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OSETLJIVOST I SPECIFIČNOST TROPONINA T ZA DIJAGNOSTIKOVANJE AKUTNOG INFARKTA MIOKARDA

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Od nedavno se u dijagnostici kardiovaskularnih oboljenja, a naročito akutnog infarkta miokarda (AIM), posebna pažnja posvećuje proučavanju i primeni niza manjih proteina koji su komponente kontraktilnog aparata srčanog mišića, kao što je srčani troponin T (cTnT). Zato je cilj ovog istraživanja bio da se obradi i uporedi specifičnost i osetljivost cTnT mioglobina i određivanih enzima za rano dijagnostikovanje AIM, kao što su: kreatin kinaza (CK), izoenzim CK MB i laktat dehiorogeneza (LDH). Obrađene su četiri grupe ispitanika. Prvu grupu su činili dobrovoljni davaoci krvi (n = 105), drugu bolesnici s potvrđenim AIM (n = 30), treću bolesnici s politraumom (n = 30) i četvrtu bolesnici s kardiovaskularnim oboljenjima (KVO) u kojih nije potvrđen AIM (n = 30). Za određivanje cTnT korišćen je komercijalni test Eleccys Troponin T STAT (treće generacije), firme Boehringer Mannheim, koji se zasniva na tehnici elektrohemijskog luminiscentnog određivanja ECLIA, namenjenoj za rad na automatskom analizatoru Elecsys 2010. Koncentracija mioglobina (Mi) je određivana imunoturbidimetrijskom metodom, a enzimi standardizovanim IFCC metodama, na biohemijskom analizatoru HITACHI 911 firme Boehringer Mannheim primenom originalnih test reagensa. Referentne granice za cTnT su određene neparametarskom metodom na osnovu dobijenih vrednosti u uzorcima krvi 105 dobrovoljnih davalaca krvi i iznose od 0,010 do 0,028 ng/mL. U grupi bolesnika s potvrđenim AIM, biohemijski markeri (cTnT, CK, CK MB, Mi I LDH) su određivani odmah po prijemu bolesnika u hitnu službu, a zatim 4, 8, 16, 24, 48, 72, 96, 120, 144, 168, 192 i 216 sati nakon prijema, u bolesnika s politraumom 8 sati nakon završetka hirurške intervencije, a u bolesnika sa KVO u kojih nije potvrđen

SENSITIVITY AND SPECIFICITY OF TROPONIN T IN DIAGNOSIS OF ACUTE MYOCARDIAL INFARCTION

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Lately, in the diagnosis of acute myocardial infarction (MI), special attention is paid to the study of small molecular weight proteins, representing the strucrutal components of cardial muscle contractile proteins, such as cardial troponin T (cTnT). Therefore, the aim of this study was to determine and compare the specificity and sensitivity of cTnT myoglobine and the activity of standard tested enzymes such as: creatine kinase (CK), CK MB isoenzymes and lactic delytrogenase (LDH) in early diagnosis of acute MI. The study concerned the four groups of patients. The first group consisted of healty blood donors (n = 105), the second of patients with verified acute MI (n = 30), the third of a patients with polytrauma (n = 30), and the fourth of patients with cardiovascular diseases with no proved MI (n = 30). For the determination of cTnT level, the commercial Eleccys Troponin T STAT test was used (third generation), Boehringer Mannheim company, based on ECLIA (tehnique of electrochemical luminiscent analysis), designated for the work with automated analysis Elecsys 2010. The concentration of myoglobine (Mi) was determined by immunoturbiometric method, while the activity of other enzymes was determined by the standard IFCC methods with biochemical analyser HITACHI 911, Boehringer Manheim, and with original test reagents. The reference values of blood donor individuals found in the blood ranged from 0.01 to 0.028 ng/mL. In the group of patients with acute MI, biochemical markers (cTnT, CK, CK MB, Mi and LDH) were determined as soon as the material was received by the 24 h service and 4, 8, 16, 24, 48, 72, 96, 120, 144, 168, 192 and 216 hours later. In patients with polytrauma the markers

