Serumski lipidi u depresivnom poremećaju s obzirom na tip depresije
Serum lipids in a depressive disorder with regard to depression type

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Sažetak

Uvod: Cilj ovog istraživanja bio je ispitati koncentracije serumskih lipida (kolesterola, triglicerida, HDL-kolestrola, LDL-kolesterola, VLDL-kolesterola) u odnosu na tip depresije u bolesnika koji boluju od velikog depresivnog poremećaja.

Ispitanici i metode: U istraživanje je uključeno 76 ispitanika oboljelih od depresije. Dijagnoza velikog depresivnog poremećaja je postavljena na temelju kriterija Dijagnostičkog i statističkog priručnika, četvrta revizija (DSM IV), te primjenom upitnika HAMD-17. Podtipovi depresije (melankolična, atipična i distimija) određeni su također pomoću MINI-upitnika. Serumske koncentracije kolesterola, triglicerida i HDL-kolesterola određivane su komercijalnim laboratorijskim kompletima enzimskom metodom. Vrijednosti VLDL-kolesterola i LDL-kolesterola određene su računskim metodama.

Rezultati: Koristeći se analizom kovarijance (engl. *one-way ANCOVA*) nakon prilagodbe za dob i BMI (engl. *body mass index*, pokazatelj tjelesne mase) našli smo značajno nižu koncentraciju kolesterola (P = 0,001), LDL-kolesterola (P = 0,022), omjera kolesterola/HDL-kolesterola (P = 0,019) i omjera LDL-kolesterola/HDL-kolesterola (P = 0,005) u ispitanika s atipičnom depresijom u odnosu na ispitanike s melankolijom ili distimičnim oblikom depresivnog poremećaja.

Zaključak: Rezultati našeg istraživanja ukazuju da bi se serumske koncentracije kolesterola i LDL-kolesterola te omjeri kolesterola/HDL-kolesterola i LDL-kolesterola/HDL-kolesterola mogli koristiti kao biološki biljezi u razlikovanju kliničkih podtipova depresivnog poremećaja.

Ključne riječi: depresivni poremećaj, kolesterol, trigliceridi, HDL-kolesterol, LDL-kolesterol, VLDL-kolesterol

Abstract

Introduction: The aim of this study was to investigate the levels of serum lipids (cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol) in relation to a type of depression in patients affected by major depressive disorder.

Subjects and methods: The study included 76 patients affected by depression. Diagnosis of major depressive disorder was made according to the criteria of a Diagnostic and Statistical Manual, 4th revision (DSM IV) and by applying HAMD-17 questionnaire. Depression subtypes (melancholic, atypical and dysthymic) were also determined using MINI questionnaire. Serum concentrations of cholesterol, triglycerides and HDL-cholesterol were determined by commercial laboratory kits and enzymatic method. VLDL-cholesterol and LDL-cholesterol concentrations were determined by calculation methods.

Results: Using one-way ANCOVA after adjustment for age and BMI, we found significantly lower levels of cholesterol (P = 0.001), LDL-cholesterol (P = 0.022), cholesterol/HDL-cholesterol ratio (P = 0.019), and LDL-cholesterol/HDL-cholesterol ratio (P = 0.005) in patients with atypical depression than in patients with melancholic or dysthymic type of depressive disorder.

Conclusion: Results of our investigation suggested that serum concentrations of cholesterol and LDL-cholesterol, and cholesterol/HDL-cholesterol ratio and LDL-cholesterol/HDL-cholesterol ratio could be employed as biological markers to differentiate clinical subtypes of depressive disorder.

Key words: depressive disorder, cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol

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Uvod

Prema rezultatima dosadašnjih istraživanja, koncentracija serumskih lipida, uključujući trigliceride, ukupni kolesterol, HDL-kolesterol (HDL, engl. *high density lipoprotein*, lipoprotein velike gustoće) i LDL-kolesterol (LDL, engl. *low density lipoprotein*, lipoprotein male gustoće), bila je u značajnoj korelaciji s brojnim psihopatološkim stanjima kao što su shizofrenija, depresija, PTSP i drugi anksiozni poremećaji, agresivnost, impulzivnost i samoubojstvo (1-6).

