

CROATIAN INTERNATIONAL PUBLICATIONS

by Ivan Boháček

ibohacek@hiim.hr



Hudetz D^{1,3}, Borić I^{4,5}, Rod E¹, Jeleč Ž¹, Radić A¹, Vrdoljak T^{1,2}, Skelin A^{1,6}, Lauc G^{6,7}, Trbojević-Akmačić I⁶, Plečko M⁸, Polašek O^{4,7}, Primorac D^{1,3,4,9-12}. The effect of intra-articular injection of autologous microfragmented fat tissue on proteoglycan synthesis in patients with knee osteoarthritis. *Genes (Basel)*. 2017;8(10).

¹St. Catherine Specialty Hospital, Zabok/Zagreb, Croatia; ²Clinical Hospital "Sveti Duh", Zagreb, Croatia; ³School of Medicine, JJ Strossmayer University of Osijek, Osijek, Croatia; ⁴School of Medicine, University of Split, Split, Croatia; ⁵University of Rijeka, Medical School, Rijeka, Croatia; ⁶Genos Glycoscience Research Laboratory, Zagreb, Croatia; ⁷Faculty of Pharmacy and Biochemistry, University of Zagreb, Zagreb, Croatia; ⁸School of Medicine, University of Zagreb, Zagreb, Croatia; ⁹Gen-info, Zagreb, Croatia; ¹⁰Children's Hospital Srebrnjak, Zagreb, Croatia; ¹¹Eberly College of Science, The Pennsylvania State University, University Park, State College, PA, USA; ¹²The Henry C. Lee College of Criminal Justice and Forensic Sciences, University of New Haven, West Haven, CT, USA.

Osteoarthritis (OA) is one of the leading musculoskeletal disorders in the adult population. It is associated with cartilage damage triggered by the deterioration of the extracellular matrix tissue. The present study explores the effect of intra-articular injection of autologous microfragmented adipose tissue to host chondrocytes and cartilage proteoglycans in patients with knee OA. A prospective, non-randomized, interventional, single-center, open-label clinical trial was conducted from January 2016 to April 2017. A total of 17 patients were enrolled in the study, and 32 knees with osteoarthritis were assessed. Surgical intervention (lipoaspiration) followed by tissue processing and intra-articular injection of the final microfragmented adipose tissue product into the affected knee(s) was performed in all

patients. Patients were assessed for visual analogue scale (VAS), delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) and immunoglobulin G (IgG) glycans at the baseline, three, six and 12 months after the treatment. Magnetic resonance sequence in dGEMRIC due to infiltration of the anionic, negatively charged contrast gadopentetate dimeglumine (Gd-DTPA2-) into the cartilage indicated that the contents of cartilage glycosaminoglycans significantly increased in specific areas of the treated knee joint. In addition, dGEMRIC consequently reflected subsequent changes in the mechanical axis of the lower extremities. The results of our study indicate that the use of autologous and microfragmented adipose tissue in patients with knee OA (measured by dGEMRIC MRI) increased glycosaminoglycan (GAG) content in hyaline cartilage, which is in line with observed VAS and clinical results.

Sikic J^{1,2}, Stipcevic M³, Vrazic H³, Cerkez Habek J¹, Margetic E^{2,4}, Guljin D^{1,2}. Nutrition in primary and secondary prevention of cardiovascular risk in the continental and Mediterranean regions of Croatia. *BMC Cardiovasc Disord*. 2017;17(1):247.

¹Division of Cardiology, Department of Internal Medicine, Sveti Duh University Hospital, Zagreb, Croatia; ²School of Medicine, University of Zagreb, Zagreb, Croatia; ³Division of Cardiology, Department of Internal Medicine, Dubrava University Hospital, Zagreb, Croatia; ⁴University Clinic of Cardiovascular Diseases, Zagreb University Hospital Centre, Zagreb, Croatia.