AIM odmah po prijemu i 4, 8, 16 i 24 sata nakon prijema. Koncentracija cTnT u bolesnika s potvrđenim AIM bila je povišena već odmah po prijemu bolesnika, dostižući maksimum 16-og sata od prijema, od kada postepeno opada, ali zadržava se iznad gornje granice referentnog intervala i nakon 216-og sata od momenta prijema. U bolesnika sa KVO u kojih nije potvrđen AIM nisu nađene povišene koncentracije cTnT. Poređenjem dobijenih vrednosti za cTnT u ove dve grupe bolesnika utvrđena je statistički značajna razlika za sve vremenske intervale. U grupi bolesnika sa politraumom jedino je koncentracija cTnT ostala u okviru referentnog intervala. Dijagnostička tačnost određivanih srčanih markera ispitana je i ROC analizom. Prema dobijenim podacima jedino cTnT ima značajnu dijagnostičku tačnost odmah po prijemu bolesnika, a izračunate ROC AUC iznose: za cTnT = 0,855, za CK = 0,716, za CK MB = 0,503 i za LDH = 0,552. Na osnovu iznetih podataka može se zaključiti da je cTnT najspecifičniji i najosetljiviji rani marker za dijagnostikovanje AIM.

Ključne reči: kardijalni markeri, srčani troponin T, kardiovaskularna oboljenja, AIM.

were tested 8 hours after surgery and in patients with other cardiovascular deseases with non documented acute MI immediattely after admission, and 4, 8, 16 and 24 hours later. The level of cTnT in patients with proved acute MI was increased at the first testing after admission. The highest values were found at hour 16, gradually declining thereafter, but maintaining above the higher control level in the next 216 hours after admission. In patients with cardiovascular diseases and non documented acute MI the level of cTnT was unchanged. Comparison of results of these two groups of patients showed statistically significant differences in cTnT levels in patients with acute MI during all tested time intervals. In the group of patients with polytrauma only the value of cTnT was within the normal level. Diagnostic precision of tested cardiac markers was also tested by ROC analysis. According to the data obtained, only cTnT exhibited statistically significiant diagnostic precision immediately after the admission of patients with the following calculated ROC AUC: 0.855 for cTnT, 0.716 for CK, 0.503 for CK MB and 0.552 for LDH, respectively. According to the presented data, it can be concluded that cTnT was the most specific and the most sensitive marker in the diagnosis of acute MI.

Key words: cardiac markers, cardiac troponin T, cardiovascular diseases, acute MI.

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IZBOR PARAMETARA HEMOSTAZE ZA PRAĆENJE NORMALNE I KOMPLIKOVANE TRUDNOĆE

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Koncentracije proteina plazme uključenih u proces koagulacije se menjaju tokom normalne trudnoće što remeti ravnotežu koja postoji između prokoagulantnog i antikoagulantnog sistema. Ove promene obuhvataju povećanje aktivnosti faktora koagulacije, povećano stvaranje fibrina i supresiju fibrinolize. Na ovaj način se fiziološkim mehanizmima smanjuje rizik od gubitka krvi u trudnoći, ali se povećava rizik od pojave tromboze. Usled tromboze placentarnih krvnih sudova može se javiti placentarna insuficijencija koja dovodi do pojave ponavljajućih abortusa, zastoja u rastu fetusa, eklampsije, intrauterine smrti ploda i prevremenog porođaja. Uzroci ovih pojava su promene koje se dešavaju unutar protein C koagulantnog sistema. Mutacija na genu za faktor V (tzv. Factor V Leiden mutacija) gde je arginin 506 zamenjen glutaminom, stvara mutirani faktor V koji ispoljava normalnu prokoagulantnu aktivnost, ali je manje osetljiv na APC. Stanje koje karakteriše slab antikoagulantni odgovor na APC naziva se APC rezistencija. Cilj ovog rada je bio da se ispita stanje koagulantnog, antikoagulantnog i fibrinolitičkog sistema u normalnoj i komplikovanoj trudnoći kao i funkcionalnost protein C antikoagulantnog sistema u trudnoći različitih gestacijskih starosti i APC rezistencija. Za procenu stanja hemostaznog sistema određivani su sledeći parametri: protrombinsko vreme, parc. protrombinsko vreme, fibrinogen, fibrin monomer, D-dimer, antitrombin III, TAT kompleks, plazminogen, PAI, faktor XIII, protein C, protein S, Protein C Global i aktivirani protein C. Ispitivane su trudnice sa normalnom i komplikovanom trudnoćom različite gestacijske starosti. Posebnu grupu činile su trudnice koje su imale dva ili više uzastopnih pobačaja. Za određivanje parametara hemostaze korišćeni su komercijalni testovi firme »Behring« zasnovani na spektrofotometrijskom i koagulometrijskom merenju i ELISA metodi. Pokazano je da su fibrinogen, fibrin

