



**Medicinska biohemija**

**Medical Biochemistry**



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## **APO E I LIPIDNI STATUS KOD PACIJENATA SA KRAJNJIM STADIJUMOM BOLESTI BUBREGA**

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Apolipoprotein E (ApoE) je glavni sastojak lipoproteina plazme. Pored velikog broja bioloških funkcija najznačajniji je uticaj na lipidni status i uloga u patogenezi i progresiji različitih bolesti bubrega i udruženih aterosklerotskih komplikacija. Cilj ovog rada je da se analizira uticaj tipa dijalize na nivo ApoE, kao i korelacija ApoE sa lipidnim i lipoproteinskim statusom kod pacijenata sa krajnjim stadijumom bolesti bubrega (KSBB).

U uzorcima seruma 224 KSBB pacijenata (114 na hemodijalizi (HD) i 110 na kontinuiranoj ambulantnoj peritonealnoj dijalizi (CAPD)) određene su vrednosti ApoE, apolipoproteina AI, apolipoproteina AII, apolipoproteina B i lipoproteina(a) (Lp(a)) metodom imunonefelometrije i vrednosti ukupnog holesterola (TC), triglicerida, holesterola lipoproteina male gustine (LDL-C) i lipoproteina velike gustine (HDL-C) metodom spektrofotometrije.

Neparametarskim Friedman-ovim testom dvostruke analize varijanse potvrđena je značajna razlika u vrednostima analiziranih parametara u odnosu na tip dijalize ( $p < 0,0001$ , CI 95%). U ispitivanim uzorcima HD pacijenata dobijene su niže vrednosti ApoE, apolipoproteina AI, apolipoproteina AII i TC u odnosu na iste parametre kod CAPD pacijenata ( $p < 0,05$ ). Dobijena je značajna pozitivna korelacija između ApoE i apolipoproteina AI u obe ispitivane grupe (za HD  $r = 0,311$  i za CAPD  $r = 0,283$ ,  $p < 0,05$ ). Literaturni podaci potvrđuju da se dislipidemija učestalije javlja kod CAPD pacijenata. Međutim, značajno niže vrednosti ApoE, apolipoproteina AI, apolipoproteina AII i TC kod HD pacijenata u ovoj studiji ukazuju da tip dijalize u izvesnoj meri utiče na lipidni i lipoproteinski status kod KSBB pacijenata. Pozitivna korelacija ApoE sa apolipoproteinom AI ukazuje na značajan efekat ovog transportnog glikoproteina u regulisanju dislipidemije kod KSBB pacijenata, nezavisno od tipa dijalize.

Mada je potvrđen efekat polimorfizma ApoE na patogenezu dislipidemija, određivanje ukupnog ApoE može da pomogne u proceni celokupnog lipidnog i lipoproteinskog statusa kod KSBB pacijenata. Takođe je važno da se u analizi optimalnih vrednosti lipoproteina uzme u obzir i značajan efekat tipa dijalize.

## **APO E AND LIPID STATUS IN END STAGE RENAL DISEASE PATIENTS**

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Apolipoprotein E (ApoE) is the main component of plasma lipoproteins. In addition to a large number of biological functions, the most significant is influence to the lipid status and role in pathogenesis and progression of various kidney diseases and associated atherosclerotic complications. The aim of this paper is to analyze the impact of the type of dialysis on the level of ApoE, as well as the correlation of ApoE with lipid and lipoprotein status in patients with end stage renal disease (ESRD).

In the serum samples of 224 ESRD patients (114 on hemodialysis (HD) and 110 on continuous ambulatory peritoneal dialysis(CAPD)), the values of ApoE, apolipoprotein AI, apolipoprotein AII, apolipoprotein B and lipoprotein (a) (Lp (a)) were determined by immunonephelometry and total cholesterol (TC), triglyceride, low density lipoprotein (LDL-C) and high density lipoprotein (HDL-C) cholesterol by spectrophotometry.

Difference in the values of the analyzed parameters according to the type of dialysis was confirmed with non-parametric test Friedman's two-way analysis of variance by ranks ( $p < 0.0001$ , CI 95%). We found lower values of ApoE, apolipoprotein AI, apolipoprotein AII and TC in HD patients in relation to the same parameters in CAPD patients ( $p < 0.05$ ). A significant positive correlation between ApoE and apolipoprotein AI was obtained in both the tested groups (for HD  $r = 0.311$  and for CAPD  $r = 0.283$ ,  $p < 0.05$ ). Literature data confirm that dyslipidemia occurs more frequently in CAPD patients. However, significantly lower values of ApoE, apolipoprotein AI, apolipoprotein AII, and TC in HD patients in this study indicate that the type of dialysis affects, to a certain extent, lipid and lipoprotein status in ESRD patients. Positive correlation of ApoE with apolipoprotein AI indicates a significant effect of this transport glycoprotein in the regulation of dyslipidemia in ESRD patients regardless of the type of dialysis.

Although the effect of ApoE polymorphism on the pathogenesis of dyslipidemia has been confirmed, the determination of total ApoE can help assess the overall lipid and lipoprotein status of ESRD patients. It is also important to consider the remarkably effect of the type of dialysis in the analysis of optimal lipoprotein values.

## DA LI JE KOD PACIJENATA SA KOLOREKTALNIM KARCINOMOM KOMPROMITOVANA SINTEZA VITAMINA D?

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Kolorektalni karcinom je treći kancer po zastupljenosti i četvrti najčešći uzrok mortaliteta. Verovatnoća oboljevanja od kolorektalnog karcinoma iznosi oko 4-5% u opštoj populaciji, a rizik za nastanak ove bolesti je povezan sa individualnim karakteristikama poput godina starosti, prisustva hroničnih bolesti i stila života. Deficijencija vitamina D se smatra jednim od faktora rizika za razvoj kolorektalnog karcinoma. Cilj studije je bio da se ispitaju povezanost statusa vitamina D sa pojavom kolorektalnog karcinoma i postojanje eventualne uzročne veze sa hepatičnom sintezom prekursora vitamina D, 7-dehidroholesterolola.

U studiji je učestvovalo 99 pacijenata koji boluju od kolorektalnog karcinoma i 99 zdravih ispitanika. U grupi pacijenata su bili zastupljeni svi TNM stadijumi i gradusi bolesti. 7-dehidroholesterol i 25-hidroksivitamin D3 su određivani LC-MS/MS metodom.

