

CROATIAN INTERNATIONAL PUBLICATIONS

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Lesin M¹, Dzaja Lozo M¹, Duplancic-Sundov Z¹, Dzaja I¹, Davidovic N², Banozic A³, Puljak L³. Risk factors associated with postoperative pain after ophthalmic surgery: a prospective study. *Ther Clin Risk Manag.* 2016;12:93-102.

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BACKGROUND: Risk factors associated with postoperative pain intensity and duration, as well as consumption of analgesics after ophthalmic surgery are poorly understood. **METHODS:** A prospective study was conducted among adults (N=226) who underwent eye surgery at the University Hospital Split, Croatia. A day before the surgery, the patients filled out questionnaires assessing personality, anxiety, pain catastrophizing, sociodemographics and were given details about the procedure, anesthesia, and analgesia for each postoperative day. All scales were previously used for the Croatian population. The intensity of pain was measured using a numerical rating scale from 0 to 10, where 0 was no pain and 10 was the worst imaginable pain. The intensity of pain was measured before the surgery and then 1 hour, 3 hours, 6 hours, and 24 hours after surgery, and then once a day until discharge from the hospital. Univariate and multivariate analyses were performed. **RESULTS:** A multivariate analysis indicated that independent predictors of average pain intensity after the surgery were: absence of premedication before surgery, surgery in ge-

neral anesthesia, higher pain intensity before surgery and pain catastrophizing level. Independent predictors of postoperative pain duration were intensity of pain before surgery, type of anesthesia, and self-assessment of health. Independent predictors of pain intensity ≥ 5 during the first 6 hours after the procedure were the type of procedure, self-assessment of health, premedication, and the level of pain catastrophizing. **CONCLUSION:** Awareness about independent predictors associated with average postoperative pain intensity, postoperative pain duration, and occurrence of intensive pain after surgery may help health workers to improve postoperative pain management in ophthalmic surgery.

Erjavec I¹, Bordukalo-Niksic T¹, Brkljacic J¹, Grcevic D², Mokrovic G³, Kesic M³, Rogic D⁴, Zavadovski W⁵, Paralkar VM⁵, Grgurevic L¹, Trkulja V⁶, Cicin-Sain L³, Vukicevic S¹. Constitutively elevated blood serotonin is associated with bone loss and type 2 diabetes in rats. *PLoS One.* 2016;11(2):e0150102.

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Reduced peripheral serotonin (5HT) in mice lacking tryptophan hydroxylase (TPH1), the rate limiting enzyme for 5HT synthesis, was reported to be anabolic to the skeleton. However, in other studies TPH1 deletion either had no bone effect or an age dependent inhibition of osteoclastic bone resorption. The role of 5HT in bone therefore remains poorly understood. To address this issue, we used selective breeding to create rat sublines with constitutively high (high-5HT) and low (low-5HT) platelet 5HT level (PSL) and platelet 5HT uptake (PSU). High-5HT rats had decreased bone volume due to increased bone turnover characterized by increased bone formation and mineral apposition rate, increased osteoclast number and serum C-telopeptide level. Daily oral administration of the TPH1 inhibitor (LX1032) for 6 weeks reduced PSL and increased the trabecular bone volume and trabecular number of the spine and femur in high-5HT rats. High-5HT animals also developed a type 2 diabetes (T2D) phenotype with increased: plasma insulin, glucose, hemoglobin A1c, body weight, visceral fat, β -cell pancreatic islets size, serum cholesterol, and decreased muscle strength. Serum calcium accretion mediated by parathyroid hormone slightly increased, whereas treatment with 1,25(OH)2D3 decreased PSL. Insulin reduction was paralleled by a drop in PSL in high-5HT rats. In vitro, insulin and 5HT synergistically up-regulated osteoblast differentiation isolated from high-5HT rats, whereas TPH1 inhibition decreased the number of bone marrow-derived osteoclasts. These results suggest that constitutively elevated PSL is associated with bone loss and T2D via a homeostatic interplay between the peripheral 5HT, bone and insulin.

Babić Leko M¹, Borovečki F², Dejanović N³, Hof PR⁴, Šimić G¹. Predictive value of cerebrospinal fluid visinin-like protein-1 levels for Alzheimer's disease early detection and differential diagnosis in patients with mild cognitive impairment. J Alzheimers Dis. 2016;50(3):765-78.