CHOICE OF HAEMOSTASIS PARAMETERS FOR MONITORING OF NORMAL AND COMPLICATED PREGNANCY

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The concentrations of plasma proteins involved in the process of coagulation are changed during the normal pregnancy, disturbing the balance between procoagulant and anticoagulant system. These changes include the increased activity of coagulation factors, the increased fibrin production and suppression of fibrinolysis. In this way, the risk of loosing blood during pregnancy is reduced by physiological mechanisms, but the hazard of developing thrombosis is increased. Placental insufficiency may occur due to thrombosis of placental blood vessels, leading to repeated miscarriages, retardation of foetal growth, eclampsia, intrauterine foetal death and preterm birth. The causes of these incidents are the changes occurring within protein C coagulation system. The mutation in gene for factor V (so-called Factor V Leiden mutation), where the arginine 506 is replaced by glutamine, produces the mutated factor V having normal procoagulant activity but it is less responsive to APC. The condition characterized by poor anticoagulant response to APC is called the APC resistance. The aim of this study was to test the condition of coagulant, anticoagulant and fibrinolytic system in normal and complicated pregnancy as well as the function of protein C anticoagulant system in pregnancy of various gestation periods and APC resistance. The following parameters were measured for the evaluation of haemostasis system: prothrombin time, partial prothrombin time, fibrinogen, fibrin monomer, D-dimer, antithrombin III, TAT complex, plasminogen, PAI, factor XIII, protein C, protein S, Protein C Global and activated protein C. The testing was performed in pregnant women with normal and complicated pregnancy of various gestation periods. A special group consisted of pregnant women having two or more consecutive miscarriages. Commercial »Behring« tests based on spectrophotometric and coagulometric measure-

monomer, TAT kompleks i PAI kao parametri hemostaze dobri markeri veličine hiperkoagulabilnog stanja kod trudnica. U ovom radu statistički značajno niže vrednosti PC-NR i APC-NR dobijene su u sva tri vremenska perioda kod trudnica sa hipertenzijom i ponavljajućim pobačajima u odnosu na zdrave trudnice čime je pokazano da je antikoagulantna aktivnost aktiviranog proteina C značajno smanjena u trudnoći, naročito u trudnoći praćenoj komplikacijama. Dijagnostička vrednost parametara hemostaze kao markera trombotičkih promena kod trudnica ispitana je analizom. Prema dobijenim podacima PC-NR i APC--NR su pokazali zadovoljavajuću dijagnostičku tačnost kao markeri trombotičkih promena u trudnoći tačnije kao dobri pokazatelji razvoja rezistencije na aktivirani protein C u trudnoći.