Studija je pokazala da pacijenti imaju statistički značajno niže koncentracije 7-dehidroholesterolola i 25-hidroksivitamina D3 u odnosu na kontrolnu grupu ( $P < 0,001$  i  $P = 0,006$ , redom). Nije uočena statistički značajna razlika u odnosu na različite stadijume i graduse karcinoma.

Snižena endogena sinteza 7-dehidroholesterolola može doprineti deficijenciji vitamina D kod pacijenata sa kolorektalnim karcinomom. Ovaj zaključak je potrebno potvrditi daljim studijama.



## IS VITAMIN D PRODUCTION COMPROMISED IN PATIENTS WITH COLORECTAL CANCER?

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Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer-related mortality. The probability of developing colorectal cancer is about 4-5% and the risk is associated with personal features or habits such as age, chronic disease history and lifestyle. Vitamin D deficiency is considered to be one of the factors often associated with colorectal cancer risk. We hypothesized that unfavorable vitamin D status is associated with colorectal cancer and that it can be attributed to decreased hepatic production of vitamin D precursor 7-dehydrocholesterol.

Our study included 99 patients suffering from colorectal carcinoma and 99 healthy subjects. Patients group was heterogenous in terms of CRC gradus and TNM stage. 7-dehydrocholesterol and 25-hydroxyvitamin D3 were determined by LC-MS/MS method.

We found that patients have significantly lower 7-dehydrocholesterol and 25-hydroxyvitamin D concentrations compared to healthy controls ( $P < 0.001$  and  $P = 0.006$ , respectively). There was no significant difference between different cancer grades and TNM stages.

Decreased endogenous production of 7-dehydrocholesterol could contribute to vitamin D deficiency in colorectal cancer patients. Nevertheless, further studies are needed to confirm this finding.

## E-KADERIN I OKSIDATIVNO-STRESNI STATUS KOD PACIJENATA SA KOLOREKTALNIM KARCINOMOM

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Kolorektalni karcinom (CRC) je maligna bolest sa visokom učestalošću, naročito kod starijih muškaraca. E-kaderin je transmembranski glikoprotein koji se nalazi na bazolateralnoj membrani epitelijalnih ćelija i učestvuje u međućelijskom povezivanju. Gubitak njegove funkcije doprinosi povećanoj invazivnosti kancera i metastazama. Oksidativni stres takođe može da dovede do smanjenog povezivanja ćelija delujući na vezu E-kaderina i ćelijskih proteina. Cilj ovog rada je bio da se ispita nivo E-kaderina i oksidativno-stresnog statusa i njihov značaj kod pacijenata sa CRC.

Ispitivanjem je obuhvaćeno 105 pacijenata sa CRC i 109 zdravih ispitanika. E-kaderin je određen ELISA (engl. enzyme linked immunosorbent assay) testom. Parametri oksidativno-stresnog statusa: prooksidativno-antioksidativni balans (PAB), totalni antioksidantni status (TAS), totalni oksidantni status (TOS) i paraoksonaza 1 (PON1) su određeni spektrofotometrijskim metodama.

Koncentracije E-kaderina ( $P < 0,0001$ ) i PAB-a ( $P < 0,0001$ ) su bile značajno više, dok su koncentracija TOS-a ( $P < 0,0001$ ) i aktivnost PON1 ( $P < 0,05$ ) bile značajno niže kod pacijenata sa CRC u odnosu na zdrave ispitanike. Koncentracija TAS-a je bila niža kod pacijenata, ali razlika nije dostigla statističku značajnost. U grupi pacijenata, utvrđena je značajna pozitivna korelacija između E-kaderina i PAB-a ( $P < 0,05$ ). E-kaderin i PAB poseduju značajan potencijal za razlikovanje pacijenata sa CRC i zdravih osoba ( $P < 0,001$ ).

Pacijenti sa CRC se karakterišu povišenim vrednostima E-kaderina i disbalansom između oksidanasa i antioksidanasa u korist prooksidanasa i ovi parametri imaju značajan potencijal za razlikovanje pacijenata i zdravih osoba.

## **E-CADHERIN AND OXIDATIVE-STRESS STATUS IN PATIENTS WITH COLORECTAL CARCINOMA**

**Jasmina Ivanišević<sup>1</sup>, Sandra Vladimirov<sup>1</sup>, Marija Mihajlović<sup>1</sup>, Dejan Zeljković<sup>2</sup>, Milica Miljković<sup>1</sup>, Aleksandra Zeljković<sup>1</sup>, Aleksandra Stefanović<sup>1</sup>**

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Colorectal Carcinoma (CRC) is a malignant disease with a high frequency, especially in older males. E-cadherin is a transmembrane glycoprotein found on the basolateral membrane of epithelial cells and participates in the intercellular connections. The loss of its function contributes to increased invasiveness of cancer and metastases. Oxidative stress can also lead to reduced cell-cell interconnection by affecting the signaling between E-cadherin and cellular proteins. The aim of our study was to examine the level of E-cadherin and oxidative-stress status and their significance in patients with CRC.

The study included 105 patients with CRC and 109 healthy subjects. E-cadherin was determined by the ELISA (enzyme linked immunosorbent) assay. The oxidative-stress status parameters: prooxidant-antioxidant balance (PAB), total antioxidant status (TAS), total oxidant status (TOS) and paraoxonase 1 (PON1) were determined by spectrophotometric methods.

The concentrations of E-cadherin ( $P < 0.0001$ ) and PAB ( $P < 0.0001$ ) were significantly higher, while the concentration of TOS ( $P < 0.0001$ ) and PON1 activity ( $P < 0.05$ ) were significantly lower in patients with CRC compared to healthy subjects. TAS concentration was lower in patients but the difference did not reach statistical significance. In the patient group, significant positive correlation between E-cadherin and PAB was found ( $P < 0.05$ ). E-cadherin and PAB had significant potential for discrimination patients with CRC from healthy individuals ( $P < 0.001$ ).

Patients with CRC were characterized by increased concentration of E-cadherin and imbalance between oxidants and antioxidants in favor of prooxidants and these parameters had significant potential for discrimination patients and healthy subjects.

