

CROATIAN INTERNATIONAL PUBLICATIONS

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Duvnjak L, Blaslov K, Vučić Lovrenčić M, Knežević Ćuća J. Persons with latent autoimmune diabetes in adults express higher dipeptidyl peptidase-4 activity compared to persons with type 2 and type 1 diabetes. *Diabetes Res Clin Pract.* 2016;121:119-126.

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AIMS: We aimed to determine serum dipeptidyl peptidase-4 (DPP-4) activity in a group of persons with latent autoimmune diabetes in adults (LADA) and to compare it with persons with type 1, type 2 diabetes and healthy controls. **METHODS:** DPP-4 activity measurement was performed in 67 persons (21 with type 1, 26 type 2 and 19 with LADA) and 13 healthy age and gender matched controls. **RESULTS:** Persons with LADA showed highest DPP-4 activity among the study groups (32.71 ± 3.55 vs 25.37 ± 2.84 vs 18.57 ± 2.54 vs 18.57 ± 2.61 U/L $p < 0.001$). Mean glutamic acid autoantibody in persons with LADA was 164.32 ± 86.28 IU/mL. It correlated with DPP-4 activity ($r = 0.484$, $p = 0.013$). Furthermore, DPP-4 activity correlated with waist circumference ($r = 0.279$, $p = 0.034$) and glycated haemoglobin A1c ($r = 0.483$, $p < 0.001$), as well as with LDL cholesterol ($r = 0.854$, $p < 0.001$) and total daily insulin dose ($r = 0.397$, $p = 0.001$). In the multinomial regression analysis DPP-4 activity remained associated with both LADA (prevalence ratio 1.058 (1.012-1.287), $p = 0.001$) and type 1 diabetes (prevalence ratio 1.506 (1.335-1.765), $p < 0.001$) while it did not show an association with type 2 diabetes (prevalence ratio 0.942 (0.713-1.988), $p = 0.564$). **CONCLUSIONS:** Persons with LADA express higher DPP-4 activity compared to persons with both type 1 and type 2 diabetes. The possible pathophysiological role of DPP-4 in the LADA pathogenesis needs to be further evaluated.

Brcic L^{1,2}, Jakopovic M³, Mistic M⁴, Seiwert F³, Kern I⁵, Smojver-Jezek S⁶, Quehenberger F⁷, Samarzija

M³, Seiwert S⁴. Analysis of the frequency of EGFR, KRAS and ALK mutations in patients with lung adenocarcinoma in Croatia. *Diagn Pathol.* 2016;11(1):90.

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BACKGROUND: Many studies have been published on the mutational status of patients with lung adenocarcinomas, and great population-based variability in mutation frequencies has been reported. The main objective of the present study was to analyze the EGFR, KRAS and ALK mutation status in a representative cohort of patients in Croatia with lung adenocarcinomas and to correlate the mutational status with clinical data. **METHODS:** All patients who were newly diagnosed within 6 months with histologically proven primary lung adenocarcinomas were included. Mutational analyses for EGFR and KRAS mutations were performed in a cobas z 480 analyzer. ALK immunohistochemistry was performed using the D5F3 clone on Benchmark XT instrument. Clinical data were obtained from the medical records. **RESULTS:** Of the 324 patients, 59.9% were male. At the time of diagnosis, the patients ranged in age range from 35 to 88 years (median 63 years). Most of the patients were current smokers or former smokers (77.2%). EGFR mutations were found in 15.7% of the patients, and of these mutations, exon 19 deletion was the most common (45.1%). KRAS mutations were present in 34.9% of the patients, while 4.1% of patients were ALK-positive. The statistical significance of the presence of mutations was detected for both gender

and smoking. **CONCLUSION:** The detected mutation rates demonstrated a slightly higher prevalence of KRAS mutations, but not a higher prevalence of EGFR mutations or ALK gene rearrangement, in comparison with the rates found in other European countries. EGFR and ALK mutational status showed a statistically significant correlation with gender as well as with smoking, while KRAS mutation status showed a statistically significant correlation only with smoking.

Pećina-Šlaus N¹, Kafka A¹, Vladušić T², Pećina H³, Hrašćan R². AXIN1 Expression and Localization in Meningiomas and Association to Changes of APC and E-cadherin. *Anticancer Res.* 2016;36(9):4583-94.