BACKGROUND: The aim of this observational study was to evaluate the effect of Mediterranean and continental nu-

trition on cardiovascular risk in patients with acute and chronic coronary heart disease in Croatia. **METHODS:** The study included 1284 patients who were hospitalized in a 28-month period due to acute or chronic ischaemic heart disease in hospitals across Croatia. An individual questionnaire was prepared which enabled recording of various cardiovascular risk factors. **RESULTS:** Patients with chronic coronary artery disease have a better index of healthy diet than patients with acute coronary disease. Women have a better index of diet than men in both Croatian regions. When the prevalence of risk factors (impaired glucose tolerance, diabetes mellitus types I and II, hypercholesterolaemia, hypertriglyceridaemia and hypertension) in patients with Mediterranean and continental nutrition is compared, a trend is seen for patients who have risk factors to consume healthier food. **CONCLUSION:** The Mediterranean diet is associated with reduced risk of developing cardiovascular disease. This effect is more evident in patients with known cardiovascular disease.

Bubalo P^{1,2}, Buterin I^{2,3}, Šalek Z^{2,4}, Đogić V⁵, Zupančić-Šalek S^{2,6,7}. Association of Plasminogen activator inhibitor-1 gene polymorphisms and Methylene tetrahydrofolate reductase polymorphisms with spontaneous miscarriages. *Acta Haematol.* 2017;138(2):111-115.

¹Zagreb County Institute of Emergency Medicine; ²School of Medicine, University of Zagreb; ³Health Care Centre Zagreb East; ⁴Department of Pediatrics, University Hospital Centre Zagreb; ⁵Croatian Institute for Transfusion Medicine; ⁶Department of Haematology, University Hospital Centre Zagreb; ⁷School of Medicine, University of Osijek, Osijek, Croatia

AIM: The objective of this study was to investigate a possible correlation between the plasminogen activator inhibitor-1 (PAI-1) and methylene tetrahydrofolate reductase (MTHFR) polymorphisms and unexplained spontaneous miscarriages (SM). **MATERIALS AND METHODS:** PAI-1 polymorphisms were evaluated in 150 women with pregnancy in their history. One hundred women with a history of SM formed the study group and 50 women with normal pregnancies served as the control group. Also, the combination of PAI-1 and MTHFR polymorphisms were evaluated in 138 women out of a total of 150, which included 92 women with SM in their history compared to 46 women in the control group. For statistical analysis, χ^2 test, Phi, and Cramer V tests were

used; $p < 0.05$ was taken as a statistically significant result. **RESULTS:** Our findings show: (a) the correlation between SM and PAI-1 mutations reaches statistical significance ($p = 0.026$); (b) there was a statistically significant difference between heterozygous PAI-1 in women with only 1 SM compared to the control group ($p = 0.047$); (c) the comparison of combinations of both mutations, PAI-1 and MTHFR, with the control group demonstrates statistical significance in favor of women with SM and both mutations ($p = 0.022$). **CONCLUSION:** PAI-1 and MTHFR polymorphisms may play an important role in pregnancy complications because heterozygous PAI-1 mutations and a combination of both PAI-1 and MTHFR mutations might contribute to SM.

Boraska Jelavić T¹, Boban T¹, Brčić L², Vrdoljak E¹. Is macrocytosis a potential biomarker of the efficacy of dose-dense paclitaxel-carboplatin combination therapy in patients with epithelial ovarian cancer? *Anticancer Drugs.* 2017;28(8):922-927.

¹Department of Oncology, University Hospital Split;

²Department of Medical Biology, School of Medicine, University of Split, Split, Croatia.

The aims of this study were to investigate a clinical observation that patients with epithelial ovarian cancer treated with first-line platinum-paclitaxel chemotherapy combination (TP) develop macrocytosis and to explore the possible predictive role of macrocytosis in response rate, progression-free survival (PFS), and overall survival. A retrospective analysis of laboratory and clinical data on 184 consecutive ovarian cancer patients treated with first-line TP chemotherapy in a single oncology center from 2004 to 2015 was carried out. Macrocytosis was defined as an increase in mean corpuscular volume of peripheral red blood cells above 97.2 fl during the treatment and/or 30 days after the last chemotherapy cycle. One hundred and forty-one patients were treated with a conventional 3-weekly TP schedule, whereas 43 patients were treated with a dose-dense schedule. Macrocytosis was induced in 35% of patients overall. It was induced significantly more often in patients treated with the dose-dense schedule than in those treated with the 3-weekly schedule (67 vs. 26%, $P=1.29 \times 10^{-4}$). Macrocytosis did not correlate with PFS and overall survival in the overall patient population, nor in patients treated with the 3-weekly schedule. It correlated with PFS (hazard ratio=0.42, 95% confidence interval=0.18-0.94, $P=0.036$) and objective response on therapy in patients treated with

