CROATIAN INTERNATIONAL PUBLICATIONS

by Ivan Bohaček

ibohacek@hiim.hr

Boban M[1,2], Pesa V[1], Antic Kauzlaric H[1], Brusich S[3], Rotim A[1], Madzar T[2], Zulj M[2], Vcev A[2]. Ventricular diastolic dimension over maximal myocardial thickness is robust landmark of systolic impairment in patients with hypertrophic cardiomyopathy. Med Sci Monit. 2018;24:1880-1886.

[1]Department of Cardiology, University Hospital "Thalassotherapia Opatija", Medical Faculty University of Rijeka, Rijeka, Croatia; [2]Department of Internal Medicine, Medical Faculty "J.J. Strossmayer" University of Osijek, Osijek, Croatia; [3]Department of Cardiology, University Hospital Centre Rijeka, Medical Faculty University of Rijeka, Rijeka, Croatia.

BACKGROUND The effects of focal hypertrophy on geometry of the left ventricle and systolic function have not been studied in patients with hypertrophic cardiomyopathy (HCM), despite the fact that the former is the most prominent disease characteristic. The aim of our study was to analyze systolic function over ventricle geometry, generating a functional index made from left ventricle end diastolic dimension (LVEDD) divided by end diastolic thickness of the region with maximal extent of hypertrophy and interventricular septum. MATERIAL AND METHODS Our hospital database of cardiac magnetic resonance was screened for HCM. Geometric functional index (GFI) was calculated for LVEDD over maximal end diastolic thickness (MaxEDT) giving GFI-M, while LVEDD over interventricular septum was expressed as GFI-I. There were 55 consecutive patients with HCM. RESULTS There were 43 males (78.2%) and 12 females (21.8%). The mean age was 52.3±16.7 years (range: 15.5-76.4 years). A significant difference of GFI was found for preserved versus impaired systolic function of the left ventricle (preserved systolic function); GFI-M 2.28±0.60 versus 3.66±0.50 (p<0.001), and GFI-I 2.75±0.88 versus 3.81±0.87 (p<0.001), respectively. Diagnostic value was tested using receiver operating curve (ROC) analyzes, with GFI-M area under curve (AUC)=0.959 (95% CI: 0.868-0.994); (p<0.001) and GFI-I-AUC=0.847 (0.724-0.930); (p<0.001). GFI-M was superior to GFI-I for appraisal of left ventricle systolic dysfunction in HCM; ΔAUC=0.112 (0.018-0.207); (p=0.020). CONCLUSIONS GFI is a simple tool, with high sensitivity and specificity for detecting impairment of systolic function in patients with HCM. Further studies would be necessary to investigate its clinical and prognostic impacts, as well as reproducibility with prospective validation.

Božek T[1], Bilić-Ćurčić I[2], Berković MC[3], Gradišer M[4], Kurir TT[5], Majanović SK[6], Marušić S[7]. The effectiveness of lixisenatide as an add on therapy to basal insulin in diabetic type 2 patients previously treated with different insulin regimes: a multi-center observational study. Diabetol Metab Syndr. 2018;10:16.

[1]University Clinic for Diabetes Vuk Vrhovac, Zagreb, Croatia; [2]Department of Pharmacology, Faculty of Medicine, University J. J. Strossmayer Osijek, Clinical Hospital Center Osijek, Osijek, Croatia; [3]Department for Endocrinology, Diabetes and Metabolism, University Hospital Centre "Sestre Milosrdnice", Zagreb, Croatia; [4]Internal Medicine Ward, General Hospital Čakovec, Čakovec, Croatia; [5]Department for Endocrinology, Diabetes and Metabolism, University Hospital Center Split, Split, Croatia; [6]Department for Endocrinology, Diabetes and Metabolism, University Hospital Center Rijeka, Rijeka, Croatia; [7]Department for Endocrinology, Diabetes and Metabolism, Clinical Hospital Dubrava, Zagreb, Croatia.

