CROATIAN INTERNATIONAL PUBLICATIONS

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Bojanić K[1], Pritišanac E[2], Luetić T[3], Vuković J[2], Sprung J[4], Weingarten TN[4], Carey WA[5], Schroeder DR[6], Grizelj R[2]. Survival of outborns with congenital diaphragmatic hernia: the role of protective ventilation, early presentation and transport distance: a retrospective cohort study. BMC Pediatr. 2015;15:155.

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BACKGROUND: Congenital diaphragmatic hernia (CDH) is a congenital malformation associated with life-threatening pulmonary dysfunction and high neonatal mortality. Outcomes are improved with protective ventilation, less severe pulmonary pathology, and the proximity of the treating center to the site of delivery. The major CDH treatment center in Croatia lacks a maternity ward, thus all CDH patients are transferred from local Zagreb hospitals or remote areas (outborns). In 2000 this center adopted protective ventilation for CDH management. In the present study we assess the roles of protective ventilation, transport distance, and severity of pulmonary pathology on survival of neonates with CDH. METHODS: The study was divided into Epoch I, (1990-1999, traditional ventilation to achieve normocapnia), and Epoch II, (2000-2014, protective ventilation with permissive hypercapnia). Patients were categorized by transfer distance (local hospital or remote locations) and by acuity of respiratory distress after delivery (early presentation-occurring at birth, or late presentation, ≥6 h after delivery). Survival between epochs, types of transfers, and acuity of presentation were assessed. An additional analysis was assessed for the potential association between survival and end-capillary blood CO2 (PcCO2), an indirect measure of pulmonary pathology. RESULTS: There were 83 neonates, 26 in Epoch I, and 57 in Epoch II. In Epoch I 11 patients (42 %) survived, and in Epoch II 38 (67 %) (P = 0.039). Survival with early presentation (N = 63) was 48 % and with late presentation 95 % (P <0.001). Among early presentation, survival was higher in Epoch II vs. Epoch I (57 % vs. 26 %, P = 0.031). From multiple logistic regression analysis restricted to neonates with early presentation and adjusting for severity of disease, survival was improved in Epoch II (OR 4.8, 95%CI 1.3-18.0, P = 0.019). Survival was unrelated to distance of transfer but improved with lower partial pressure of PcCO2 on admission (OR 1.16, 95%CI 1.01-1.33 per 5 mmHg decrease, P = 0.031). CONCLUSIONS: The introduction of protective ventilation was associated with improved survival in neonates with early presentation. Survival did not differ between local and remote transfers, but primarily depended on severity of pulmonary pathology as inferred from admission capillary PcCO2.

Vuica A, Ferhatović Hamzić L, Vukojević K, Jerić M, Puljak L, Grković I, Filipović N. Aging and a long-term diabetes mellitus increase expression of 1 α-hydroxylase and vitamin D receptors in the rat liver. Exp Gerontol. 2015;72:167-176.

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Diabetes mellitus (DM) is a metabolic disorder associated with serious liver complications. As a metabolic chronic disease, DM is very common in the elderly. Recent studies suggest ameliorating effects of vitamin D on metabolic and oxidative stress in the liver tissue in an experimental model of DM. The aim of this study was to investigate the expression of vitamin D receptors (VDRs) and 1α-hydroxylase, the key enzyme for the production of active vitamin D form (calcitriol) in the liver during long-term diabetes mellitus type 1 (DM1) in aging rats. We performed immunohistochemical analysis of liver expression of 1α-hydroxylase and VDRs during aging in long-term streptozotocin-induced DM1. 1α-Hydroxylase was identified in the monocyte/macrophage system of the liver. In addition to the nuclear expression, we also observed the expression of VDR in membranes of lipid droplets within hepatocytes. Aging and long-term DM1 resulted in significant increases in the number of 1α-hydroxylase immunoreactive cells, as well as the percentage of strongly positive VDR hepatocytes. In conclusion, the liver has the capacity for active vitamin D synthesis in its monocyte/macrophage system that is substantially increased in aging and long-term diabetes mellitus. These conditions are also characterized by significant increases in vitamin D receptor expression in hepatocytes. The present study suggests that VDR signaling system could be a potential target in prevention of liver complications caused by diabetes and aging.

Murgic L[1], Hébert PC[2], Sovic S[3], Pavlekovic G[4]. Paternalism and autonomy: views of patients and providers in a transitional (post-communist) country. BMC Med Ethics. 2015;16:65.