the dose-dense schedule ($P=0.0285$). Dose-dense TP chemotherapy induces macrocytosis significantly more often than does a 3-weekly schedule in ovarian cancer patients. In patients treated with a dose-dense schedule, macrocytosis can potentially be predictive for longer PFS and better response rate. This finding needs further confirmation, preferentially in a prospective study.

Kudlek Mikulic S¹, Mihaljevic-Peles A², Sagud M², Bajs Janovic M¹, Ganoci L³, Grubisin J¹, Kuzman Rojnic M², Vuksan Cusa B^{1,4}, Bradaš Z¹, Božina N⁵. Brain-derived neurotrophic factor serum and plasma levels in the treatment of acute schizophrenia with olanzapine or risperidone: 6-week prospective study. Nord J Psychiatry. 2017;71(7):513-520.

¹Department of Psychiatry, Clinical Hospital Center Zagreb, Zagreb, Croatia; ²Department of Psychiatry, School of Medicine, Clinical Hospital Center Zagreb, University of Zagreb, Zagreb, Croatia; ³Department of Laboratory Diagnostics, Clinical Hospital Centre Zagreb, Zagreb, Croatia; ⁴Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia; ⁵Department of Laboratory Diagnostics, School of Medicine, Clinical Hospital Centre Zagreb, University of Zagreb, Zagreb, Croatia.

Antipsychotics have been the mainstay of the treatment of schizophrenia, and their potential role in neuroprotection could be related to brain-derived neurotrophic factor (BDNF). So far different effects on both serum and plasma levels of BDNF were reported related to the various antipsychotic treatments. Aim of this study was to investigate the influence of olanzapine or risperidone on both plasma and serum levels of BDNF in patients with acute schizophrenia. For 50 participants with acute episode of schizophrenia both plasma and serum BDNF, along with the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression scale, were assessed pretreatment and post treatment - after 6 weeks of either risperidone or olanzapine. Results show that a weak correlation between pretreatment plasma and serum levels of BDNF was found no longer significant after 6 weeks of treatment. Antipsychotics, olanzapine and risperidone showed no significant effect on post treatment plasma and serum levels of BDNF. Pretreatment plasma level of BDNF and PANSS positive

subscale were positively correlated. Post treatment serum level of BDNF and Clinical Global Impression were negatively correlated. In conclusion, plasma and serum BDNF levels could be different markers to some extent with regard to clinical symptoms, response to therapy and outcome. The interrelation between serum and plasma BDNF should be established in further studies.

Pogorelić Z¹, Kadić S², Milunović KP³, Pintarić I⁴, Jukić M³, Furlan D³. Flexible intramedullary nailing for treatment of proximal humeral and humeral shaft fractures in children: A retrospective series of 118 cases. Orthop Traumatol Surg Res. 2017;103(5):765-770.

¹Department of Pediatric Surgery, University Hospital of Split, School of Medicine, University of Split, Split, Croatia; ²University of Split, School of Medicine, Split, Croatia; ³Department of Pediatric Surgery, University Hospital of Split, Split, Croatia; ⁴Department of Anatomy, University of Split, School of Medicine, Split, Croatia.