Ključne reči: tromboza placente, Protein C rezistencija, faktor V Leiden, trudnoća.

ments and ELISA method were used to determine the parameters of haemostasis. It was shown that fibrinogen, fibrin monomer, TAT complex and PAI, as parameters of haemostasis, were good markers for the extent of hypercoagulable condition in pregnant women. In this study, significantly lower values of PC-NR and APC-NR were obtained in all three time periods in pregnant women with hypertension and repeated miscarriages in comparison to healthy controls, what verified that anticoagulant activity of activated protein C was significantly reduced during pregnancy, and especially in pregnancy associated with complications. The diagnostic value of haemostasis parameters as markers of thrombotic changes in pregnant women was tested by ROC analysis. According to the obtained results, PC-NR and APC-NR showed satisfactory diagnostic accuracy as markers of thrombotic changes in pregnant women, more precisely, they were found to be good indicators of resistance to activated protein C in pregnancy.

Key words: placental thrombosis, protein C resistance, Factor V Leiden, pregnancy.

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UTICAJ CITOKINA NA ISPOLJAVANJE ADHEZIVNIH MOLEKULA U KULTURI ĆELIJA ENDOTELA KRVNIH SUDOVA

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Ključnu ulogu pri inflamaciji ima interakcija leukocita i endotelskih ćelija. Endotelske ćelije ispoljavaju na svojoj površini veliki broj adhezivnih receptora koji regulišu adheziju leukocita na endotel, a takođe i vezivanje ekstracelularnog matriksa. Ove interakcije su kompleksan fenomen u koji je uključeno više mehanizama koji dovode najpre do kotrljanja leukocita po endotelu, a potom do stabilne adhezije i sledstvene transmigracije leukocita. Citokini imaju regulatorni efekat na ispoljavanje adhezivnih molekula. U ovom radu ispitivan je uticaj citokina (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ), kao i efekat kombinovanog dejstva IL-2, IL-4, IL-6 IL-8 ili IL-10 sa IL-1β, TNF-α ili IFN-γ na ispoljavanje adhezivnih molekula u kulturi ćelija endotela krvnih sudova nakon 16-časovne stimulacije. Takođe je ispitan *in vitro* model kojim se oponaša aktivacija endotelskih ćelija primenom citokina koji su povišeni pri inflamatornim procesima. Medijatori pomenutih procesa su specifične adhezivne molekule i glavni su regulišući faktor nastanka imunskog i inflamatornog odgovora. Endotelske ćelije su tretirane s dve kombinacije citokina koje su se sastojale od IL-2, IL-6, IL-8, IFN-γ i TNF-α ili IL-1β, IL-2, IL-4, IL-6, IL-10, IFN-γ i TNF-α. Endotelske ćelije su izdvojene iz humane umbilikalne vene enzimskim putem primenom kolagenaze tip II, a potom pripremane ćelijske kulture koje su čuvane u kompletnom hranljivom medijumu u inkubatoru (37,4 C i 5% CO_2). Nakon stimulacije ćelije su tripsinizacijom odvojene od podloge i dalje analizirane. Primenom flow-citometrijske analize ispitivano je ispoljavanje sledećih molekula na endotelske ćelije iz kulture humane umbilikalne vene (HUVECs): CD 62P (P-selektin), CD 62E (E-selektin, ELAM-1), CD 106 (VCAM-1), CD 54 (ICAM-1), CD 31 (PECAM-1) i CD 34 (L-selektin ligand). Najveći efekat na ispoljavanje mo-