## **KARAKTERISTIKE LIPOPROTEINA NISKE GUSTINE KOD METABOLIČKI ZDRAVOG I NEZDRAVOG FENOTIPA KOD OSOBA SA PREKOMERNOM TELESNOM MASOM I KOD GOJAZNIH**

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Iako su prekomerna telesna masa i gojaznost faktori rizika za razvoj kardiovaskularnih bolesti (KVB), ove grupe nisu homogene. Cilj rada je bio procena karakteristika lipoproteina niske gustine (LDL) kod metabolički zdravih (MZ) i nezdravih (MNZ) ispitanika.

Učesnici su regrutovani na Odeljenju za ishranu i prevenciju dijabetesa tipa 2 u sklopu Klinike za endokrinologiju, dijabetes i bolesti metabolizma. MZ fenotip je definisan kao odsustvo faktora rizika: povećana koncentracija triglicerida, niska koncentracija HDL-holesterola, povećan krvni pritisak i povećana koncentracija glukoze. LDL subfrakcije su razdvojene vertikalnom gradijent gel elektroforezom.

Kod ispitanika sa prekomernom telesnom masom, udeo malih, gustih LDL čestica je bio značajno viši kod MNZ (N=38) nego kod MZ osoba (N=18) (MZ: 33,7±11,9% vs. MNZ:47,1±14,2%, p=0,017). Kod gojaznih, dominantni LDL dijametar je bio značajno manji kod MNZ (N=43) (medijana: 27,10 nm; interkvartilni raspon: 25,49-27,85 nm) nego kod MZ osoba (N=16) (medijana: 27,91 nm; interkvartilni raspon: 27,05-28,30 nm; p=0,019).

Karakterizacija metaboličkog fenotipa i analiza LDL subfrakcija može biti od značaja kod osoba sa prekomernom telesnom masom i kod gojaznih radi adekvatne procene rizika od KVB.

## **LOW-DENSITY LIPOPROTEINS CHARACTERISTICS IN METABOLICALLY HEALTHY AND UNHEALTHY PHENOTYPE IN OVERWEIGHT AND OBESE SUBJECTS**

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Although overweight and obesity are cardiovascular diseases' (CVD) risk factors, these groups are not homogeneous. This study aim was to evaluate low density lipoproteins (LDL) characteristics in metabolically healthy (MH) and unhealthy (MUH) participants.

Participants were recruited at the Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, at the Department for Nutrition and diabetes type 2 prevention. MH was defined as an absence of risk factors: elevated triglycerides, reduced HDL-cholesterol, elevated blood pressure, and elevated fasting glucose. LDL subfractions were separated using vertical gradient gel electrophoresis.

In overweight group, the relative proportion of small, dense LDL particles was significantly higher in MUH (N=38) than in MH subjects (N=18) (MH: 33.7±11.9% vs. MUH: 47.1±14.2%, p=0.017). In obese group, dominant LDL diameter was significantly lower in MUH (N=43) (median: 27.10 nm; interquartile range: 25.49-27.85 nm) than in MH subjects (N=16) (median: 27.91 nm; interquartile range: 27.05-28.30 nm; p=0.019).

Metabolic phenotype characterization and LDL subfractions analysis could be of importance in adequate assessing CVD risk in overweight and obese persons.

## PROCJENA LIPIDNOG I OKSIDATIVNOG STATUSA POMOĆU ODGOVARAJUĆIH SKOROVA KOD DJECE SA HRONIČNOM BUBREŽNOM BOLEŠĆU

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Primarni uzrok smrti kod djece sa hroničnom bubrežnom bolešću (HBB) danas su kardiovaskularne bolesti i infekcije prije nego sama renalna insuficijencija, a dislipidemija i oksidativni stres se navode kao značajni faktori rizika za razvoj kardiovaskularnih komplikacija. Cilj ove studije je bila procjena lipidnih parametara i parametara oksidativnog stresa kroz izračunavanje odgovarajućih skorova kod djece sa hroničnom bubrežnom bolešću i kod zdrave djece.

U studiju je uključeno 20 pedijatrijskih pacijenata (10 u predijaliznom stadijumu bubrežne bolesti i 10 na dijalizi), kao i 50 zdrave djece. Određeni su osnovni parametri lipidnog profila (ukupni holesterol, trigliceridi i holesterol u lipoproteinskim česticama male (LDL-C) i velike gustine (HDL-C)), prooksidativni (superoksidni anjon, malondialdehid i uznapredovali produkti oksidacije proteina) i parametri antioksidativne zaštite (diazoksonazna aktivnost, paraoksonazna aktivnost, sulfhidrilne grupe i superoksid dismutaza), te su na osnovu odgovarajućih vrijednosti z-skorova izračunati skor dislipidemije i oksidativni skor.

Djeca sa HBB su imala značajno više vrijednosti skora dislipidemije ( $p=0,001$ ) i oksidativnog skora u odnosu na zdravu djecu ( $p<0,001$ ), pri čemu su vrijednosti prooksidativnog skora bile značajno više ( $p<0,001$ ), a vrijednosti antioksidativnog skora statistički značajno niže ( $p<0,001$ ) kod pacijenata u odnosu na zdrave ispitanike. Uočena je i značajna pozitivna korelacija između skora dislipidemije i oksidativnog skora u grupi ispitanika sa HBB ( $\rho=0,669$ ,  $p=0,001$ ).

Kod djece sa HBB dolazi do skretanja lipidnog profila ka proaterogenom, a dislipidemija je praćena prooksidativnim promjenama, što ih svrstava u kategoriju pacijenata sa visokim rizikom zarazvoj kardiovaskularnih oboljenja. Dobro je poznato da slobodni radikali dovode do oksidacije LDL čestica, čime značajno utiču na lipidni profil, a pojedini lipidni parametri imaju prooksidativni karakter. U prilog tome govori i jaka pozitivna korelacija između skora dislipidemije i oksidativnog skora zabilježena u ovoj studiji.

## **ASSESSMENT OF LIPID AND OXIDATIVE STATUS BY CORRESPONDING SCORES IN CHILDREN WITH CHRONIC KIDNEY DISEASE**

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The primary death cause in children with chronic kidney disease (CKD) today are cardiovascular diseases and infections, rather than renal failure, while dyslipidemia and oxidative stress are identified as significant risk factors for cardiovascular complications development. The aim of this study was to evaluate the lipid and oxidative stress parameters through appropriate scores calculation in healthy and children with CKD.

