic indicator of gastric cancer.

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## LETTER TO THE EDITOR

**REACTIVITY OF PATIENTS WITH MAINTENANCE HEMODIALYSIS TO ERYTHROPOIETIN IN THE TREATMENT OF RENAL ANEMIA**

JP. HU<sup>1</sup>, X. CHENG<sup>1</sup>, XF. XU<sup>1</sup>, GJ. YU<sup>2</sup>, F. LUO<sup>3</sup>, GS. ZHANG<sup>1</sup>, N. YANG<sup>4</sup>,  
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To explore the reactivity of patients with renal anemia (MHD) to erythropoietin (EPO) in maintenance hemodialysis (HD), 31 patients were enrolled in this study. According to the level of serum ferritin (SF), they were divided into two groups; one group received treatment using recombinant human erythropoietin (rHuEPO) and the other group was given iron sucrose. Taking terminal EPO dosage, terminal erythropoietin resistance index (ERI) and rate of change of ERI ( $\Delta$ ERI) as target indexes, the influence of SF level on dosage of EPO was evaluated after usage conditions of relevant substances in a 3-month period. The results revealed that differences of dialysis age, albumin (ALB), blood calcium, initial and terminal SF, variable quantity of hemoglobin (Hb), terminal EPO and ERI between two groups had statistical significance. Furthermore, SF level and terminal EPO ( $r = -0.37$ ,  $P < 0.05$ ) as well as SF level and terminal ERI ( $r = -0.39$ ,  $P < 0.05$ ) were negatively correlated. Difference of terminal ERI between the two groups had statistical significance. It can therefore be summarized that supplementing an iron agent intravenously to maintain SF level between 500 ng/ml and 1200 ng/ml may improve reactivity of patients with MHD to EPO. In addition, rHuEPO therapy in treating anemia of patients with MHD has the same effect with intravenous drug delivery, less side effects and is easy to administer.

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*LETTER TO THE EDITOR*

**ROLE OF ANTI-INFLAMMATORY CYTOKINES IN PATHOGENESIS OF PEDIATRIC MYCOPLASMA PNEUMONIAE PNEUMONIA**

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*Received January 29, 2016 – Accepted May 6, 2016*

Through detection and analysis of the changes of interleukin (IL)-2 and IL-10 in children with mycoplasma pneumoniae pneumonia (MPP), this study aimed to explore the role of cytokines in the pathogenesis of pediatric MPP as well as immunological pathogenesis of MPP, to provide guidance for clinical diagnosis, assessment and treatment of MPP. Enzyme linked immunosorbent adsorption (ELISA) analysis was applied to determine the expression level of IL-2 and IL-10 in serum. According to the experimental results, we found that the expression levels of IL-2 and IL-10 changed significantly in different phases of MPP in comparison with a healthy control group and a case control group. The expression levels of IL-2 and IL-10 can be used as an important indicator for early diagnosis of MPP. Accordingly, detection of IL-2 and IL-10 is of great significance to the diagnosis of MPP and studies on their roles can provide guidance for treatment.

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## LETTER TO THE EDITOR

**FLOW CYTOMETER ANALYSIS OF CELL APOPTOSIS OF ENDOMETRIAL CARCINOMA WITH Wnt10b**Y. ZHOU<sup>1</sup>, XL. ZHAO<sup>1</sup>, RX. GUO<sup>2</sup>, YH. QIAO<sup>2</sup>, XY. ZHANG<sup>1</sup> and ZH. CHEN<sup>2</sup>

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The aim of this study is to analyze the cell apoptosis of endometrial carcinoma (EC) with Wnt10b by Fluorescence Activated Cell Sorting (FACS) technology. AN3CA cell lines and Ishikawa-H-12 cell lines were taken as the *in-vitro* cell models to observe the influence of Wnt10b on key factors of Wnt signal pathway. Methyl thiazolyl tetrazolium (MTT) was applied for the detection of cell proliferation while FACS was used for the detection of cell apoptosis. Data were analyzed using statistical software SPSS14.0. After the overexpression of Wnt10b in AN3CA cells, the apoptosis rate dropped significantly compared with the two control groups ( $p < 0.05$ ); while the apoptosis rate increased significantly compared with the control groups ( $p < 0.01$ ) after Wnt10b knock-off in Ishikawa3-H-12 cells. In normal endometrium, Wnt10b gene expression was negative, while that in EC cells was positive. It can be concluded that Wnt10b gene can promote EC cell proliferation and inhibit its apoptosis.