EFFECT OF CYTOKINES ON ADHESION MOLECULES EXPRESSION IN CELL CULTURE OF BLOOD VESSEL ENDOTHELIUM

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The interaction between leukocytes and endothelial cells plays the essential role in inflammation. Endothelial cells express a variety of adhesive receptors that regulate their adhesion to leukocytes and also to the extracellular matrix. These interactions are complex phenomena that require multiple recognition mechanisms, and include the first rolling and later the stationary adhesion and transmigration of leukocytes. It is known that cytokines have regulatory effects on cell adhesion molecules expression. In the present study we investigated the influence of cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ) and the combined use of IL-2, IL-4, IL-6, IL-8 and IL-10 with IL-1β, TNF-β or IFN-g on the expression of adhesion molecules of cultured human umbilical vein endothelial cells (HUVECs) after stimulation for 16 hours. Likewise, in vitro model described herein is designed to mimic the activation of endothelial cells by cytokines as seen during inflammatory processes. This process is mediated by specific cell adhesion molecules being crucial for the generation of immune and inflammatory responses. Therefore, HUVECs are treated with two different cytokine combinations consisting of either IL-2, IL-6, IL-8, IFN-γ and TNF-α or IL-1β, IL-2, IL-4, IL-6, IL-10, IFN-γ and TNF-α. Endothelial cells were collected from hunam umbilical vain using collagense type II, and cell cultures in complete medium were kept in the incubator (37.4[3]C, 5% CO_2). After stimulation cells were prepared for analysis using tripsinisation procedure. The surface expression of the following adhesion molecules was determined in cultured human umbilical vein endothelial cells (HUVECs) by means of flow-cytometric analysis: CD 62P (P-selectin), CD 62E (E-selectin, ELAM-1), CD 106

lekula CD 62E bio je nakon stimulacija ćelija s TNF-α. Ovaj molekul takođe je bio povišen nakon stimulacije endotelskih ćelija s IL-1β, dok je IL-4 doveo do sniženja ispoljavanja ovog molekula. Nakon stimulacije endotelskih ćelija s IL-1β, IL-4, TNF-α i IFN-γ došlo je do sniženja molekula CD 34, dok ostali citokini nisu uticali na ispoljavanje ovog molekula na površini ćelija. Nijedan od ispitivanih citokina nije doveo do promene ispoljavanja molekula CD 62P nakon pojedinačne stimulacije. Molekul CD 54 bio je povišen nakon stimulacije ćelija s IL-1γ, TNF-α i IFN-γ. Nakon stimulacije ćelija s IL-1β, IL-4, TNF-α i IFN-γ bio je povišen molekul CD 106. Količina ispoljenog molekula CD 31 nije se menjala nakon pojedinačne stimulacije ispitivanim citokinima. Nakon 16-časovne stimulacije endotelskih ćelija kombinacijom citokina koja se sastojala od IL-2, IL-4, IL-6, IL-8 ili IL-10 sa IL-1β, TNF-α ili IFN-γ, utvrđeno je da postoje razlike u efektima u odnosu na pojedinačnu stimulaciju citokinima i to: molekul CD 62E bio je povišen kada su endotelske ćelije stimulisane kombinacijom IL-1β i IFN-γ, IL-6 i IL-1β, kao i u svim kombinacijama citokina s TNF-α. Takođe je zabeležena značajna razlika u ispoljavanju molekula CD 62P nakon stimulacije kombinacijom citokina u odnosu na pojedinačnu stimulaciju gde nije nađena stimulacija ispoljavanja ovog molekula. Nakon stimulacije endotelskih ćelija kombinacijom IL-1β i IFN-γ, kao i u svim kombinacijama citokina sa TNF-α nađeno je povećanje ispoljavanja molekula CD 62P. Molekul CD 34 bio je snižen nakon stimulacije kombinacijom IL-10 i IL-1β, TNF-α ili IFN-γ, potom IL-8 i IL-1β ili IFN-γ, IL-6 i IFN-γ, IL-4 i TNF-α ili IFN-γ i IL-2 sa IFN-γ. Stimulacija ćelija s IL-1β i IFN-γ, kao i kombinacijama TNF-α sa svim ispitivanim citokinima dovela je do povećanja broja ispoljenih molekula CD 54. Nakon stimulacije ćelija sa kombinacijama svih ispitivanih citokina sa TNF-α došlo je do stimulacije ispoljavanja molekula CD 106, a isti efekat je bio i nakon stimulacije sa kombinacijom citokina IL-4 ili IL-10 sa IL-1β. Ovi nalazi ukazuju na modulaciju pojedinačnih efekata citokina. Intraćelijski mehanizmi koji dovode do ovakvih efekata nisu još uvek poznati. Takođe su zabeleženi modulatorni efekti kombinacije citokina, odnosno nađeno je da se pojedini efekti kombinacije u potpunosti razlikuju od efekata koje pokazuju citokini nakon pojedinačne stimulacije. Ovo ide u prilog činjenici da postoje intraćelijski mehanizmi odgovorni za modulaciju signala koji stvaraju pojedini citokini, a koji su za sada nepoznati. Primena obe kombinacije citokina koje oponašaju inflamatorne reakcije dovela je do sličnih rezultata i nađeno je statistički značajno povećanje adhezivnih molekula E-selektina, VCAM-1 i ICAM-1 praćeno povećanjem P-selektina. Eksperimenti pokazuju veliku ushodnu regulaciju ovih molekula na površini endotelskih ćelija tokom procesa inflamacije ukazujući na značaj ćelija endotela za ovaj proces.