The study included 20 pediatric patients (10 in pre-dialysis stage of CKD and 10 on dialysis) and 50 healthy children. Basic lipid profile parameters (total cholesterol, triglycerides and cholesterol in low and high density lipoproteins), prooxidative (superoxide anion, malondialdehyde and advanced protein oxidation products) and antioxidant protection parameters (diazoxone activity, paraoxonase activity, sulfhydryl groups and superoxide dismutase) were determined, while score of dyslipidemia and oxidative score were calculated on the basis of the corresponding z-score values.

Children with CKD had significantly higher score of dyslipidemia ( $p = 0.001$ ) and oxidative score compared to healthy children ( $p < 0.001$ ), whereby the prooxidative score values were significantly higher ( $p < 0.001$ ) and antioxidant score values were statistically lower ( $p < 0.001$ ) in patients compared to healthy subjects. There was also a significant positive correlation between the score of dyslipidemia and the oxidative score in the patients group ( $\rho = 0.669$ ,  $p = 0.001$ ).

In children with CKD, there is lipid profile switch towards the proatherogenic one, and dyslipidemia is followed by prooxidative changes, placing them in the category of patients with a high risk for developing cardiovascular disease. It is well known that free radicals lead to the LDL particles oxidation, significantly affecting the lipid profile, while some lipid parameters have a prooxidative character. This is supported by a strong positive correlation between the score of dyslipidemia and the oxidative score recorded in this study.

## POVEZANOST IZMEĐU DISLIPIDEMIJE I OKSIDATIVNOG STRESA KOD DECE SA HRONIČNIM BUBREŽNIM BOLESTIMA I POSLE TRANSPLANTACIJE BUBREGA

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S obzirom na ulogu dislipidemije i oksidativnog stresa u razvoju kardiovaskularne bolesti (KVB) kao komorbiditeta hroničnih bubrežnih bolesti (HBB), cilj ovog istraživanja je bio da se ispituju razlike u parametrima oksidativnog stresa i lipidnog statusa između dece sa HBB i dece sa transplantiranim bubregom, kao i da se ispita povezanost lipidnog i oksidativnog statusa u obe grupe.

U istraživanju je učestvovalo 20 dece sa HBB i 21 dete sa transplantiranim bubregom koji su lečeni na Univerzitetskoj dečjoj klinici Tiršova. Određeni su osnovni parametri lipidnog statusa, kao i apolipoproteini A i B (apoA i apoB) i lipoprotein (a) (Lp(a)). U okviru procene redoks statusa određeni su aktivnost paraoksonaze 1 (PON1) i superoksid dizmutaze (SOD), koncentracija sulfhidrilnih grupa (SH), malondialdehida (MDA), superoksid anjon radikala ( $O_2^-$ ) i uznapredovalih produkta oksidacije proteina (AOPP). Iz datih parametara izračunati su oksidativni skor i skor dislipidemije.

Od svih parametara, samo Lp(a) pokazuje značajne razlike između grupa ( $p=0,012$ ) sa višim vrednostima kod transplantiranih pacijenata. Kod pacijenata sa HBB, apoA pozitivno korelira sa koncentracijom SH grupa ( $p=0,029$ ), a negativno sa aktivnošću SOD ( $p=0,007$ ) i koncentracijom MDA ( $p=0,025$ ). HDL-holesterol korelira negativno ( $p=0,012$ ), a trigliceridi pozitivno sa MDA ( $p<0,001$ ) u HBB, kao i nakon transplantacije ( $p=0,023$ ). Oksidativni i skor dislipidemije pozitivno koreliraju u grupi HBB ( $p=0,002$ ). Kod pacijenata nakon transplantacije apoA i HDL-holesterol negativno koreliraju sa koncentracijom SH grupa ( $p=0,003$  i  $p=0,007$ ), a apoB i LDL-holesterol pozitivno sa  $O_2^-$  ( $p=0,002$  i  $p=0,004$ ).

Iako transplantacija rešava osnovni problem uremije, kod ovih pacijenata ne dolazi do značajne promene lipidnog profila, niti oksidativnog statusa u odnosu na pacijente sa HBB, što ih svrstava u grupu povišenog rizika za razvoj KVB u odrasloj dobi.



## ASSOCIATIONS BETWEEN DYSLIPIDEMIA AND OXIDATIVE STRESS IN PEDIATRIC PATIENTS WITH CHRONIC KIDNEY DISEASE AND AFTER RENAL TRANSPLANTATION

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Dyslipidemia and oxidative stress have a role in development of cardiovascular disease (CVD)– a main comorbidity of chronic kidney disease (CKD). The aim of this study was to explore the differences and associations between oxidative stress and lipid status parameters in pediatric patients with CKD and in those that had a kidney transplant.

The study included 20 patients with CKD and 21 patients with a kidney transplant, who were treated at the University clinic „Tiršova”. Standard lipid profile biomarkers were determined, as well as apolipoprotein A and B (apoA and apoB) and lipoprotein (a) (Lp(a)) concentrations. For oxidative status assessment, activity of paraoxonase 1 (PON1) and superoxide dismutase (SOD), concentration of sulfhydryl groups (SH), malondialdehyde (MDA), superoxide anion radical ( $O_2^-$ ) and advanced oxidation protein products (AOPP) were determined. Oxidative and dyslipidemia scores were calculated from the mentioned markers.

Only Lp(a) showed significant difference between the groups, with higher values ( $p=0.012$ ) in the kidney transplant group. In the CKD group, apoA correlated positively with the concentration of SH groups ( $p=0.029$ ), and negatively with SOD activity ( $p=0.007$ ) and MDA ( $p=0.025$ ). HDL-cholesterol had a negative ( $p=0.012$ ) and triglycerides a positive correlation with MDA ( $p<0.001$ ) in CKD, as well as in the transplant group ( $p=0.023$ ). Oxidative and dyslipidemia scores correlated positively in CKD group ( $p=0.002$ ). In the transplant group, apoA and HDL-cholesterol had a negative correlation with SH groups ( $p=0.003$  and  $p=0.007$ ), while apoB and LDL-cholesterol correlated positively with  $O_2^-$  ( $p=0.002$  and  $p=0.004$ ).

Although kidney transplantation does correct uremia in these patients, there is no significant amelioration of lipid profile, nor that of oxidative status compared to CKD group, indicating that renal transplant recipients remain with an increased risk for the development of CVD in adulthood.