Kolesterol ima više važnih funkcija u središnjem živčanom sustavu. Građevna je komponenta membrane neurona, ima važnu ulogu u procesu neurotransmisije kao i u sustavu drugog glasnika u mozgu (7). Smatra se da niska koncentracija kolesterola povećava rizik od depresije zbog neuronske disfunkcije koja nastaje zbog promjena u mikroviskoznosti stanične membrane ili zbog poremećaja u provođenju signala (8,9). Većina dosadašnjih istraživanja ukazuje na povezanost depresivnih simptoma i koncentracije kolesterola u serumu. U nekim je istraživanjima opisana niska koncentracija kolesterola u depresivnih bolesnika (7,9-13), dok u drugim studijama nisu potvrđeni takvi rezultati (14). Steegmans i suradnici su našli značajno veći rizik od depresivnih simptoma u srednjovječnih muškaraca s kronično nižom koncentracijom kolesterola u serumu (15). Kako je depresija jedan od glavnih uzroka samoubojstava, istraživanja povezanosti između niskog kolesterola i depresije mogu biti od velike važnosti, na što upućuje istraživanje u kojem je opisana korelacija između koncentracije kolesterola i sklonosti samoubojstvu (suicidalnosti) (8).

Iako je povezanost između koncentracije ukupnog kolesterola u serumu i depresivnih simptoma bila često istraživana, manji broj istraživanja opisuje povezanost drugih lipida i depresivnog poremećaja (16). Tako je u jednoj studiji pronađena značajno niža koncentracija serumskog kolesterola, HDL-kolesterola i omjera kolesterola/HDL-kolesterola u ispitanika s depresivnim poremećajem u odnosu na zdravu kontrolnu skupinu (17). Rezultati druge studije pokazuju značajne razlike u razini triglicerida, VLDL-kolesterola (VLDL, engl. *very low density lipoprotein*, lipoprotein vrlo male gustoće), i HDL-kolesterola između melankolične i atipične depresije (16). Također je u jednom istraživanju pronađena značajno niža koncentracija LDL-kolesterola u depresivnih pacijenata nego u kontrolnoj skupini, ali nije nađena značajna razlika u koncentraciji triglicerida (12).

Iako je proveden veći broj istraživanja na lipidima u depresivnom poremećaju, postoji tek nekoliko izvješća koja uzimaju u razmatranje razlike u koncentracijama serumskih lipida po pojedinim podtipovima depresije, ali s oprečnim rezultatima. Tako u nekim istraživanjima nije nađena razlika u koncentracijama serumskih lipida u pacijenata s melankolijom i nemelankolijom (17,18), kao ni u pacijena-

Introduction

Based on results of past investigations, the levels of serum lipids including triglycerides, total cholesterol, high density lipoprotein cholesterol (HDL-cholesterol) and low density lipoprotein cholesterol (LDL-cholesterol), were in significant correlation with numerous psychopathological conditions like schizophrenia, depression, PTSD, and other anxiety disorders, aggressiveness, impulsiveness and suicide (1-6).

Cholesterol has several important functions in the central nervous system. It is a constituent of the neuronal membrane, and plays a significant role in the process of neurotransmission and in the second messenger system in the brain (7). Low cholesterol level is believed to enhance the risk of depression due to the neuronal dysfunction occurring because of changes in microviscosity of the cellular membrane or disorders in signal transduction (8-9). Most past studies have indicated a correlation between depression symptoms and serum cholesterol level. Low cholesterol concentration was observed in depressive patients in some studies (7,9-13), while in others this finding was not confirmed (14). Steegmans et al. observed significantly elevated risk of depression symptoms in middle-aged men with chronically lowered serum cholesterol concentration (15). As depression is one of the major causes of suicide, the studies of association between low cholesterol and depression may be of substantial importance, which was indicated by a study describing a correlation between cholesterol level and suicidality (8).