Ključne reči: adhezivne molekule, HUVEC, citokini.

(VCAM-1), CD 54 (ICAM-1), CD 31 (PECAM-1) and CD 34 (L-selectin ligand). The highest CD 62E expression on the surface of HUVECs was found when endothelial cells were stimulated with TNF-a alone. Also they were increased after stimulation with IL-1β, while IL-4 led to down-regulation of CD 62E. Incubation of HUVEC monolayers with IL-1β, IL-4 as well as TNF-α and IFN-γ, statistically significant, reduced the surface expression of CD 34 while other cytokines did not affect CD 34 expression. Incubation of HUVECs with a single cytokine caused no statistically significant changes in CD 62P expression compared to controls. The most potent effect on CD 54 expression was found under TNF-α stimulation; IL-1β and IFN-γ had also amplifying effects, while all other tested cytokines caused no significant changes in surface molecule expression. Surface expression of CD 106 was amplified during incubation with IL-1β, IL-4, TNF-α and IFN-γ. Single stimulation of tested cytokines did not significantly alter the cell surface expression of CD 31. Concomitant stimulation with IL-2, IL-4, IL-6, IL-8 or IL-10 with IL-1β, TNF-α or IFN-γ led to different effects compared with effects of single cytokine stimulation: CD 62E were up-regulated under co-stimulation with combination of IL-1β and IFN-γ, IL-6 and IL-1β, and also in all combinations with TNF-α. Statistically significant differences were found in CD 62P surface expression after concomitant stimulation with IL-1β and IFN-γ, and in combinations with TNF-a. Co-stimulation with IL-10 and IL-1β, TNF-α or IFN-γ, or IL-8 with IL-1β or IFNγ, IL-6 with IFN-γ, IL-4 with TNF-α or IFN-γ and IL-2 with IFN-γ significantly decreased the level of CD 34 surface expression.

CD 54 expression was up-regulated after stimulation with IL-1β and IFN-γ, and under concomitant stumulation with TNF-α. Surface expression of molecule CD 106 was higher after co-stimulation of cytokines with TNF-α, and IL-4 or IL-10 with IL-1β. These effects indicate modulation of single cytokine effects. Intracellular mechanisms included in those effects need to be investigated. Also there were found modulatory effects of cytokine combinations. Some effects of cytokine combinations were different in comparison to single cytokine effect. This finding indicates that intracellular mechanisms are present and responsible for signal modulation of single cytokine. The application of these two cytokine combinations mimicing inflammation reactions results in effects of comparable dimensions significantly increasing the mean fluorescence intensity of E-selectin, VCAM-1 and ICAM-1 surface expression accompanied by the induction of P-selectin expression. The experiments reveal a strong up-regulation of these cell surface antigens under conditions mimicing inflammation. This is an essential finding stressing the importance of endothelial cells during inflammatory processes.

Key words: adhesion molecules, HUVEC, cytokines.