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Visinin-like protein 1 (VLIP-1) recently emerged as a potential biomarker of Alzheimer's disease (AD). This neuronal calcium sensor protein previously used as a marker of acute ischemic stroke is elevated in the cerebrospinal fluid (CSF) of AD patients. The goal of this study was to assess CSF VLIP-1 potential in early AD diagnosis and in differentiating mild cognitive impairment (MCI) patients with and without risk of AD. Additionally, we tested VLIP-1 ability to differentiate AD from other primary causes of dementia, and predict the progression of AD-related cognitive decline. VLIP-1 levels were compared with five CSF AD biomarkers (t-tau, A β 1-42, p-tau181, p-tau199, and p-tau231). VLIP-1 successfully differentiated two MCI patient groups characterized by absence or presence of pathological levels of these CSF biomarkers, except for t-tau. VLIP-1/A β 1-42 and VLIP-1/p-tau181 ratios also differentiated MCI patients with pathological CSF biomarker levels. However, there was no difference in VLIP-1 levels between AD and MCI patients. VLIP-1/A β 1-42 and VLIP-1/p-tau231 ratios reached high sensitivities (above 70%) and very high specificities (above 85%) in differentiating AD patients from HC. Additionally, VLIP-1 differentiated AD from patients with Lewy body disease with 77.1% sensitivity and 100% specificity. VLIP-1 potential as a prognostic biomarker of cognitive decline in AD was also proved since VLIP-1/t-tau, VLIP-1/p-tau181, and VLIP-1/p-tau231 ratios correlated with MMSE scores. These data indicate that VLIP-1 alone or in combination with other AD CSF biomarkers represent a valuable marker for the early diagnosis of AD, recognition of MCI patients at higher risk to develop dementia, and in differentiating AD from LBD.

Kulić A¹, Plavetić ND^{2,3}, Gamulin S⁴, Jakić-Razumović J^{5,3}, Vrbanec D^{2,3}, Sirotković-Skerlev M^{6,7}. Telomerase activity in breast cancer patients: association with poor prognosis and more aggressive phenotype. Med Oncol. 2016;33(3):23.

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Telomerase expression is an important mechanism of tumor unlimited replicative potential. The aim of this study was to evaluate prognostic impact of telomerase activity in breast cancer patients and to correlate telomerase activity with established prognostic factors. We analyzed tissue of 102 malignant breast lesions and 20 healthy breast tissues. Telomerase activity was determined by telomeric repeat amplification protocol assay. Telomerase activity was present in 77 (75.49 %) of 102 breast cancers. Telomerase activity in breast cancers was statistically significantly higher in comparison with the activity in normal breast tissue. The levels of telomerase activity were significantly positively correlated with tumor size, axillary nodal status, histological grade, HER-2/neu protein expression in tumor tissue and expression of the nuclear antigen Ki-67. A statistically significant negative correlation was found between the presence of ER and telomerase activity. There was no correlation between telomerase activity and concentration of PR or the age of patients. Kaplan-Meier analysis showed that patients with higher telomerase activity had significantly shorter 10-year disease-free survival ($p < 0.0001$) and 10-year overall survival ($p < 0.0001$) than those with lower telomerase activity. These results were confirmed by logistic regression analysis. Our results support the prognostic role of telomerase activity and its relationship with the more aggressive phenotype of breast cancer.

Karabuva S¹, Vrkić I¹, Brizić I², Ivić I^{1,3}, Lukšić B^{1,3}.
Venomous snakebites in children in southern Croatia.
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This retrospective study represents observation of 160 children and adolescents aged up to 18 years that experienced venomous snakebites in southern Croatia and were

treated in the Clinical Department of Infectious Diseases in the University Hospital Centre Split from 1979 to 2013. The main purpose of this research was to determine the epidemiological characteristics, clinical presentation, local and general complications, and received treatment. Most bites occurred during warm months, from early May to late August (80%), mostly in May and June. Upper limb bites were more frequent (59%) than lower limb bites (40%). Out of the total number of poisoned children, 24% developed local, and 25% general complications. The most common local complications were haemorrhagic blisters that occurred in 20% children, followed by compartment syndrome presented in 7.5% patients. The most dominated general complication was cranial nerve paresis or paralysis, which was identified in 11.2% patients, whereas shock symptoms were registered in 7% children. According to severity of poisoning, 9.4% children had minor, 35% mild, 30.6% moderate, and 24.4% had severe clinical manifestation of envenomation. Only one (0.6%) child passed away because of snakebite directly on the neck. All patients received antivenom produced by the Institute of Immunology in Zagreb, tetanus prophylaxis as well, and almost all of them received antibiotics, and a great majority of them also received corticosteroids and antihistamines. Neighter anaphylactic reaction nor serum disease were noticed in our patients after administrating antivenom. A total of 26% children underwent surgical interventions, and incision of haemorrhagic blister was the most common applied surgical treatment, which was preformed in 15.6% patients, while fasciotomy was done in 7.5% subjects. All of our surgically treated patients recovered successfully.