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LETTER TO THE EDITOR

**EFFECT OF X-RAY IRRADIATION ON EPITHELIAL-MESENCHYMAL TRANSITION OF COLORECTAL CANCER SW480 CELLS**

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The first two authors contributed equally to this work

**This study was carried out to explore the effect of X-ray irradiation on epithelial-mesenchymal transition (EMT) of colorectal cancer SW480 cells. Human colorectal cancer SW480 cells used in this study were irradiated by X-rays in 0 Gy, 4 Gy and 8 Gy doses, respectively. Transwell method was adopted to detect the changes of invasion and migration ability of SW480 cells cultured for 24 h after being irradiated by X-rays in 0 Gy, 4 Gy and 8 Gy doses. After X-ray irradiation, invasion ability of cells in 4 Gy dose group and 8 Gy dose group strengthened significantly compared with that of the 0 Gy dose group ( $p < 0.05$ ); invasion ability of cells in 8 Gy dose group also strengthened significantly compared to the 4 Gy dose group ( $p < 0.05$ ). After X-ray irradiation, migration ability of cells also changed: migration ability of cells in 4 Gy dose group and 8 Gy dose group strengthened significantly compared with that of the 0 Gy group ( $p < 0.05$ ). Results of QRT-PCR and Western blot detection showed that after X-ray irradiation, the expression of epithelial index E-cadherin in 4 Gy dose group and 8 Gy dose group decreased significantly compared with that of the 0 Gy dose group ( $p < 0.05$ ); moreover, the higher the dose was, the more significantly the expression decreased. Therefore, X-ray irradiation-induced EMT is in positive correlation with the irradiation dose to some extent. Besides, X-ray irradiation can enhance the invasion and migration ability of human colorectal cancer cells.**

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## LETTER TO THE EDITOR

**CORRELATION BETWEEN IL-6 AND INVASIVENESS OF ECTODERM CELLS OF EMBRYO IN EARLY PREGNANCY**XY. JIANG<sup>1</sup>, TM. LU<sup>1</sup>, WH. SHU<sup>2</sup> and HY. ZHOU<sup>1</sup>

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**This study aimed to explore the correlation between Interleukin-6 (IL-6) and invasiveness of ectoderm cells of embryo in early pregnancy, in order to further discuss whether IL-6 can enhance invasiveness of ectoderm cells. The study lays the foundation for determination of pathogenesis of some gestation period-related diseases. Differences in mRNA and protein expression of trophoblastic cell line JEG-3 cells in IL-6, matrix metalloproteinase-2 (MMP-2) and MMP-9 were analyzed; the regulating effect of different concentrations of IL-6 on invasive ability of trophoblast cells was studied by Transwell assay; the effect of IL-6 on proliferation of ectodermal cell line JEG-3 of embryo was analyzed by methyl thiazolyl tetrazolium (MTT) assay. The invasive number of JEG-3 cells incubated by IL-6 (10 ng/ml) was higher than that of the control group, and the difference had statistical significance ( $p < 0.05$ ). Results of using MMT assay to detect the effect of IL-6 on proliferation of trophoblastic cell line JEG-3 showed that JEG-3 cells before and after processing had no significant difference from the control group ( $p > 0.05$ ). Therefore, IL-6 can enhance invasiveness of ectoderm cells of embryo through activation of MMP-2.**

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LETTER TO THE EDITOR

**MECHANISM OF AGE-RELATED CHANGES OF BONE MARROW MESENCHYMAL STEM CELLS IN SENILE OSTEOPOROSIS**

C. HUANG, G.F. ZHANG, J. HAN, G.J. LIAO and B.G. ZOU

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*Received January 29, 2016 – Accepted April 27, 2016*