Although the association between serum total cholesterol level and depression symptoms has been frequently investigated, few studies described the correlation of other lipids and depressive disorder (16). Thus, one study established a significantly lower concentrations of serum cholesterol, HDL-cholesterol, and cholesterol/HDL-cholesterol ratio in patients with depressive disorder in comparison to a healthy control group (17). Results of another study demonstrated considerable differences in the levels of triglycerides, very low density lipoprotein cholesterol (VLDL-cholesterol), and HDL-cholesterol between melancholic and atypical depression (16). Also, one study found a significantly lower LDL-cholesterol level in depressive patients than in the control group, but no such difference was recorded for the level of triglycerides (12).

Despite the fact that a large number of studies of lipids in depressive disorder have been conducted, there have been only several reports that considered differences in serum lipid concentrations according to individual depression subtypes, and these yielded contrary results. Thus, in some studies no differences were found in serum lipid levels of patients with melancholic and non-melancholic depression (17,18), or in patients with melancholy and atypical depression (19), while Huang TL et al. in their

ta s melankolijom i atipičnom depresijom (19), dok je u istraživanju koje su proveli Huang TL i sur. nađena značajna razlika u koncentracijama triglicerida, VLDL-kolesterola i HDL-kolesterola u ispitanika s melankolijom i atipičnom depresijom (16).

Cilj ovog istraživanja je ispitati koncentracije serumskih lipida (kolesterola, triglicerida, HDL-kolesterola, LDL-kolesterola, VLDL-kolesterola), omjere lipidnih frakcija (kolesterol/HDL-kolesterol i LDL-kolesterol/HDL-kolesterol) u odnosu na tip depresivnog poremećaja (melankolična, atipična i distimija).

Materijali i metode

Ispitanici

U istraživanje je uključeno 76 ispitanika oboljelih od depresivnog poremećaja primljenih na liječenje u Kliničku bolnicu „Sestre milosrdnice" tijekom razdoblja od 12 mjeseci u 2005. i 2006. godini. Uzorak je činilo 30 muškaraca i 46 žena prosječne dobi ($\bar{x} \pm SD$) 53 ± 10 godina i prosječnog indeksa tjelesne mase (BMI) ($\bar{x} \pm SD$) 25,66±4,29 kg/m^2. Prosječna dob početka bolesti bila je ($\bar{x} \pm SD$) 45 ± 10 godina, a prosječno vrijeme trajanja bolesti je bilo ($\bar{x} \pm SD$) 8 ± 6 godina uz prosječan broj hospitalizacija ($\bar{x} \pm SD$) 3,11 ± 2,55. Sociodemografska obilježja ispitanika prikazana su u tablici 1. Ispitanici su liječeni psihofarmakološki antidepresivima (fluoksetin, fluvoksamin, paroksetin, sertra-

study established a significant difference in the concentrations of triglycerides, VLDL-cholesterol, and HDL-cholesterol in patients affected by melancholy and atypical depression (16).

The aim of this study was to examine the concentrations of serum lipids (cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol) and lipid fraction ratios (cholesterol/HDL-cholesterol and LDL-cholesterol/HDL-cholesterol) in relation to a type of depressive disorder (melancholic, atypical and dysthymic).