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BACKGROUND: Patient autonomy is a fundamental, yet challenging, principle of professional medical ethics. The idea that individual patients should have the freedom to make choices about their lives, including medical matters, has become increasingly prominent in current literature. However, this has not always been the case, especially in communist countries where paternalistic attitudes have been interwoven into all relationships including medical ones. Patients' expectations and the role of the doctor in the patient-physician relationship are changing. Croatia, as a transitional country, is currently undergoing this particular process. METHODS: Qualitative research was conducted by means of six focus group discussions held in the years 2012 and 2013 in Croatia. Focus groups were held separately with each of the following: first year and final (6(th)) year medical students, physicians engaged in medical ethics education, physicians practicing in a clinical hospital, family medicine residents and individuals representing patients with chronic disease. This research specifically addresses issues related to patient autonomy, in particular, the principles of truth telling, confidentiality, and informed consent. All focus group discussions were audio taped and then transcribed verbatim and systematized according to acknowledged qualitative analysis methods. RESULTS AND DISCUSSION: Patient autonomy is much more than a simple notion defined as the patient's right to make treatment decisions independently. It has to be understood in context of the broader socio-cultural setting. At present, both patients and medical doctors in Croatia are increasingly appreciating the importance of promoting the principle of autonomy in medical decision-making. However, the current views of medical students, physicians and patients reveal inconsistencies. CONCLUSIONS: Knowing how to respect the various facets of patients' autonomy should be part of physician's professional duties, and also be reflected in his or her core clinical competencies. For this reason greater importance should be dedicated to patient autonomy issues in medical education in Croatia.

Macan M[1], Vukšić A[2], Žunec S[3], Konjevoda P[4], Lovrić J[5], Kelava M[6], Štambuk N[4], Vrkić N[7], Bradamante V[6]. Effects of simvastatin on malondialdehyde level and esterase activity in plasma and tissue of normolipidemic rats. Pharmacol Rep. 2015;67:907-13.

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BACKGROUND: We investigated the possible non-lipid effects of simvastatin (SIMV) on paraoxonase 1 (PON1) and butyrylcholinesterase (BuChE) activity, as well as on malondialdehyde (MDA) levels in normolipidemic rats. METHODS: Two experimental groups of Wistar rats (10mg/kg/day of SIMV) and two control groups (saline) underwent a 21-day treatment period (TP). On the 22nd day one experimental and one control group of rats were sacrificed. Remaining groups of animals were sacrificied on the 32nd day of the study (10-day after-treatment period (AT)). Blood samples and slices of liver, heart, kidney, and brain tissue were obtained for the measurement of PON1 and BuChE activity and levels of MDA. Data were analyzed by means of t-test for independent samples. p values≤0.05 were considered as statistically significant. RESULTS: SIMV caused a significant decrease of serum and liver PON1 activity (18-24%, p≤0.05) and MDA concentrations in the plasma, heart, liver, kidney, and brain (9-40%, p≤0.05), while plasma and liver BuChE activity increased by 29% (p≤0.05) and 18%, respectively. All effects of SIMV were largely diminished following AT. The exception was MDA, which remained significantly decreased in plasma and all tissues analyzed. CONCLUSION: SIMV significantly decreased PON1 activity and MDA levels and increased BuChE activity. We suggest that the decrease of MDA levels is a beneficial therapeutic effect of SIMV, for example in cardiovascular disorders, while the increase of BuChE activity, especially in brain, may be a potential adverse effect in patients with Alzheimer disease.

Vrselja Z[1], Šram M[2], Andrijevic D[3], Takač B[4], Lekšan I[5], Radić R[2], Curic G[6]. Transcardial gradient of adiponectin, interleukin-6 and tumor necrosis factor-α in overweight coronary artery disease patients. Cytokine. 2015;76:321-7.

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BACKGROUND: Obesity is associated with coronary artery disease (CAD), where epicardial adipose tissue (EAT) express proatherogenic cytokines (i.e., interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α)) and decreases production of beneficial adiponectin. Studies on endocrine role of EAT are mostly based on assessing cytokines' mRNAs, whereas cytokine blood levels might not readily correlate. In order to get better insight into the endocrine role of thickened EAT in CAD, we assessed transcardial gradient of adiponectin, IL-6 and TNF-α. METHODS: We assessed anthropometric and ultrasound measures in cohort of fifty nondiabetic subjects (21 CAD and 29 non-CAD). Blood sampled from aortic root and coronary sinus was assayed for adiponectin, IL-6 and TNF-α, using ELISA. RESULTS: Except thicker EAT in CAD subjects, anthropometric measures were similar (overweight), with higher adiponectin in coronary sinus than in aortic root (p<0.001) in both groups. CAD subjects had lower adiponectin in aortic root (p<0.001) and higher levels of TNF-α in coronary sinus than in aortic root (p=0.05). EAT thickness positively correlated with hip circumference (p=0.038) and negatively correlated with adiponectin levels (for both p<0.05). CONCLUSIONS: Transcardial gradient of adiponectin in non-CAD and CAD overweight subjects was similar, while latter had lower systemic adiponectin level and thicker EAT. EAT with thickening reaches the threshold level of near-maximal downregulation of adiponectin and its further thickening is not associated with continued decrease of adiponectin production. In CAD patients levels of TNF-α were higher, but IL-6 were not, and these cytokines might be flush out by lymphatic route.

Trnski D[1], Sabol M[1], Gojević A[2], Martinić M[1], Ozretić P[1], Musani V1, Ramić S[3], Levanat S[1]. GSK3β and Gli3 play a role in activation of Hedgehog-Gli pathway in human colon cancer - Targeting GSK3β downregulates the signaling pathway and reduces cell proliferation. Biochim Biophys Acta. 2015;1852:2574-84.