**This study was carried out to explore the age-related changes of bone marrow mesenchymal stem cells (BMMSCs) in mice as well as the influence of autophagy on the age-related changes of BMMSCs. BMMSCs aging-associated protein acetylation P53, P21 and P16 expressions in young and senile mice, protein expression of telomerase reverse transcriptase (TERT) as well as reactive oxygen species (ROS) level were detected and compared; the expression of BMMSCs autophagy associated gene, autophagy related protein molecule and LC3 molecule were detected; the influence of differently concentrated rapamycin and 3-MA on BMMSCs autophagy level was observed to select effective concentrations; the influence of rapamycin and 3-MA on BMMSCs cell cycle-related gene expression, apoptosis related gene expression and ROS level were discussed. Results revealed that the senile BMMSCs group had higher acetylation P53, P21 and P16 expression and fluorescence intensity than the young group, but its TERT expression, Beclin1 and LC3 gene expression and fluorescence intensity were lower than the young group. Both rapamycin and 3-MA inhibited CyclinD1 (CCND1) and CyclinD2 (CCND2) expression. Rapamycin promoted the expression of apoptosis-related genes Caspase3 and Caspase8 in the senile group, while 3-MA inhibited them in both the young and senile groups. It can therefore be concluded that senile BMMSCs have multiple age-related changes, performing as decrease of osteogenic capability and multiplication capacity, increase of acetylation P53, P21 and P16 protein expression, apoptosis and ROS level as well as decrease of telomerase activity. Furthermore, the autophagy level in senile BMMSCs reduced compared with young cells; autophagy activation can decrease ROS level and autophagy suppression improves ROS level; and autophagy regulation affects cell cycle and apoptosis.**

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## LETTER TO THE EDITOR

**MULTICENTER STUDY OF AUTOVERIFICATION METHODS  
OF HEMATOLOGY ANALYSIS**

X. ZHAO<sup>1</sup>, XF. WANG<sup>2</sup>, JB. WANG<sup>2</sup>, XJ. LU<sup>1</sup>, YW. ZHAO<sup>3</sup>, CB. LI<sup>1</sup>, BH. WANG<sup>3</sup>, J. WEI<sup>2</sup>, P. GUO<sup>2</sup>,  
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The first five authors contributed equally to this paper

**This study was designed to establish and validate a set of autoverification methods for hematology analysis. One thousand and twenty-four samples were selected from Shanghai Ruijin Hospital and 999 from Beijing Hospital, China. False positive, false negative and autoverification pass rates were verified and the rules were then adjusted and confirmed according to the verification results. After confirmation, at least 10,000 sample cases were selected from Shanghai Ruijin Hospital, Beijing Hospital and China Armed Police General Hospital and checked automatically. The differences in the autoverification pass rate and average report delivery time before and after the application of the autoverification methods were compared between the three hospitals. Preliminary validation results showed that the false negative rates of the Shanghai Ruijin Hospital and Beijing Hospital were less than 2%. The false positive rates of these two hospitals were high, close to 18%. After rule adjustment, the false negative rate was basically the same as before adjustment, but the false positive rate declined obviously while the pass rate of autoverification improved significantly. The autoverification pass rates of the three hospitals were 76.4%, 85.1% and 84.2%, respectively. The turnover time (TAT, time from receipt of sample to report of the result) of the three hospitals decreased by 4.1 min, 8.8 min and 10.2 min, respectively. Autoverification systems using a Mindray BC-6800 auto hematology analyzer and labXpert were confirmed as being effective in reducing TAT and enhancing working efficiency on the premise of ensuring low false negative rate.**

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LETTER TO THE EDITOR

**EFFICACY AND SAFETY OF OMALIZUMAB IN PAEDIATRIC AGE:  
AN UPDATE OF LITERATURE DATA**

N. MATIN<sup>1</sup>, O. TABATABAIE<sup>1</sup>, R. FALSAPERLA<sup>2</sup>, P. PAVONE<sup>2</sup>, A. SERRA<sup>3</sup>, S. COCUZZA<sup>3</sup>,  
P. DI MAURO<sup>3</sup>, L. LICCIARDELLO<sup>3</sup>, R. LUBRANO<sup>4</sup> and G. VITALITI<sup>2</sup>

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*Received January 15, 2016 – Accepted March 11, 2016*