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BACKGROUND/AIM: Tumor suppressor gene AXIN1 is an inhibitor of Wnt signaling pathway. It down-regulates the pathway's main signaling effector molecule, beta-catenin, in an AXIN-based destruction complex. In the present study we investigated the involvement of AXIN1 in intracranial meningioma. **MATERIALS AND METHODS:** Loss of heterozygosity and microsatellite instability analyses were performed. The consequences of genetic changes on protein expression levels were studied in the same patients by immunohistochemistry. **RESULTS:** Allelic deletions of AXIN1 gene were found in 21.1% of meningiomas. Microsatellite instability was also observed in 5.3% of cases. Weak or lack of AXIN1 expression was found in 21.9% of meningiomas. We found strong statistical correlations between cytoplasmic localization of AXIN1 and its weak expression and also between the simultaneous cytoplasmic and nuclear localizations and moderate and strong expression levels ($p < 0.000$). The findings on AXIN1 were compared to concomitant expression of APC, beta-catenin and E-cadherin in the same patients by Chi-Square tests and Pearson's correlations. Analysis revealed that AXIN1 genetic changes were significantly associated to lack of the expression of APC and presence of mutant APC proteins ($p < 0.018$). Moderate and strong cytoplasmic and nuclear AXIN1 expressions were positively correlated to strong expression of E-cadherin ($p < 0.05$). **CONCLUSION:** Our findings on genetic

changes and expression levels of AXIN1 bring novel data on its involvement in meningeal brain tumors and reveal AXIN1's relation to specific Wnt molecules.

Mihaljevic S¹, Aukst-Margetic B², Karnicnik S³, Vuksan-Cusa B⁴, Milosevic M⁵. Do spirituality and religiousness differ with regard to personality and recovery from depression? A follow-up study. *Compr Psychiatry.* 2016;70:17-24.

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BACKGROUND: The studies show that both spirituality and religiousness are protective for mental health. Personality is related with course and outcome of depression, as well as spirituality and religiousness, and their relations toward to recovery from depression are underresearched. This study followed influence of spirituality and religiousness on course and outcome of depression in patients with depressive episode, controlled for personality dimensions. **METHODS:** The patients were assessed with self-report measures of depression (Beck Depression Inventory), spirituality (WHO-Quality of Life-Spiritual, Religious, Personal Beliefs), religiousness (Duke University Religion Index) and personality (Temperament and Character Inventory). Ninety nine patients finished a year long follow up. **RESULTS:** Higher spirituality influenced recovery of depression in patients with depressive episode, but religiousness did not show to be significant predictor of recovery for depression. Dimension harm avoidance was significant predictor of improvement of depression in all points of measurement. **LIMITATIONS:** Some limitations of this research are small sample size, usage of the self-report measures of depression in follow-up period, and the predominantly Catholic affiliation of the participants that can impact the generalizability of our data to other denominations. **CONCLUSION:** Spirituality and dimension harm avoidance are significant predictors of recovery from depression during a year long follow up.

Milošević M¹, Friedrich L¹, Tomasović S², Bielen I². Online epilepsy counseling in Croatia: What do users want to know? *Seizure.* 2016;41:116-9.

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PURPOSE: The purpose of this study is to better understand which specific epilepsy-related issues are cause for seeking out professional advice online. **METHOD:** An online epilepsy counseling service introduced by the Croatian Epilepsy Association allows users to anonymously submit questions related to epilepsy via e-mail or online contact form, which are later answered by an epilepsy professional. The questions were classified both by inquirers and by content. Inquirers were classified as patients, patient's parents, family members, partners, and friends of patients with epilepsy. In terms of content, questions were divided into three groups: medical, socially-oriented, and unclassifiable questions. **RESULTS:** In sum, 355 e-mails, which included 513 questions, were analyzed. The vast majority of inquirers were patients themselves (48%) and parents of patients (28%). While 76% of questions concerned the medical aspects of epilepsy, there was as well significant interest in administrative and practical issues associated with the diagnosis of epilepsy. Among medical questions, the most popular concerned prognosis (15%) and second opinions (14%); among socially-oriented questions, inquirers were primarily interested in matters associated with their profession (28%). As well, the parents of patients were more likely to question an epilepsy diagnosis than the patients themselves ($p < 0.001$). **CONCLUSION:** According to the results of this study, it is clear that epilepsy professionals should invest more time in discussing with patients the topics which interest them the most, as well as refer them to other professionals that can help them with non-medical epilepsy-related issues, and advise them on reliable Internet sources.

Bojanić K¹, Grubić M², Bogdanić A², Vuković J², Weingarten TN³, Huebner AR⁴, Sprung J⁵, Schroeder DR⁶, Grizelj R². Neurocognitive outcomes in congenital diaphragmatic hernia survivors: a cross-sectional prospective study. J Pediatr Surg. 2016;51(10):1627-34.

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BACKGROUND/PURPOSE: Congenital diaphragmatic hernia (CDH) survivors may have persistent neurocognitive delays. We assessed neurodevelopmental outcomes in CDH survivors from infancy to late teenage years. **METHODS:** A cross-sectional study was conducted on 37 CDH survivors to examine neurocognitive functioning. Overall cognitive score was tested with the early learning composite (ELC) of Mullen Scales of Early Learning ($n=19$), and Full Scale IQ (FSIQ) of Wechsler Intelligence Scale for Children-Fourth Edition ($n=18$). **RESULTS:** ELC was 85.7 ± 16.4 , lower than the expected norm of 100, $P=0.004$, and 6 survivors had moderate, and 3 severe delay, which is not greater than expected in the general population ($P=0.148$). FSIQ was 99.6 ± 19.1 , consistent with the expected norm of 100, $P=0.922$, and 3 survivors had moderate and 2 severe delay, which is greater than expected ($P=0.048$). Although ELC was lower than FSIQ ($P=0.024$), within each testing group overall cognitive ability was not associated with participant age (ELC, $P=0.732$; FSIQ, $P=0.909$). Longer hospital stay was the only factor found to be consistently associated with a worse cognitive score across all participants in our cohort. **CONCLUSIONS:** A high percentage of survivors with CDH have moderate to severe cognitive impairment suggesting that these subjects warrant early testing with implementation of therapeutic and educational interventions.