## **DISLIPIDEMIJA KAO FAKTOR RIZIKA ZA RAZVOJ KARDIOVASKULARNIH BOLESTI KOD GOJAZNIH PACIJENATA SA SUBKLINIČKIM HIPOTIREOIDIZMOM**

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Gojaznost i hipotireoidizam predstavljaju dva međusobno povezana klinička stanja. Hipotireoidizam može dovesti do usporavanja metabolizma, povećanja indeksa telesne mase (ITM) i prevalencije gojaznosti, te nepravilnosti srčanog rada. Gojaznost dovodi do poremećaja koncentracije lipida u krvi, dislipidemije, koja uz ostale faktore metaboličkog sindroma predstavlja jedan od glavnih faktora rizika za nastanak kardiovaskularnih oboljenja. Cilj ovog istraživanja bio je, određivanjem lipidnog statusa i dislipidemijskog skora, proceniti stepen rizika za nastanak kardiovaskularnih oboljenja kod gojaznih osoba sa hipotireoidizmom.

Studija je obuhvatila 165 ispitanika sa subkliničkim hipotireoidizmom i kardiovaskularnim oboljenjima (113 žena, 52 muškarac; starost 60,5±6,98). Ispitanici su podeljeni prema vrednosti ITM na tri grupe: ITM1<25,0 kg/m<sup>2</sup>, ITM2=25,1-30,0 kg/m<sup>2</sup> i ITM3≥30,1kg/m<sup>2</sup>. Da bi se procenio efekat dislipidemije izračunat je zbirni skor rizika koji potiče od parametara lipidnog statusa. Rezultati ispitivanja su predstavljeni lipidnim skorom rizika, lipidno-zaštitnim (HDLz) i dislipidemijskim skorom.

Uočene suviše koncentracije triglicerida i značajno niže koncentracije HDL- holesterola kod ITM3 i ITM2 u odnosu na ITM1 grupu, dok je razlika između ITM2 i ITM3 grupe značajna u koncentraciji triglicerida. Koncentracije ukupnog i LDL- holesterola nisu se značajno razlikovale između ITM podgrupa.

HDLz je niži kod gojaznih pacijenata u odnosu na predgojazne i normalno uhranjene (p<0,01, p<0,001), dok između normalno uhranjenih i predgojaznih nema razlike. Lipidni skor rizika jeviši kod gojaznih pacijenata u odnosu na grupe sa nižim ITM (vs. ITM2 p<0,05, vs. ITM1 p<0,01). Dislipidemija skor jeviši kod gojaznih ispitanika u odnosu na normalno uhranjene (p<0,001) i predgojazne (p<0,05), a značajno višikod predgojaznih u odnosu na normalno uhranjene (p<0,05). Dislipidemija i lipidni skor rizika su viši (p<0,001), a HDLz niži kod osoba sa metaboličkim sindromom u odnosu na one bez (p<0,001). Rezultati pokazuju da dislipidemiju kod ovakvih ispitanika nije moguće proceniti samo određivanjem osnovnih parametara lipidnog statusa već je potrebno proceniti zbirni rizik koji potiče od međusobne interakcije tih parametara.

# **DYSLIPIDEMIA AS A RISK FACTOR FOR THE DEVELOPMENT OF CARDIOVASCULAR DISEASES IN OBESE PATIENTS WITH SUBCLINICAL HYPOTHYROIDISM**

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Obesity and hypothyroidism present two interconnected clinical conditions. Hypothyroidism could cause decreased metabolism, increased body mass index (BMI) and obesity prevalence, and cardiac abnormalities. Obesity leads to disorder of lipid concentrations in blood, dyslipidemia, which, with other metabolic syndrome factors, is one of the main risk factors for cardiovascular diseases.

The aim of this study was to determine the degree of risk for development of cardiovascular diseases in obese individuals with hypothyroidism, by determining lipid status and dyslipidemia score.

Study included 165 subjects with subclinical hypothyroidism and cardiovascular diseases (113 females, 52 males; age 60.5±6.98). Subjects were divided, according to BMI values, in three groups : BMI1<25.0 kg/m<sup>2</sup>, BMI2=25.1-30.0 kg/m<sup>2</sup> and BMI≥30.1 kg/m<sup>2</sup>. To evaluate the effect of dyslipidemia, a summarized risk score, derived from the lipid status parameters, was calculated. Results of the study were presented by lipid risk, lipid-protective (HDLz) and dyslipidemia score.

There are higher triglyceride and lower HDL-cholesterol levels in BMI3 and BMI2 compared to BMI1 group, while the difference between BMI2 and BMI3 group was significant only in triglyceride concentration. Total and LDL-cholesterol concentrations don't differ significantly between BMI-subgroups.

HDLz is lower in obese compared to overweight and normally nourished subjects (p<0.01, p<0.001), while between normally nourished and overweight subjects was no difference. Lipid risk score is higher in obese subjects compared to groups with lower BMI (vs. BMI2 p<0.05, vs. BMI1 p<0.01). Dyslipidemia score is higher in obese compared to normally nourished (p<0.001) and overweight subjects (p<0.05), and higher in overweight compared to normally nourished (p<0.05). Dyslipidemia and lipid risk score are higher (p<0.001), and HDLz lower in people with metabolic syndrome compared to those without (p<0.001).

Dyslipidemia can not be estimated only by determining the basic parameters of lipid status. It's necessary to estimate the cumulative risk arising from the interaction between these parameters.

## **GENSKA EKSPRESIJA REZISTINA I PROTEINA UDRUŽENOG SA ADENILAT CIKLAZOM 1 U MONONUKLEARNIM ĆELIJAMA PERIFERNE KRVI ZDRAVIH ŽENA I MUŠKARACA**

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Kardiovaskularne bolesti (KVB) danas predstavljaju jedan od najznačajnijih uzroka smrtnosti u svetu. U osnovi kardiovaskularnih bolesti leži ateroskleroza, oboljenje koje nastaje sinergističkim dejstvom većeg broja faktora rizika kao što su gojaznost, dislipidemija, dijabetes, sedentaran način života, pušenje i dr. Takođe, poznato je da muškarci imaju veću sklonost ka razvoju KVB u odnosu na žene. Narušavanje balansa između antiinflamatornih i proinflamatornih molekula u organizmu podstiče hroničnu inflamaciju i doprinosi napredovanju ateroskleroze. Rezistin predstavlja potentan proinflamatorni citokin koji se oslobađa iz mononuklearnih ćelija periferne krvi, makrofaga i ćelija kostne srži. Njegovi proinflamatorni efekti se ostvaruju preko proteina udruženog sa adenilat ciklazom 1 (CAP1). Brojne studije su ukazale na značajan uticaj koji rezistin ima na razvoj i destabilizaciju aterosklerotskog plaka. Cilj naše studije je bio da se ispita da li postoji značajna razlika u nivou genske ekspresije proinflamatornog citokina rezistina i CAP1 u mononuklearnim ćelijama periferne krvi između zdravih žena i muškaraca.