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PROMENE HORMONSKIH I LIPIDNIH PARAMETARA U DECE SA HIPOTIROIDIZMOM; UTICAJ BOLESTI I SUPSTITUCIONE TERAPIJE

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Zavisno od uzroka koji su doveli do hipotiroidnog stanja kod deteta (dishormonogeneza, hipoplazija, ektopija, atireoza), a time i težine poremećaja, klinički znaci deficita hormona štitne žlezde ispoljavaju se u različitom uzrastu deteta, s različitim koncentracijama ispitivanih hormona. U cilju utvrđivanja promena nastalih pod uticajem bolesti i supstitucione terapije kod dece s hipotiroidizmom određene su koncentracije hormonskih parametara: tT_3, tT_4, TSH, fT_3, fT_4, TBG i Tg (fluoroimunotest DELFIA), kao i lipidnih: ukupni holesterol, trigliceridi, HDL-holesterol i LDL-holesterol. Za utvrđivanje uticaja starosti deteta na ispitivani parametar isti su obrađeni u uzorku zdrave dece. Grupa zdrave dece N=100 uzrasta od 1 meseca do 18 godina podeljena je u 5 starosnih podgrupa. Posebnu grupu sačinjava uzorak uzet iz pupčane vrpce, zdravo rođene dece. Grupa obolele dece je podeljena po istim starosnim grupama kao i zdrava grupa i to: u momentu otkrivanja bolesti (N=58) i u momentu kasnijeg pregleda, posle dugovremene supstitucione terapije sa L-T4 (N=56). Metaboličko stanje deteta utvrđeno je po kriterijumu specifičnih kliničkih znakova i simptoma. ANOVA testom po metodi Tudey Snedecor-a utvrđena je statistički značajna razlika između starosnih podgrupa za sledeće parametre: T_3 (d=0,35 p<0,001), fT3 (d=1,63 p<0,001) fT4 (d=2,59 p<0,001), TSH (d=2,27 p<0,001), TBG (d=90,82 p<0,001), Tg (d=4,59 p<0,02), holesterola (d=0,48 p<0,001) i LDL-holesterola (d=0,51 p<0,001), što se mora uzeti u obzir kod tumačenja uticaja supstitucione terapije na izmenu koncentracija posmatranih parametara. Koncentracije svih hormonskih parametara u uzorku pupčane vrpce se raz-

CHANGES OF HORMONES AND LIPOPROTEIN PARAMETERS IN INFANTS WITH HYPOTHYROIDISM; INFLUENCE OF THE DISEASE AND REPLACEMENT THERAPY

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Clinical signs of thyroid gland hormones deficiency appear at different ages in infants with different concentrations of hormones. They depend on causes which had caused the hypothyroid degree of subsequents. Concentrations of hormones parameters: tT_3, tT_4, TSH, fT_3, fT_4, TBG and Tg (fluoroimmunoassay, DELFIA) and lipid parameters: total cholesterol (Chol), triglycerides (TRG), high density lipoprotein, (HDL-chol) and density lipoprotein, (LDL-chol) were determined in order to establish changes that appear under the influence of the disease and replacement therapy in infants with hypothyroidism. In order to establish the influence of infant's age on a determined parameter, all parameters where determined in the sample of healthy infants. A group of healthy infants (N=100) aged one mounth to 18 years, was devided in 5 age subgroups. The group of patients was devided into the same age groups as healthy group of the moment of diagnosis (N=56). Metabolic condition of an infant was established according to found by ANOVA test according to Tudey Snedecor method for the following parameters; T_3 (d=0.35 p<0.001), fT_3 (d=1.63 p<0.001) fT4 (d=2.59 p<0.001), TSH (d=2.27 p<0.001), TBG (d=90.82 p<0.001), Tg (d=4.59 p<0.02), Cho. (d=0.48 p<0.001) and LDL-chol. (d=0.51 p<0.001). These findings must be taken into account when the influence of replacement therapy on the observed parameters concentration changes is interpreted. The average concentration values were compared by Student's t-test in infant before replacement therapy with that of the control subgroup of infants of the same age in order to evaluate the influence on values of the examined parameters. The average concentra-