BACKGROUND: The aim of this study was to analyze outcomes of treatment and complications in children treated with flexible intramedullary nailing (FIN) due to humeral fracture. **HYPOTHESIS:** The FIN for treatment of humeral fractures in children would allow an early functional and cast-free follow-up with a quick pain reduction and low complication rate. **PATIENTS AND METHODS:** From May 2002 until May 2016 case records of all children who underwent fixation with titanium intramedullary nails because of humeral fracture were retrospectively reviewed. The study included 118 patients treated with FIN for proximal humeral or humeral shaft fracture. The average age at the time of trauma was 12 years. Mean follow-up was 77 months. Left hand was affected in 51% of patients. The most common mechanism of injury was fall ($n=58$), followed by sports injuries, road traffic accidents, pathological fractures, motor-bike accidents and bicycle riding. **RESULTS:** There were no residual valgus/varum deformities. All patients achieved complete radiographic healing at a mean of 7.5 weeks. Nine complications were recorded: 1 humeral shaft fracture in patient with osteogenesis imperfecta, 4 entry site skin irritations, 2 skin infections and 2 radial nerve injuries. There were no cases of delayed union, nonunion or malunion. After removal of the nails, all patients regained full function and all complications resolved. **DISCUSSION:** The FIN for humeral fractures is a minimally invasive, simple

and well reproducible technique with very low complication rate. CONCLUSION: The FIN for treatment of humeral fractures shows very good functional and cosmetic results. It allows an early functional and cast-free follow-up with a quick pain reduction.

Božina N^{1,2}, Lalić Z³, Nađ-Škegro S⁴, Borić-Bilušić A⁵, Božina T⁶, Kaštelan Ž⁷, Trkulja V⁸. Steady-state pharmacokinetics of mycophenolic acid in renal transplant patients: exploratory analysis of the effects of cyclosporine, recipients' and donors' ABCC2 gene variants, and their interactions. Eur J Clin Pharmacol. 2017;73(9):1129-1140.

¹Division of Pharmacogenomics and Therapy

Individualization, Department of Laboratory Diagnostics, University Hospital Center Zagreb, Zagreb, Croatia;

²Department of Pharmacology, Zagreb University School of Medicine, Zagreb, Croatia. ³Department of Laboratory

Diagnosics, Analytical Toxicology and Pharmacology Division, University Hospital Center Zagreb, Zagreb, Croatia;

⁴Department of Urology, University Hospital Center Zagreb, Zagreb, Croatia; ⁵Agency for Medicinal Products and Medical

Devices of Croatia, Zagreb, Croatia; ⁶Department of Medical Chemistry, Biochemistry and Clinical Chemistry, Zagreb

University School of Medicine, Zagreb, Croatia; ⁷Department of Urology, University Hospital Center Zagreb, Zagreb

University School of Medicine, Zagreb, Croatia; ⁸Department of Pharmacology, Zagreb University School of Medicine,

Zagreb, Croatia.

PURPOSE: The study aims to evaluate the impact of recipients' and donors' polymorphisms in multidrug resistance-associated protein 2 (MRP2) gene ABCC2 -24C>T and 1249G>A on disposition of mycophenolic acid (MPA) and their interaction with cyclosporine (CsA) (compared to tacrolimus, TAC) in stable de novo adult renal transplant patients of Croatian origin. **METHODS:** A total of 68 recipient-donor pairs were genotyped. Steady-state pharmacokinetics of MPA was assessed by the model-independent method. **RESULTS:** Adjusted for MPA formulation, renal function, type of calcineurin inhibitor and recipients' and donors' genotypes at the two loci, donors' A-allele at 1249G>A was associated with a reduced peak (29%) and early (AUC₀₋₂, 33%) exposure and increased MPA clearance (26%). Donors' A-allele combined with CsA was associated with 78% higher MPA clearance, 49% lower early and 48% lower total exposure as compared to wild type

homozygosity + TAC. Recipients' SNPs per se did not reflect on MPA disposition. However, A-allele at 1249G>A + CsA (compared to wild type + TAC) was associated with a numerically greater increase in MPA clearance (59 vs. 41%), reduction in total exposure (36 vs. 27%) and increase in absorption rate (C_{max}/AUC) (56 vs. 37%) than observed for the main effect of CsA. Less pronounced effects were observed for the combination of variant allele at -24C>T and CsA. **CONCLUSION:** Considering MPA disposition, data indicate: donors' ABCC2 1249G>A polymorphism increases clearance and reduces exposure; CsA increases clearance and reduces exposure by inhibiting MRP2 in the gut, the liver, and the kidney; donors' ABCC2 1249G>A polymorphism enhances the renal CsA effect, while recipients' polymorphism seems to enhance the liver and the gut CsA effects.