U ovoj studiji je učestvovalo 50 zdravih muškaraca (52±9 godina) i 64 zdrave žene (50±10 godina). Nijedan učesnik nije imao srčana, renalna ili hepatična oboljenja niti je primao farmakološku terapiju.

Nivo genske ekspresije rezistina i CAP1 je određen kvantitativnim PCR-om. Koncentracije biohemijskih parametara su određene rutinskim laboratorijskim metodama.

Nivo genske ekspresije rezistina i CAP1 bili su značajno viši kod muškaraca u odnosu na žene ( $P < 0,001$  i  $P = 0,001$ , redom). Uočena je značajna pozitivna korelacija između nivoa genske ekspresije CAP1 i sistolnog krvnog pritiska ( $\rho = 0,201$ ;  $P = 0,035$ ), kao i nivoa genske ekspresije rezistina sa indeksom telesne mase ( $\rho = 0,19$ ;  $P = 0,044$ ) i koncentracijom mokraćne kiseline ( $\rho = 0,373$ ;  $P = 0,001$ ).

Povećani nivoi genske ekspresije rezistina i njegovog receptora CAP1 u mononuklearnim ćelijama periferne krvi muškaraca sugerišu da bi ove ćelije mogle ostvariti proinflamatorni uticaj, olakšavajući tako progresiju aterosklerotskog plaka i povećavajući rizik za razvoj kardiovaskularnih bolesti u muškoj populaciji.

# RESISTIN AND ADENYLYL CYCLASE-ASSOCIATED PROTEIN 1 GENE EXPRESSION IN PERIPHERAL BLOOD MONONUCLEAR CELLS OF HEALTHY MEN AND WOMEN

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Cardiovascular diseases (CVD) are one of the most common cause of mortality in the world today. The main pathophysiological mechanism in CVD is atherosclerosis, a multi-factorial complex disease that is product of synergistic effects of various risk factors such as obesity, dyslipidemia, diabetes, smoking, sedentary lifestyle etc. Also, it is well known that men are more prone to CVD than women. Imbalance between antiinflammatory and proinflammatory molecules leads to chronic inflammation and contributes to atherogenesis. Resistin is a very potent proinflammatory cytokine which is in humans mainly produced by peripheral blood mononuclear cells (PBMC), macrophages and bone marrow. Its proinflammatory effects are mainly exerted via adenylyl cyclase-associated protein 1 (CAP1). Previous studies have shown significant influence of resistin on atherosclerosis progression and plaque vulnerability. The aim of this study was to evaluate if resistin and CAP1 mRNA levels in PBMCs are different between healthy men and women.

This study included 50 healthy men (age: 52±9 years) and 64 healthy women (age: 50±10 years). All were free of known cardiac, renal or liver diseases and were not taking any prescribed medication.

Resistin and CAP1 mRNA levels were measured by qPCR. Levels of biochemical parameters were measured by routine laboratory methods.

Resistin and CAP1 mRNA levels were significantly higher in men compared to woman ( $P < 0.001$  i  $P = 0.001$ , respectively). CAP1 mRNA levels positively correlated with systolic blood pressure ( $\rho = 0.201$ ;  $P = 0.035$ ). Also, resistin mRNA levels positively correlated with body mass index ( $\rho = 0.190$ ;  $P = 0.044$ ) and uric acid levels ( $\rho = 0.373$ ;  $P = 0.001$ ).

Upregulation of resistin and CAP1 mRNA levels in PBMCs of men suggests that these cells could be able to exert proinflammatory effects, thus facilitating atherosclerotic plaque progression and increasing CVD risk in men population.

## **EFFECT OF EXENATIDE LAR IN TYPE-2 DIABETIC PATIENTS WITH VS. WITHOUT ELEVATED CARDIOMETABOLIC RISK SCORE AT BASELINE: AN 8-MONTH PROSPECTIVE INTERVENTION STUDY**

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The gluco-metabolic effects of exenatide once-weekly (long-acting release, LAR) on traditional cardiovascular (CV) risk factors are well known. However, additional predictive value may be obtained if several factors are assessed simultaneously. We evaluated different cytokines associated with glycemic decompensation and increased CV risk in subjects with type 2 diabetes (T2DM), in order to make a new cardiometabolic risk score. The effect of exenatide LAR was then assessed in such T2DM patients in relation to the presence of elevated cardiometabolic risk score at baseline.

Sixty subjects with T2DM (41 men and 19 women) naïve to incretin-based therapies were treated with exenatide LAR as add-on to metformin (from 1500 up to 3000 mg/day) for 8 months. Elevated cardiometabolic risk score at baseline was defined by the combination of the following 7 cytokines: adiponectin, leptin, resistin, monocyte chemotactic protein 1, plasminogen activator inhibitor-1, E-Selectin, and soluble intercellular adhesion molecule. The median value of each cytokine was used as cut-off for defining the „abnormal value” of each cytokine, and the cohort of patients was then subdivided in 2 groups: with elevated cardiometabolic risk score at baseline (n=28) and without elevated cardiometabolic risk score at baseline (n=32). Carotid intima media thickness (cIMT) was assessed by B-mode real-time ultrasound, while endothelial function by flow mediated dilation (FMD) of the brachial artery. We found improvements in most of the investigated cardio-metabolic parameters among subjects with and without elevated cardiometabolic risk score at baseline, and did not find any significant difference among the two subgroups of patients.

Exenatide LAR similarly improved cardio-metabolic parameters in T2DM subjects with vs. without elevated cardiometabolic risk score at baseline. This is consistent with previous findings of exenatide efficacy in T2DM subjects at lower and higher cardiovascular risk, including subgroup analyses from the DURATION and EXSCEL trial.

## **LONGITUDINALNE PROMENE SKORA DISLIPIDEMIJE I OKSIDATIVNOG STRESA KOD ZDRAVIH OSOBA I RIZIK ZA RAZVOJ KARDIOVASKULARNIH BOLESTI**

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Dislipidemija i oksidativni stres predstavljaju glavne faktore rizika za kardiovaskularne bolesti (KVB). Periodičnim praćenjem parametara lipidnog i oksidativno-stresnog (OS) statusa moguće je otkriti evoluciju pojedinačnih faktora rizika ili njihovo interaktivno dejstvo u razvoju KVB. Cilj ove studije bio je izračunavanje i evaluacija promena skorova dislipidemije (DYS) i oksidativnog stresa (OXY) kod zdravih osoba.