Materials and methods

Subjects

The study included 76 subjects affected by depressive disorder and hospitalized in Sestre milosrdnice University Hospital during a 12-month period in years 2005 and 2006. The patient sample consisted of 30 men and 46 women, mean age ± SD = 53 ± 10 years, mean body mass index (BMI) (mean ± SD) 25.66 ± 4.29 kg/m^2. Mean age ± SD at disease onset was 45 ± 10 years, while disease duration (mean ± SD) was 8 ± 6 years with mean number of hospitalizations (mean ± SD) 3.11 ± 2.55. Patient sociodemographic characteristics are shown in Table 1. Subjects were treated pharmacologically by antidepressants (fluoxetine, fluvoxamine, paroxetine, sertraline, clomipramine) and anxiolytics (alprazolam, oxazepam, diazepam, clo-

Tablica 1. Sociodemografska obilježja ispitanika s depresivnim poremećajem uključenih u istraživanje.

Table 1. Sociodemographic characteristics of patients with depressive disorder who participated in the study.

Variables	N	%	χ^2	P
Gender				
Men	30	39.5	3.37	0.66
Women	46	60.5		
Qualification				
Primary school education	16	21.1	30.73	< 0.001
Secondary school education	48	63.2		
University degree	12	15.8		
Marriage status				
Married	52	68.4	10.32	0.001
Single	24	31.6		
Employment status				
Employed	28	36.8	0.74	0.692
Unemployed	22	28.9		
Pensioners	26	34.2		
Residence				
Village	18	27.3	13.64	< 0.001
Town	58	72.7		
Economic status				
Low	24	32.4	0.11	0.947
Middle-class	26	35.1		
High	24	32.4		

lin, clomipramin) i anksioliticima (alprazolam, oksazepam, diazepam, clonazepam). Nijedan od gore spomenutih psihofarmaka nema utjecaja na serumske koncentracije lipida (20). Nitko od ispitanika nije liječen hipolipemicima prije uključivanja u studiju. Kriteriji isključenja iz studije su bili drugi psihijatrijski poremećaji u komorbiditetu, ovisnost o drogama, alkoholizam, hipertenzija, kardiovaskularne bolesti, bolesti štitnjače, šećerna bolest, poremećaji metabolizma lipoproteina, poremećaji prehrane i organski moždani sindromi. Kako prehrambene navike i fizička aktivnost mogu utjecati na rezultate pretraga, sve pretrage su vršene između 14. i 16. dana boravka u bolničkim uvjetima, u vrijeme u koje su svi ispitanici imali ujednačenu prehranu i razinu fizičke aktivnosti.
Svi ispitanici su dali informirani pristanak za sudjelovanje u studiji, studija je odobrena od strane nadležnog etičkog povjerenstva.

Dijagnostički instrumenti i formiranje ispitivanih skupina

Dijagnoza depresivnog poremećaja je postavljena na temelju kriterija za depresivni poremećaj Dijagnostičkog i statističkog priručnika za duševne poremećaje, četvrto izdanje (DSM IV) (21), te primjenom Hamiltonove ocjenske ljestvice za depresiju (HAMD-17) (23). Podtip depresije (melankolična, atipična, distimija) je dijagnosticiran pomoću MINI-upitnika temeljenog na kriterijima DSM IV (21,22). Ispitanici su podijeljeni u skupine po tipu depresije na tri različite dijagnostičke kategorije: skupinu s melankoličnim obilježjima, skupinu s atipičnim obilježjima i skupinu s distimijom.