**Immunoglobulin E (IgE) was discovered in 1966 and was found responsible for immune defense against helminths, type I hypersensitivity and allergic diseases. IgE mediates allergic responses by binding to Fc receptors (the high affinity Fc-epsilon receptor I and the low affinity Fc-epsilon receptor II or CD23) expressed on tissue mast cells and blood basophils. This binding leads to degranulation and release of pro-inflammatory mediators. Considering the pivotal role of IgE in allergic diseases, antibodies against IgE potentiate an array of new therapeutic strategies and in this regard omalizumab (rhuMab-E25, Xolair) has been developed as a monoclonal biologic drug to block serum IgEs. Although the use of omalizumab has been studied vigorously in many adult populations with allergic diseases, there are few heterogenous studies on children. There are very few ongoing clinical trials with omalizumab exclusively on children, although some adult studies have concluded pediatric patients as a part of their studies. Nevertheless, in pediatric clinical trials omalizumab has been demonstrated to be effective and safe also in this age group. Herein, the authors present a systematic review of extensive literature data on the use of omalizumab in children and adolescents.**

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## LETTER TO THE EDITOR

**PNEUMOMEDIASTINUM, SUBCUTANEOUS EMPHYSEMA AND  
PNEUMORRHACHIS IN ASTHMATIC CHILDREN**

L. COLAVITA<sup>1</sup>, C. CUPPARI<sup>1</sup>, M.R. PIZZINO<sup>1</sup>, M. STURIALE<sup>1</sup>, B. MONDELLO<sup>2</sup>,  
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**Pneumomediastinum (PM), subcutaneous emphysema (SE) and pneumorrhachis (also known as epidural air (EDA) or epidural emphysema) are very rare findings in children. PM is defined as the passage of air from intra-alveolar space to interstitium and, later, to the mediastinum. From the mediastinum, the air may catch up subcutaneous tissue (usually of the neck) and/or epidural space via the cervical fascial planes and neural foramina, forming respectively SE and EDA. The PM can be divided in spontaneous (or idiopathic) and secondary PM. Only few studies have evaluated the exact incidence of PM and its complications in children, and to define the correct diagnostic work up, treatment and outpatient follow-up. We report the case of a 9-year-old child with undiagnosed asthma that, during severe asthmatic flare secondary to acute infection of high airway, developed PM, SE and EDA.**

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LETTER TO THE EDITOR

AN UNUSUAL CASE OF MAMMARY PAGET'S DISEASE IN A WOMAN  
WITH PSORIASIS

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Mammary Paget's disease (MPD) is a malignant breast tumor, which is characterized by intraepidermal infiltration from malignant glandular epithelial cells. Often it may include an underlying ductal carcinoma in situ or an invasive ductal carcinoma. Clinically it appears as an erythematous patch, moist or crusted, with or without desquamation that in some cases becomes ulcerated, causing infiltration and inversion of the nipple. We report the clinical case of a 60-year-old woman, treated in our department for psoriasis, presenting with erythema of nipple and areola with nipple erosion, ulceration and poor secretion. Suspecting Paget's disease of the nipple, radiological exams (mammography and breast MRI) were performed. A biopsy for histological examination was carried out and confirmed the diagnosis of mammary Paget's disease. MPD is sometimes difficult to diagnose both clinically and radiologically, therefore it is important to distinguish from other conditions: in literature MPD is reported in differential diagnosis with psoriasis given its similar clinical features, and in some cases MPD has been treated with topical and systemic steroids due to a wrong diagnosis. However, the concomitance, in the same individual, of mammary Paget's disease and psoriasis has never been described.

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**DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.**

*LETTER TO THE EDITOR***EFFICACY AND TOLERABILITY OF A COMBINED LIPID-LOWERING NUTRACEUTICAL ON CHOLESTEROLEMIA, hs-CRP LEVEL AND ENDOTHELIAL FUNCTION IN MODERATELY HYPERCHOLESTEROLEMIC SUBJECTS**