likuje od koncentracija u ostalim starosnim grupama dece, osim za T_4. Da bi se procenio uticaj bolesti na vrednosti ispitivanih parametara, upoređene su vrednosti srednjih koncentracija Studentovim T-testom podgrupa dece pre supstitucije sa kontrolnim grupama dece iste starosne dobi. Za procenu uticaja supstitucije na ispitivane parametre upoređene su srednje koncentracije ispitivanih parametara, grupe dece posle supstitucije sa grupom dece pre supstitucije kao i sa kontrolnom grupom. Za posmatrane hormonske parametre imamo značajne izmene u svim starosnim podgrupama, sa nastankom hipotiroidnog stanja i vraćanje na nivo vrednosti kontrolne grupe sem za T_4 kada su vrednosti značajno više u svim starosnim grupama ($p<0,05$) u odnosu na kontrolu. Kod lipida značajno veće vrednosti nađene su u svim starosnim podgrupama za holesterol ($p<0,01$) i LDL-holesterol ($p<0,001$) koje se ne razlikuju od kontrolne grupe posle supstitucione terapije. Pacijente su u momentu kliničkog pregleda razvrstali u kategorije normometabolični (NM) i hipometabolični (HM) i upoređeni Studentovim T-testom razlike parova sa sopstvenim stanjem pre supstitucione terapije. Procentualni udeo u izmeni koncentracija triglicerida ($p<0,02$) LDL-holesterola ($p<0,025$) i T_3 ($p<0,001$) je značajno različit između NM I HM, a dugogodišnja supstituciona terapija dovodi do značajnih interindividualnih razlika u koncentracijama holesterola (NM 37,90% $p<0.001$, HM 15,14% $p<0,001$) HDL-holesterola (NM 7,81% $p<0.001$, HM 12,0,05% $p<0.001$), LDL-holesterola (NM 50,15% $P<0,001$ HM 20,03 $p<0,01$) i T3 (NM 105,04% $p<0,001$, HM 32,18% $p>0,005$). Zaključujemo da hipotiroidizam dovodi do značajnih hormonskih i metaboličkih promena kod obolele dece, ali ne postoji generalni klinički i laboratorijski indeks postignutog rezultata supstitucione terapije, te zbog toga se individualno procenjuje stanje bolesnika.

Ključne reči: kongenitalni hipotiroidizam, supstituciona terapija, hormonski parametri, lipidni parametri.

tion values in infants after the replecement therapy were compared that before the replacement therapy as well as the control group, findings in order to the influence on the examined parameters. We observed significant changes hormone parameters in all age-subgroups under hypothyroid condition and return to control levels, except for T_4 where the values were significantly higher in all age groups ($p<0.05$) in comparison to the control group. As for lipids, we found significantly higher values in all age subgroups for chol ($p<0.01$) and LDL-chol ($p<0.001$); they did not differ from that in control group after the replacement therapy. Patients were classified at the moment of clinical examination into the following categories: normometabolic (NM) and hypometabolic (HM). They were compared by Student's T-test of different pairs with the condition before the replacement therapy. The percentage share in the change of TRG concentrations ($p<0.02$), LDL-chol ($p<0.025$) and T3 ($p<0.001$) was significantly different between NM and HM, and the long-lasting replacement therapy caused significant individual differences in Chol concentrations (NM 37.90% $p<0.001$, HM 15.14% $p<0.001$), HDL-chol (NM 7.81% $p<0.001$, HM 12.05% $p<0.001$), LDL-chol (NM 50.15% $P<0.001$ HM 20.03 $p<0.01$) and T_3 (NM 105.04% $p<0.001$, HM 32.18% $p>0.005$). We conclude that hypothyroidism caused significant hormonal and metabolic changes in infants; however there is no clinical and laboratory index regarding the results of replacement therapy; this is the reason why the patient's condition must be evaluated individually.

Key words: congenital hypothyroidism, replacement therapy, lipid parameters, hormone parameters.