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The role of Hedgehog-Gli (Hh-Gli) signaling in colon cancer tumorigenesis has not yet been completely elucidated. Here we provide strong evidence of Hh-Gli signaling involvement in survival of colon cancer cells, with the main trigger of activation being deregulated GSK3β. Our clinical data reveals high expression levels of GSK3β and Gli3 in human colon cancer tissue samples, with positive correlation between GSK3β expression and DUKES' stage. Further experiments on colon cancer cell lines have shown that a deregulated GSK3β upregulates Hh-Gli signaling and positively affects colon cancer cell survival. We show that inhibition of GSK3β with lithium chloride enhances Gli3 processing into its repressor form, consequently downregulating Hh-Gli signaling, reducing cell proliferation and inducing cell death. Analysis of the molecular mechanisms revealed that lithium chloride enhances Gli3-SuFu-GSK3β complex formation leading to more efficient Gli3 cleavage and Hh-Gli signaling downregulation. This work proposes that activation of the Hh-Gli signaling pathway in colon cancer cells occurs non-canonically via deregulated GSK3β. Gli3 seems to be the main pathway effector, highlighting the activator potential of this transcription factor, which is highly dependent on GSK3β function and fine tuning of the Gli3-SuFu-GSK3β platform.

Kocijancic M1, Vujicic B2, Racki S2, Cubranic Z3, Zaputovic L3, Dvornik S4. Serum omentin-1 levels as a possible risk factor of mortality in patients with diabetes on haemodialysis. Diabetes Res Clin Pract. 2015;110:44-50.

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AIM: The main cause of mortality in haemodialysis (HD) patients is cardiovascular disease. Serum omentin-1 level was found to be associated with cardio-metabolic disorders. The aim of this study was to examine the role of omentin-1 as a predictor of mortality in a group of diabetes positive HD patients. METHODS: A total of 120 prevalent HD patients were included in the study from December 2012 to May 2014. Patients were divided into two groups according to the presence or absence of diabetes. Venous blood samples were taken at months 0 and 18 following an overnight fast (prior to a midweek HD session). Serum omentin-1 level was assessed by enzyme-linked immunosorbent assay. RESULTS: A total of 84 HD patients were analysed at the end of an 18-month follow-up. Omentin-1 levels of HD patients with diabetes were found to be lower than of HD patients without diabetes (9.1±5.8ng/mL vs. 11.4±4.1ng/mL, respectively; P=0.015) at the end of follow-up. Omentin-1 levels of survived patients with diabetes were found to be higher than of nonsurvived patients with diabetes (16.5±10.1ng/mL vs. 12.9±5.3ng/mL, respectively; P=0.045). During follow-up, 36 patients (30%) died, of whom 25 had diabetes (34%). CONCLUSIONS: Serum omentin-1 levels were significantly lower in HD patients with diabetes. A decrease in omentin-1 levels could be an independent mortality risk factor in this patient group. Further investigation in a greater number of patients is needed.

Jukić A[1], Carević V[1], Zekanović D[2], Stojanović-Stipić S[3], Runjić F[1], Ljubković M[4], Fabijanić D[1].Impact of Percutaneous Coronary Intervention on Exercise-Induced Repolarization Changes in Patients With Stable Coronary Artery Disease. Am J Cardiol. 2015;116:853-7.

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Recent reports suggest T peak to T end (Tpe) interval and Tpe/QT ratio as valuable indicators of increased arrhythmogenic risk in patients with coronary artery disease (CAD). We aimed to examine the exercise-induced changes in these indexes in patients with stable CAD, before and after percutaneous coronary intervention (PCI). Forty patients were consecutively included in the interventional group (n = 20), with significant lesions (≥75% luminal narrowing) suitable for PCI and in the control group (n = 20), with no significant coronary artery lesions (<50% luminal narrowing). One day before and 30 days after the coronarography, all patients performed treadmill exercise stress testing, and the electrocardiographic

(ECG) indexes of repolarization were assessed during baseline and at peak exercise intensity. In the control group, the QT interval, QTc (QT-corrected) interval, Tpe interval, and Tpe/QT ratio measured at peak exercise significantly decreased from baseline values ($p = 0.001$, $p = 0.004$, $p < 0.001$, and $p = 0.017$, respectively). Conversely, in interventional patients before the PCI, an increase in the Tpe interval and the Tpe/QT ratio was observed at exercise ($p = 0.009$, and $p < 0.001$, respectively), with only the QT interval exhibiting a significant decrease from baseline ($p < 0.001$). Thirty days after the PCI, all the ECG arrhythmogenic indexes measured at peak exercise significantly decreased from baseline values, thus assuming the same trend as detected in controls. In conclusion, restoration of blood supply normalized exercise-induced repolarization changes, suggesting that revascularization of previously ischemic myocardium lowers the cardiac arrhythmogenic potential in patients with stable CAD.