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**Our aim was to test, by a double-blind, placebo-controlled randomized clinical trial, whether a short-term treatment with a combined lipid-lowering nutraceutical could improve endothelial function in a cohort of moderately hypercholesterolemic subjects. Thus, 80 healthy, moderately hypercholesterolemic subjects were consecutively enrolled and, after 4 weeks of stabilization diet, they were randomized to either the tested lipid-lowering nutraceutical or placebo for 8 weeks. At the beginning and end of treatment a complete lipid pattern, safety parameters, hs-CRP and endothelial function were measured. When compared to placebo, during nutraceutical treatment patients experienced a more favorable percentage change in total cholesterol (TC vs baseline: -17.9%; TC vs placebo: -5.6%), LDL-cholesterol (LDL-C vs baseline: -23.3%; LDL-C vs placebo: -2.8%), hs-CRP (hs-CRP vs baseline: -2.4%; hs-CRP vs placebo: -1.5%), and endothelial function (pulse volume displacement vs baseline: +17%; pulse volume displacement vs placebo treatment: -3.3%). No significant difference was observed in respect to effects on triglycerides, HDL-cholesterol and safety parameters. On the basis of our data, the tested lipid-lowering nutraceutical seems to significantly improve endothelial function in moderately hypercholesterolemic subjects. These results have to be confirmed on larger patient samples and over longer periods.**

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LETTER TO THE EDITOR

**DOES CYCLIC GUANOSINE MONOPHOSPHATE INDUCE AUTOPHAGY IN THYROID MALIGNANT CARCINOMA THROUGH DOWN-REGULATION OF CYCLIC GUANOSINE MONOPHOSPHATE PHOSPHODIESTERASE?**

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The aim of this study was to evaluate whether or not the expression of cGMP- phosphodiesterases (cGMP-PDE) varies in different thyroid pathologies and to elucidate the relationship between the expression of cGMP-PDE, cGMP, and autophagy. Fifty-four thyroid biopsy samples, excised to perform the biopsy, were split into two parts and randomly assigned: one part was microscopically examined and histological classified, and the other was frozen and analysed in order to evaluate the cGMP-PDE activity. Intracellular cGMP was also measured. A strong expression of intracellular cGMP and cGMP-PDE activity was observed in carcinoma in respect to controls and benign pathologies. The level of cGMP-PDE in papillary carcinoma without lymph node involvement (N-) was approximately four-fold higher compared to those with lymph node invasion (N±). On the contrary, the cGMP was one and a half times higher in N± than N-. Our results are promising, although further epigenetical studies are needed to confirm this association. A correlation between the cGMP-degrading activity and the severity of thyroid pathology has been shown. The decrease of cGMP-PDE and the increase of cGMP in N± papillar carcinoma could be an autophagic stimulus, a defence mechanism of the body, against the cancer that is expanding and invading other tissues and organs.

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## LETTER TO THE EDITOR

**ISOTONIC SALINE IN CHILDREN WITH PERENNIAL ALLERGIC RHINITIS**S. BARBERI<sup>1</sup>, E. D'AURIA<sup>2</sup>, L. BERNARDO<sup>1</sup>, F. PINTO<sup>1</sup>, B. PIETRA<sup>2</sup> and G. CIPRANDI<sup>3</sup>

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Children with HDM allergy suffer from perennial allergic rhinitis (PAR). The present pilot study evaluated nasal lavage with isotonic saline (0.9%) in 25 children (mean age 8.9 years; 13 males) with HDM-dependent PAR, assessing: nasal symptoms severity and parental perception of rhinitis control, sleep, and school performance. Nasal symptoms, rated by total symptom score, parental perception of PER control, sleep quality, and school performance, measured by visual analogue scale, were significantly improved by nasal lavage ( $p < 0.001$ ) after treatment. The effects tended to persist also during the follow-up. In conclusion, the present pilot study provides the first evidence that nasal lavage with isotonic saline relieved the nasal symptoms of children with PAR and improved the parental perception of the disease.