Boban M¹, Barisic M², Persic V¹, Zekanovic D³, Medved I⁴, Zulj M⁵, Vcev A⁵. Muscle strength differ between patients with diabetes and controls following heart surgery. J Diabetes Complications. 2016;30(7):1287-92.

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BACKGROUND: The aim of our study was to analyze muscle strength in patients with recent surgical treatment for ischemic and combined ischemic-valvular heart disease, based on existence of diabetes mellitus. Connections existing between muscle strength and patient characteristics or conventional diagnostic tests were analyzed as well. **METHODS:** Study prospectively included consecutive patients scheduled for cardiovascular rehabilitation 0-3 months after heart surgery. Diagnostics covered drug utilization, anthropometrics, demographics, echocardiography, conventional laboratory, echocardiography, bioelectrical impedance analysis (BIA), and hand grip test (HGT). HGT was analyzed for dominant hand. **RESULTS:** Patients with diabetes had significantly weaker muscle strength on HGT than controls; 29.4 ± 12.2 kg vs. 38.2 ± 14.7 kg ($p=0.029$), respectively. ROC analysis for HGT and existence of diabetes mellitus were significant; ≤ 40 kg had sensitivity of 89.7% (95%CI: 72.6-97.8), specificity 43.7% (31.9-56.0); AUC 0.669 (0.568-0.760); $p=0.002$. HGT significantly correlated with hematocrit (Rho CC=0.247; $p=0.013$), whilst other laboratory or echocardiographic parameters were insignificant (all $p>0.05$). HGT also correlated with body weight (Rho CC=0.510; $p<0.001$); height (Rho CC=0.632; $p<0.001$); waist circumference (Rho CC=0.388; $p<0.001$); waist-to-hip ratio (Rho CC=0.274; $p=0.006$) and BIA (Rho CC=-0.412; $p<0.001$). **CONCLUSIONS:** In postoperative recovery of patients with diabetes, muscle strength assessed by HGT is decreased and in relation with nutritional status. Clinically resourceful connections of HGT were also found to hematocrit and utilization of loop diuretics.

aim of our study was to analyze prolonged utilization of proton pump inhibitors in medical therapy of patients with ischemic and valvular heart disease. Secondly, profile of utilization was scrutinized to patient characteristics and type of cardiovascular treatments. **METHODS:** The study included consecutive patients scheduled for cardiovascular rehabilitation 2-6 months after index cardiovascular treatment. **RESULTS:** Two hundred ninety-four patients ($n=294/604$; 48.7%) have been using proton pump inhibitor in their therapy after index cardiovascular treatment. Cardiovascular treatments were powerfully connected with utilization of PPIs; surgery 5.77 (95%-confidence intervals [CI]: 4.05-8.22; $p<0.001$) and PCI 0.15 (CI: 0.10-0.22; $p<0.001$). The odds for having proton pump inhibitor in their chronic therapy were increased for atrial fibrillation 1.87 (CI: 1.08-3.23; $p=0.025$) and decreased for obesity 0.65 (CI: 0.45-0.96; $p=0.035$); surviving myocardial infarction 0.49 (CI: 0.29-0.83; $p=0.035$). Multinomial logistic regression controlled for existence of chronic renal disease found no significant association of renal dysfunction and PPI therapy. The existence of anemia was significantly increased in patients taking PPIs than controls; 6.00 (CI: 3.85-9.33; $p<0.001$). The use of PPI was also associated with worsening of metabolic profile, in part due to decreased utilization of ACE-inhibitors and statins. PPI consumption correlated with age of patients (Rho=0.216; $p<0.001$). **CONCLUSIONS:** High proportion of cardiovascular, particularly surgical patients with ischemic and valvular heart disease utilized proton pump inhibitor in prolonged courses. Prolonged courses of PPIs were connected with existence and worsening of red blood count indexes, older age, lesser weight of patients and underutilization of cardioprotective drugs.

Boban M¹, Zulj M², Persic V¹, Medved I³, Zekanovic D¹, Vcev A². Prolonged utilization of proton pump inhibitors in patients with ischemic and valvular heart disease is associated with surgical treatments, weight loss and aggravates anemia. Int J Cardiol. 2016;219:277-81.

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BACKGROUND: Proton pump inhibitors (PPIs) are among the commonest drugs used nowadays. The