U studiji je učestvovalo 37 zdravih osoba. Kod 12 osoba ispitivane su promene parametara lipidnog (ukupan, LDL i HDL-holesterol i trigliceridi) i OS statusa u periodu 2012-2016. godine, a kod 25 ispitanika analizirane su promene lipidnog profila u periodu 2006-2018. godine, u vremenskim intervalima od 4 godine. Tokom perioda praćenja, 8 od 25 ispitanika razvilo je KVB. Svim ispitanicima izračunat je DYS skor kao razlika lipidnog skora rizika (standardizovane vrednosti LDL-h i triglicerida) i protektivnog lipidnog skora (standardizovane vrednosti HDL-h). OXY skor je izračunat kao razlika između skora oštećenja (standardizovane vrednosti parametara OS) i protektivnog skora (standardizovane vrednosti parametara antioksidativne zaštite).

Kod 12 zdravih ispitanika, praćenih u periodu 2012-2016.godine, utvrđen je značajan porast DYS ( $p=0,016$ ) i OXY skora ( $p=0,002$ ). U grupi koja je praćena tokom dužeg vremenskog perioda (2006-2018. godine) utvrdili smo značajan, progresivan rast DYS skora kod osoba koje su razvile KVB ( $p=0,021$ ). Kod osoba koje nisu razvile KVB promene DYS skora nisu bile značajne. Ni u jednoj od ispitivanih grupa nije bilo značajne promene u koncentraciji pojedinačnih parametara lipidnog profila tokom vremena.

Povišeni DYS skor udružen je sa povećanim rizikom za razvoj KVB. Izračunavanje DYS skora može poboljšati predviđanje rizika za razvoj KVB u odnosu na pojedinačne parametre lipidnog statusa. Određivanje OXY skora, koji predstavlja odnos stepena oksidativnog stresa i antioksidativne zaštite, može značajno doprineti u proceni rizika za razvoj KVB.

# LONGITUDINAL CHANGES OF DYSLIPIDEMIA AND OXIDATIVE STRESS SCORE IN HEALTHY SUBJECTS AND CARDIOVASCULAR RISK

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Dyslipidemia, inflammation and oxidative stress represent major risk factors for cardiovascular disease (CVD) development. Periodical monitoring of lipid and oxidative stress (OS) status parameters enables identification and etiological determination of risk factors or their interactive role in CVD development. The aim of this study was to calculate dyslipidemia (DYS) and oxidative stress (OXY) score and evaluate their contribution to CVD risk assessment.

This study was comprised of 37 healthy individuals. Changes of lipid (total, HDL and HDL cholesterol, triglycerides) and oxidative stress status parameters were determined in 12 healthy individuals in period of 2012-2016., while in 25 individuals lipid profile changes were analysed in period from 2006—2018, in 4 years time intervals. During this follow up period, of 25 individuals, 8 developed CVD. DYS score was calculated for all participants as a difference in lipid risk score (standardised values of LDL-C and triglycerides) and protective lipid score (standardised values of HDL-C). OXY score was calculated as a difference in damage (standardised values of oxidativestress parameters) and protective (standardised values of anti-oxidative stress parameters) score.

A significant increase in DYS ( $P=0.016$ ) and OXY score( $P=0.002$ ) was observed in 12 healthy individuals from 2012-2016. DYS score showed progressive significant increase during time ( $P=0.021$ ) in subjects who developed CVD, while no significant change was observed in subjects without CVD. Moreover, lipid parameters alone were not significantly different among subjects in different time periods.

The results from this study indicate that increased DYS score is associated with increased risk for CVD. DYS score calculation could significantly contribute to CVD risk estimation compared to standard lipid parameters used. Calculation of OXY score, which reflects balance between oxidative stress and anti-oxidative protection, could significantly contribute to CVD risk assessment.



## POVEZANOST SERUMSKE KONCENTRACIJE 25-HIDROKSI VITAMINA D I ANKSIOZNOSTI KOD DECE SA ASTMOM

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Prevalenca psihijatrijskih poremećaja i deficijencija vitamina D kod dece sa astmom su u porastu. Cilj ove studije je bila procena anksioznih poremećaja kod dece sa astmom kao i otkrivanje potencijalnih faktora koji mogu biti povezani sa anksioznošću, među koje spada i serumska koncentracija vitamina D.

Prilikom posete pedijatru, vanbolnički pacijenti Klinike za pedijatriju popunjavali su SCARED upitnik koji ispituje anksiozne poremećaje. Određivanje serumske koncentracije vitamina D, kao i druge biohemijske metode, vršene su u biohemiskoj laboratoriji Kliničkog centra Kragujevac. Statistička analiza je izvedena korišćenjem SPSS softvera, kao i pomoću deskriptivne statistike i logističke regresije.

Studijsku populaciju su činila većinom školska deca, starosti od 8-12 godina i adolescenti (13-17 godina). Od ukupno 74 dece kojima je određivana serumska koncentracija vitamina D, samo kod troje dece te vrednosti su bile optimalne. Približno 33,8% ispitanika je pokazalo pozitivne rezultate na neki anksiozni poremećaj. Separaciona anksioznost je bila prisutna kod 49,3%, a socijalna anksioznost kod 32,4% ispitanika. Serumska koncentracija vitamina D nije bila faktor koji je pokazao povezanost sa anksioznošću. Od ostalih ispitivanih faktora, samo sledeći su pokazali značajan efekat: test za vršni ekspirijumski protok je bio povezan sa opštom anksioznošću, godine i pol pacijenata sa paničnim poremećajem, a mesto stanovanja, kontrola astme u skladu sa GINA klasifikacijom i godine pacijenata sa generalizovanom anksioznošću. Pokazano je i da je upotreba cigareta od strane roditelja povezana sa separacionom anksioznošću, godine i stepen uhranjenosti pacijenata sa socijalnom fobijom, a GINA kontrola astme sa izbegavanjem škole.