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LETTER TO THE EDITOR

**MANDIBULAR THIRD MOLAR DISPLACED IN THE SUBLINGUAL SPACE:  
CLINICAL MANAGEMENT AND MEDICOLEGAL CONSIDERATIONS**

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**This paper describes the management of a failed mandibular third molar extraction, resulting in tooth displacement in the sublingual space, the discussion of the diagnosis, surgery and medico-legal considerations. A 28-year-old male patient underwent an unsuccessful attempt of the 4.8 tooth extraction. The clinician lost visual contact after luxation and the patient was not recalled for post-operative follow-up. After 24 hours, a severe trismus started. Orttopantomography and cone beam computer tomography revealed the displacement in the sublingual space. The tooth was removed under general anaesthesia with intraoral approach. The follow-up was uneventful and the paraesthetic area on the tongue did not enlarge after the retrieval. The displaced mandibular third molar is a rare but potentially serious complication of extraction. This event should be avoided with correct diagnosis and surgical technique. Cone beam computed tomography was useful to determine the three-dimensional position of the displaced tooth.**

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## LETTER TO THE EDITOR

**EFFICACY OF PULSED LOW-INTENSITY ELECTRIC NEUROMUSCULAR STIMULATION IN REDUCING PAIN AND DISABILITY IN PATIENTS WITH MYOFASCIAL SYNDROME**P. IODICE<sup>1</sup>, G. LESSIANI<sup>2</sup>, G. FRANZONE<sup>2</sup> and G. PEZZULO<sup>1</sup><sup>1</sup>*Institute of Cognitive Sciences and Technologies, National Research Council, Rome, Italy;*<sup>2</sup>*Center of Intensive Rehabilitation, 'S'Agnese', Pineto (TE), Italy**Received February 1, 2016 – Accepted May 3, 2016*

Myofascial pain syndrome (MPS) is characterized by chronic pain in multiple myofascial trigger points and fascial constrictions. In recent years, the scientific literature has recognized the need to include the patient with MPS in a multidimensional rehabilitation project. At the moment, the most widely recognized therapeutic methods for the treatment of myofascial syndrome include the stretch and spray pressure massage. Microcurrent electric neuromuscular stimulation was proposed in pain management for its effects on normalizing bioelectricity of cells and for its sub-sensory application. In this study, we tested the efficacy of low-intensity pulsed electric neuromuscular stimulus (PENS) on pain in patients with MPS of cervical spine muscles. We carried out a prospective-analytic longitudinal study at an outpatient clinic during two weeks. Forty subjects (mean age  $42 \pm 13$  years) were divided into two groups: treatment (TrGr, n=20) and control group (CtrlGr, n=20). Visual-analog scale (VAS) values, concerning the spontaneous and movement-related pain in the cervical-dorsal region at baseline (T0) and at the end of the study (T1), showed a reduction from 7 to 3.81 ( $p < 0.001$ ) in TrGr. In the CtrlGr, VAS was reduced from 8.2 to 7.2 (n.s.). Moreover, the pressure pain threshold at T0 was 2.1 vs 4.2 at T1 ( $p < 0.001$ ) in TrG. In the CtrlGR we observed no significant changes. Modulated low-intensity PENS is an innovative therapy permitting to act on the transmission of pain and on the restoration of tissue homeostasis. It seems to affect the transmission of pain through the stimulation of A-beta fibers. The above results show that low-intensity PENS can be considered as an effective treatment to reduce pain and disability in patients with MPS.

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LETTER TO THE EDITOR

**COMPARISON BETWEEN INTRARTICULAR INJECTION OF HYALURONIC ACID, OXYGEN OZONE, AND THE COMBINATION OF BOTH IN THE TREATMENT OF KNEE OSTEOARTHRISIS**

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**This study aimed to compare short-term clinical outcomes between intra-articular injection of hyaluronic acid (HA), oxygen ozone (O2O3), and the combination of both, in patients affected by osteoarthritis (OA) of the knee. Seventy patients (age 45-75 years) with knee OA were randomized to intra-articular injections of HA (n=23), or O2O3 (n=23) or combined (n=24) one per week for 5 consecutive weeks. KOOS questionnaire and visual analog scale (VAS), before treatment (pre) at the end (post), and at 2 months after treatment ended (follow-up) were used as outcome measures. Analysis showed a significant effect (P<0.05) of the conditions (pre, post and follow-up) in all parameters of the KOOS score and a significant effect (P<0.05) of groups (HA, O2O3 and combined) for pain, symptoms, activities of daily living and quality of life. The combined group scores were higher compared to the HA and O2O3 groups, especially at follow-up. The combination of O2O3 and HA treatment led to a significantly better outcome especially at 2-month follow-up compared to HA and O2O3 given separately to patients affected by OA of the knee.**

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