Starčević M¹, Predojević M², Butorac D³, Tumbri J¹, Konjevoda P⁴, Kadić AS⁵. Early functional and morphological brain disturbances in late-onset intrauterine growth restriction. *Early Hum Dev*. 2016;93:33-8.

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AIMS: To determine whether the brain disturbances develop in late-onset intrauterine growth restriction (IUGR) before blood flow redistribution towards the fetal brain (detected by Doppler measurements in the middle cerebral artery and umbilical artery). Further, to evaluate predictive values of Doppler arterial indices and umbilical cord blood gases and pH for early functional and/or morphological brain disturbances in late-onset IUGR. **STUDY DESIGN:** This cohort study included 60 singleton term pregnancies with placental insufficiency caused late-onset IUGR (IUGR occurring after 34 gestational weeks). Umbilical artery resistance index (URI), middle cerebral artery resistance index (CRI), and cerebroumbilical (C/U) ratio (CRI/URI) were monitored once weekly. Umbilical blood cord samples (arterial and venous) were collected for the analysis of pO₂, pCO₂ and pH. Morphological neurological outcome was evaluated by cranial ultrasound (cUS), whereas functional neurological outcome by Amiel-Tison Neurological Assessment at Term (ATNAT). **RESULTS:** 50 fetuses had C/U ratio > 1, and 10 had C/U ratio ≤ 1; among these 10 fetuses, 9 had abnormal neonatal cUS findings and all 10 had non-optimal ATNAT. However, the total number of abnormal neurological findings was much higher. 32 neonates had abnormal cUS (53.37%), and 42 (70.00%) had non-optimal ATNAT. Furthermore, Doppler indices had higher predictive validity for early brain disturbances than umbilical cord blood gases and pH. C/U ratio had the highest predictive validity with threshold for adverse neurological outcome at value 1.13 (ROC analysis), i.e., 1.18 (party machine learning algorithm). **CONCLUSION:** Adverse neurological outcome at average values of C/U ratios > 1 confirmed that early functional and/or structural brain disturbances in late-onset IUGR develop even before activation of fetal cardiovascular compensatory mechanisms, i.e., before Doppler signs of blood flow redistribution between the fetal brain and the placenta.

Pustišek N¹, Vurnek Živković M², Šitum M³. Quality of life in families with children with atopic dermatitis. *Pediatr Dermatol.* 2016;33(1):28-32.

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BACKGROUND: Atopic dermatitis (AD) is a common childhood disease of increasing prevalence that not only changes the life of the affected children, but also affects the social and emotional functioning of their families. **OBJECTIVES:** The aim of our study was to assess the quality of life (QOL) of parents with children with AD and its predictors. **METHODS:** One hundred seventy-one parents of children with AD attending the outpatient Pediatric Dermatology Unit, Children's Hospital Zagreb, participated in the study. The severity of AD was estimated using the Scoring Atopic Dermatitis (SCORAD) index. Parents were asked to complete the Croatian version of the Family Dermatology Life Quality Index (FDLQI), the Patient-Oriented (PO) SCORAD, the Perceived Stress Scale (PSS), and a general questionnaire during a regular follow-up visit. **RESULTS:** Family QOL is significantly correlated with the SCORAD score (correlation coefficient [r] = 0.578), PO SCORAD (r = 0.447), itching (r = 0.528), sleeplessness (r = 0.583), and PSS (r = 0.464). When these factors were entered into a regression analysis, they predicted as much as 67% of the variance of QOL (FDLQI), with significant predictors being PO SCORAD, PO sleeplessness, and PSS, and they remained significant even after controlling for a number of general and medical factors. **CONCLUSIONS:** The severity of illness as perceived by dermatologists and parents is similar, and itching, sleeplessness, and perceived stress are strong QOL predictors of parents caring for children with AD.