Prisustvo astme kod dece zbog narušenih fizičkih i društvenih aktivnosti može dovesti do nastanka anksioznosti. Dobijeni rezultati ukazuju da su anksiozni poremećaji prisutni kod dece i adolescenata sa astmom, kao i da je prisutna deficijencija i insuficijencija vitamina D. Dalja istraživanja su potrebna da bi se utvrdilo da li korišćenje suplemenata vitamina D utiče na anksioznost kod dece sa astmom.

## COHERENCE OF 25-HYDROXY VITAMIN D SERUM CONCENTRATION AND ANXIETY IN CHILDREN WITH ASTMA

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The prevalence of psychiatric disorders and vitamin D deficiency in children with asthma are increasing. The aim of this study was to evaluate anxiety disorders in children with asthma, as well as to detect potential factors that may be associated with anxiety, including serum vitamin D concentration.

During routine visit to the pediatrician, pediatric outpatients in the Pediatric Clinic filled out a SCARED questionnaire that examines anxiety disorders. The determination of serum vitamin D concentration, as well as other biochemical methods, was performed in the biochemical laboratory of the Clinical Center of Kragujevac. Statistical analysis was performed using SPSS software, as well as descriptive statistics and logistic regression.

The study population consisted mainly of school children, aged 8-12 and adolescents (13-17 years). Out of a total of 74 children only three children had normal concentration of serum vitamin D. Approximately 33.8% of the subjects showed positive results on an anxiety disorder. Separation anxiety was present in 49.3%, and social anxiety in 32.4% of subjects. Serum concentration of vitamin D was not a factor that showed an association with anxiety. Of the other factors, following showed significant effect: the peak expiratory flow test was associated with general anxiety, age and gender with panic disorder, place of residence, asthma control according to GINA classification and age with generalized anxiety. Parent's smoking is associated with separation anxiety, age and patients' weight status with social phobia, and GINA asthma control with avoiding school.

The presence of asthma in children due to impaired physical and social activity can lead to anxiety. The obtained results indicate that anxiety disorders are present in respondents as well as deficiency and insufficiency of vitamin D. Further studies are needed to determine whether the use of vitamin D supplements affects the anxiety among children with asthma.

## **AUTOMATSKI ON-LINE KALKULATOR KARDIOVASKULARNOG RIZIKA KOJI KOMBINUJE DISLIPIDEMIJU I INFLAMACIJU**

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Kardiovaskularne bolesti (KVB) kao najčešće bolesti u populaciji starijoj od 60 godina mogu biti dijagnostikovane kao: koronarna bolest srca, cerebrovaskularna bolest, periferna arterijska bolest i ateroskleroza aorte sa mogućom aneurizmom. KVB su vodeći uzrok mortaliteta širom sveta. Dislipidemija je tradicionalni faktor rizika za razvoj ovih bolesti, odnosno niska koncentracija HDL-holesterola, povišena koncentracija LDL-holesterola i visoka koncentracija triglicerida. U poslednjoj deceniji je inflamacija prepoznata kao jedan od faktora rizika. U kardiovaskularnim bolestima inflamacija je hronična i niskog stepena i može biti merena preko visoko senzitivnog C-reaktivnog proteina (*high sensitive C-reactive protein, hsCRP*).

Cilj ove studije je bio da se izračuna ukupni kardiovaskularni rizik koji proističe iz dislipidemije i inflamacije – DI skor (DIS) kao zbir dislipidemijskog (DS) i inflamatornog skora (IS). DS se računa kao razlika između lipidnog profila rizika (srednja vrednost između LDL-C z skora i TG z skora) i lipidnog protektivnog profila (HDL-C z skor). Inflamatorni skor je izračunat kao hsCRP z skor. Populacione vrednosti za z skorove smo dobili iz uzoraka krvi zdrave populacije Srbije, tokom 20 godina u našoj laboratoriji.

Drugi cilj naše studije je bio da se programira automatski on-line kalkulator koji bi bio u mogućnosti da izračuna zbirni DI skor i da pruži odgovarajuću poruku o nivou rizika, na osnovu vrednosti dislipidemijskog i inflamatornog skora. Koristeći programski jezik C, u programu *Visual Studio*, napisali smo kod za program koji računa skorove rizika za različite parametre. Korisnik treba da izabere pol iz menija i da upiše koncentracije svojih parametara lipidnog statusa i hsCRP, a nakon toga program računa skor i pruža povratnu informaciju. Korisnik potom ima opciju da izabere da li želi da uporedi rezultate sa prethodnim rezultatima, ukoliko postoje, i dobija poruku o poboljšanju/pogoršanju. Program je intuitivan i lak za razumevanje. Smatramo da bi šira upotreba ovog programa, doprinela boljoj kontroli kardiovaskularnih bolesti.

## **AUTOMATIC ON-LINE CARDIOVASCULAR RISK CALCULATOR WHICH COMBINES DYSLIPIDEMIA AND INFLAMMATION**

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Cardiovascular disease (CVD) is the most frequent disease in population older than 60 years. CVD could be diagnosed as: coronary heart disease, cerebrovascular disease, peripheral artery disease and aortic atherosclerosis with possible aneurism. CVD are the leading cause of mortality worldwide. Dyslipidemia is one of the established, traditional cardiovascular risk factors i.e. low HDL-cholesterol, high LDL-cholesterol and high triglycerides concentration. One of the emerging, new risk factors recognized in the last decade was inflammation. Regarding cardiovascular disease inflammation is low-grade and chronic and could be assessed through the high sensitive C-reactive protein measurement.

The aim of this study was to calculate summary cardiovascular risk evolved from dyslipidemia and inflammation – DI Score (DIS) as a sum of Dyslipidemia (DS) and Inflammation scores (IS). DS is calculated as a difference between lipid risk profile (average value between LDL-C z score and TGz score) and lipid protective profile (HDL-C z score). Inflammation score was calculated as hsCRP z score. Population values for z scores calculation we have generated from Serbian healthy control group values analyzed during 20 years in our laboratory.

Second aim of our study was to make an automatic on-line calculator which could be able to calculate summary DIS score and to give appropriate message about risk level, according to the dyslipidemia and inflammation scores values. In Visual Studio, using programming language C we wrote a code for a program that calculates risk scores for different parameters. A user is supposed to select gender from a menu, and then inserts his/her lipid status and CRP concentrations. The program calculates the risk and gives feedback. The user has additional option of choosing to compare current results with previous, and gets a message about improvement/worsening. The program is intuitive, easy to comprehend and its wider use would contribute to better CV control.