INTRODUCTION: This observational study aimed to assess the effectiveness of lixisenatide as add on therapy to basal insulin in diabetic type 2 patients previously treated with different insulin regimes. METHODS: Patients with diabetes type 2, prescribed with lixisenatide and basal insulin were divided in three groups (premixed insulin, basal bolus insulin and basal oral therapy (BOT). Difference in mean change in HbA1c, body mass index, total

insulin doses, fasting blood glucose (FPG) and prandial blood glucose (PPG) were assessed after 3-6-months of follow-up. RESULTS: The primary outcomes were assessed in 111 patients. Lixisenatide added to basal insulin, reduced HbA1c and body weight significantly in all three groups of patients ($p < 0.001$ for all), with the most prominent reduction in the basal bolus group of patients which had the highest baseline HbA1c compared to premix and BOT treatment groups. Regarding a difference in total insulin dose the reduction was statistically significant in the basal bolus ($p = 0.006$) and premix group ($p < 0.001$). FPG and PPG were also significantly reduced over time in all three groups ($p < 0.001$ for all). A composite outcome (reduction of HbA1c below 7% (53 mmol/mol) with any weight loss) was achieved in 27% of total patients included in the study, reduction of HbA1c below 7% was observed in 30% of patients, while 90% of patients experienced weight reduction. CONCLUSION: These results indicate that lixisenatide add on basal insulin treatment (BIT) can improve glycemic control in a population with long-standing type 2 diabetes and previously uncontrolled on other insulin therapy.

Antunac Golubić Z[1], Baršić I[2], Librenjak N[1], Pleština S[1]. Vitamin D supplementation and survival in metastatic colorectal cancer. Nutr Cancer. 2018;70(3):413-417.

[1]Department of Oncology, University Hospital Centre Zagreb, Zagreb, Croatia; [2]Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia

BACKGROUND: Some studies have demonstrated that higher baseline plasma levels of 25-hydroxivitamin D [25(OH)D] are associated with a significant reduction in colorectal cancer (CRC) incidence. Patients with metastatic CRC (mCRC) tend to be vitamin D insufficient, but the effect of vitamin D on the survival of mCRC patients still remains uncertain. In this study, we evaluated the association between cholecalciferol 2,000 IU daily supplementation and survival of mCRC patients. METHODS: Seventy-two patients with mCRC were included. Seventy-one patients with 25(OH)D levels <75 nmol/l were randomized to receive standard chemotherapy or standard chemotherapy with cholecalciferol 2,000 IU daily. The primary endpoint was overall survival (OS) and the secondary endpoint was progression-free survival (PFS). The follow-up period was 46 mo. RESULTS: All but one patient (98.6%) was vitamin D insufficient. There was no statistically significant difference in OS or PFS between those who received vitamin D supplements and controls. CONCLUSIONS: The majority of patients with mCRC are vitamin D insufficient at the time of diagnosis. In our study, adding 2,000 IU of cholecalciferol daily for 2 yr to standard chemotherapy did not show any benefit in OS or PFS.

Maric LS[1,2], Lepej SZ[1], Gorenec L[1], Grgic I[1], Trkulja V[3], Rode OD[1], Roglic S[1], Grmoja T[4], Barisic N[3,5], Tesovic G[1,3]. Chemokines CXCL10, CXCL11, and CXCL13 in acute disseminated encephalomyelitis, non-polio enterovirus aseptic meningitis, and neuroborreliosis: CXCL10 as initial discriminator in diagnostic algorithm? Neurol Sci. 2018;39(3):471-479.

[1]Pediatric Infectious Diseases Department, University Hospital for Infectious Diseases "dr.Fran Mihaljevic", Zagreb, Croatia; [2]University of Zagreb School of Dental Medicine, Zagreb, Croatia; [3]University of Zagreb School of Medicine, Zagreb, Croatia; [4]Department of Radiology, Children's Hospital Zagreb, Zagreb, Croatia; [5]Department of Pediatrics, University Hospital Center Zagreb, Zagreb, Croatia

We investigated potential diagnostic usefulness of serum and cerebrospinal fluid (CSF) concentrations of chemokines CXCL10, CXCL11, and CXCL13 in pediatric patients with acute disseminated encephalomyelitis (ADEM) ($n = 23$), non-polio enterovirus aseptic meningitis (NPEV AM) ($n = 20$), and neuroborreliosis (NB) ($n = 21$) and children with acute infectious diseases with neurological symptoms but with excluded neuroinfection/neuroinflammation (controls, $n = 20$). CSF levels of CXCL10 and CXCL11 were higher in patients with NPEV AM than those in other children, and CXCL10 levels showed a high discriminative potential (area under the receiver operating characteristic curve, ROC, 0.982) with high specificity and sensitivity (both 95%). CSF levels of CXCL13 were higher in NB patients than those in other children; however, discriminative potential (area under ROC curve 0.814) and diagnostic properties were moderate (sensitivity 67%, specificity 97%). Data suggest usefulness of chemokine quantification as a diagnostic aid in children with suspected ADEM, NPEV AM, or NB.

Vucak J[1], Turudic D[2], Milosevic D[2,3], Bilic M[2], Salek Z[2], Rincic M[4], Bilic E[2,5]. Genotype-phenotype correlation of β-thalassemia in Croatian patients: A specific HBB gene

mutations. J Pediatr Hematol Oncol. 2018;40(2):e77-e82.

[1]Primary Health Care Pediatrician, Sibenik; [2]Department of Pediatrics, University Hospital Centre Zagreb; [3]University of Zagreb School of Medicine; [4]Croatian Brain Research Institute, University of Zagreb School of Medicine; [5]Department of Pediatrics, Referral Centre for Pediatrics Hematology and Oncology, University of Zagreb School of Medicine, Zagreb, Croatia

An analysis of genotype-phenotype correlation was performed for 14 patients with beta-thalassemia who had been registered in Referral Centre for hematology and oncology of the University Hospital Centre, Zagreb, Croatia. HBB gene mutations were determined using a gene-specific Q5 High-Fidelity PCR analysis with direct DNA sequencing of amplified transcripts. Mahidol score index used for classification of thalassemia severity was found to be low for all the patients enrolled in the study, indicating a mild β-thalassemia phenotype with no signs of disease progression. Most of the patients have already described gene mutations: IVS-II-666 C>T (HBB:c.316-185C>T) and IVS-II-16 G>C (HBB:c.315+16G>C). Each of the aforementioned mutations was found in (11/14; 78,57%) and (10/14; 71,43%) of our patients, respectively. Recently published HBB:c.9T>C mutation was found in 8 of 14 (57,14%) in our study group. IVSII-74 T>G (HBB:c.315+74T>G) is a worldwide mutation found in 6 of 14 (42.86%) of our patients. All these mutations occur among Croatian children with no obvious Indian/Near Eastern/Iranian ancestry. We also identified 7 de novo mutations (c.316-135het_dupT, c.316-133A>G, c.93-54-G>A, c.316-68_316-67het_insCGG, c.316-342delA, c.316-312delT, c.316-209delT) of mild severity phenotype according to Mahidol classification score index. We did not find children or adults with thalassemia major severity phenotype.

Kokic V[1], Martinovic Kaliterna D[2], Radic M[2], Tandara L[3], Perkovic D[2]. Association between vitamin D, oestradiol and interferon-gamma in female patients with inactive systemic lupus erythematosus: A cross-sectional study. J Int Med Res. 2018;46(3):1162-1171.

[1]Division of Endocrinology, Diabetes and Metabolic Disease, University Hospital of Split, School of Medicine, Split, Croatia; [2]Division of Rheumatology and Clinical Immunology, University Hospital of Split, Split, Croatia; [3]Department of Medical Laboratory Diagnostic, University Hospital of Split, Split, Croatia.

OBJECTIVES To investigate possible associations between 25-hydroxyvitamin D3 (25(OH)D3), oestradiol (E2) and IFN-gamma (IFNγ) in female patients with inactive systemic lupus erythematosus (SLE). METHODS Female patients with inactive SLE and age-matched healthy controls were recruited into this cross-sectional study. Serum concentrations of 25(OH)D3, E2 and IFNγ were measured by radioimmunoassay with gamma-counters and enzyme-linked immunosorbent assay. RESULTS 36 patients and 37 controls were enrolled. In patients with SLE, the concentration of 25(OH)D3 was lower and E2 was higher compared with controls. In vitamin D deficient (i.e., 25(OH)D3≤20 ng/ml) patients, IFNγ was 150% higher compared with patients with 25(OH)D3>20 ng/ml and controls. The concentration of E2 was higher in all patients compared with controls independently of the vitamin D level. A difference was found between patients and controls in the correlation of 25(OH)D3 with E2 and a positive correlation was found between E2 and IFNγ in all participants. CONCLUSIONS Our results suggest that E2 may have a strong modulating effect on vitamin D function which is significant only at low concentration of E2.

Ban M, Miše BP, Majić A, Dražić I, Vrdoljak E. Efficacy and safety of palbociclib in heavily pretreated patients with HR+/HER2- metastatic breast cancer. Future Oncol. 2018;14(6):537-544.

Department of Oncology & Radiotherapy, University Hospital Centre Split, Split School of Medicine, Split, Croatia

AIM: CDK4/6 inhibitors in the first and second treatment line in patients with HR+/HER2- metastatic breast cancer (mBC) in combination with hormonal therapy improve progression-free survival. Role of CDK4/6 inhibitors in further treatment lines remains unclear. METHODS: Retrospective analysis of 24 HR+/HER2- heavily pretreated mBC patients is presented. RESULTS: A total of 58.3% patients achieved stable disease. No objective response was observed. Median progression-free survival was 4.8 months; median overall survival was 11 months. Treatment was well tolerated. CONCLUSION: Favorable toxicity profile and efficacy of palbociclib/aromatase inhibitors combination in heavily pretreated luminal mBC patients in this study emphasize the need for further investigation of such drugs in this population.

Crnogorac M[1], Horvatic I[1], Kacinari P[1], Ljubanovic DG[2], Galesic K[1]. Serum C3 complement levels in ANCA associated vasculitis at diagnosis is a predictor of patient and renal outcome. J Nephrol. 2018;31(2):257-262.

[1]Department of Nephrology and Dialysis, Dubrava University Hospital, Zagreb, Croatia; [2]Department of Pathology, Dubrava University Hospital, Zagreb, Croatia.

AIM: To determinate the prognostic significance of low serum C3 at the time of diagnosis of ANCA-associated vasculitis (AAV). METHODS: Our cohort included 75 consecutive patients with AAV diagnosed from January 2005 to December 2015. C3 levels were measured at the time of diagnosis. Patients were divided into two groups, those with low serum C3 levels (< 0.9 g/l) and those with normal serum C3 levels (0.9-1.8 g/l). We analyzed association between serum C3 levels and both combined and singularly patient and renal survival (ESRD). Small number of relapsed patients did not allow for the statistical analysis to be performed as to whether the low serum C3 is associated with relapse rate in AAV patients. RESULTS: Low serum C3 levels were significantly associated with worse combined end-point patient and renal survival (HR 3.079; 95% CI 1.231-7.701; p = 0.016), and on multivariate adjusted analysis association remained significant (HR 2.831; 95% CI 1.093-7.338; p = 0.032). For both end-points individually low serum C3 levels were significantly associated with poorer patient survival (HR 6.378; 95% CI 2.252-18.065; p < 0.001; on multivariate adjusted analysis HR 4.315 95% CI 1.350-13.799; p = 0.014) and renal survival (HR 3.207; 95% CI 1.040-9.830; p = 0.043; on multivariate adjusted analysis HR 3.679; 95% CI 1.144-11.827; p = 0.029). In our study there was no significant association between serological and pathohistological phenotypes and serum C3 levels. CONCLUSION: Lower serum C3 levels at the diagnosis is associated with poorer patient and renal outcomes in AAV patients.