Laboratorijske pretrage i antropometrijske mjere

Uzorci krvi su uzimani iz kubitalne vene u staklene vakuumske epruvete bez antikoagulanta ujutro između 8 i 9 sati nakon cjelonoćnog gladovanja u trajanju od najmanje 12 sati, te 30 minuta odmora neposredno prije uzimanja uzorka. Serumske koncentracije kolesterola, triglicerida i HDL-kolesterola određivane su enzimskom metodom neposredno nakon uzimanja uzoraka komercijalnim laboratorijskim kompletima. (Olympus Diagnostic, GmbH, Hamburg, Germany) na automatskom analizatoru Olympus AU 600. Međuanalitički koeficijent varijacije u laboratoriju bio je: 3,2 % za kolesterol, 2,5 % za trigliceride i 3,0 % za HDL-kolesterol. Vrijednosti LDL-kolesterola i VLDL-kolesterola izračunate su pomoću uvriježenih formula iz vrijednosti triglicerida, kolesterola i LDL-kolesterola (LDL-kolesterol = kolesterol – trigliceridi/2,2 – HDL-kolesterol; VLDL-kolesterol = trigliceridi/5). Preporučene laboratorijske vrijednosti za mjerene parametre su bile: kolesterol < 5,0 mmol/L, LDL < 3,0 mmol/L, HDL > 1,0 mmol/L, VLDL-kolesterol < 1 mmol/L, omjer LDL/HDL < 4,0, omjer kolesterola/HDL-kolesterola < 2,5, i trigliceridi < 1,7 mmol/L. Svakom pacijentu su izmjerene visina i težina u stojećem

nazepam). None of the psychopharmaceutics above has any effect on serum lipid concentrations (20). None of the subjects had been treated by hypolipemics prior to their participation in the study. Criteria for exclusion from the study were other concurrent psychiatric disorders, drug addiction, alcoholism, hypertension, cardiovascular diseases, thyroid disorders, diabetes mellitus, lipoprotein metabolism disorders, nutrition disorders and organic brain syndromes. Since dietary habits and physical activity may affect test results, all tests were conducted between days 14 and 16 of hospital stay, i.e. during the period of uniform diet and level of physical activity of all subjects.
All subjects signed their written consent for participation in the study, and the study was approved by a competent ethical committee.

Diagnostic instruments and formation of subject groups

Diagnosis of depressive disorders was made according to criteria for depressive disorders of the Diagnostic and Statistical Manual for mental disorders, 4th revision (DSM IV) (20), and application of the Hamilton Rating Scale for Depression (HAMD-17) (22). Depression subtype (melancholic, atypical, dysthymia) was diagnosed using MINI questionnaire based on DSM IV criteria (21, 20). Subjects were divided into groups according to depression type into three different diagnostic categories: a group with melancholic characteristics, a group with atypical characteristics, and a group with dysthymia.

Laboratory tests and anthropometric measurements

Blood samples were taken from the cubital vein into glass vacuum test-tubes without an anticoagulant at 8-9h a.m. after minimum 12h overnight fast and 30 min rest immediately prior to sample collection. Serum concentrations of cholesterol, triglycerides and HDL-cholesterol were determined by enzymatic method immediately after sample collection using commercial laboratory kits (Olympus Diagnostic, GmbH, Hamburg, Germany) on Olympus AU 600 automated analyzer. Interassay coefficients of variation in the laboratory were 3.2% for cholesterol, 2.5% for triglycerides, and 3.0% for HDL-cholesterol. LDL-cholesterol and VLDL-cholesterol levels were calculated by conventional formulas from triglyceride, cholesterol, and LDL-cholesterol levels (LDL-cholesterol = cholesterol - triglycerides /2.2 - HDL-cholesterol; VLDL-cholesterol = triglycerides/5). Recommended laboratory intervals for the measured parameters were: cholesterol < 5.0 mmol/L, LDL < 3.0 mmol/L, HDL > 1.0 mmol/L, VLDL-cholesterol < 1 mmol/L, LDL/HDL ratio < 4.0, cholesterol/HDL-cholesterol ratio < 2.5, and triglycerides < 1.7 mmol/L. The height and weight of each patient, who were barefoot and in light clothes, were measured in standing position on a medical scale that measures height and weight. Body

stavu bez obuće u laganoj odjeći na medicinskoj vagi za mjerenje visine i težine. Indeks tjelesne mase (BMI) je računan tako da se tjelesna težina u kilogramima podijelila s kvadratom visine u metrima.

Statistička obrada podataka

Podatci su pohranjivani u bazu podataka MS Access 2000, za statističku analizu je korišten statistički program SPSS (SPSS for Windows 11.0, SPSS, Chicago, IL, SAD). U obradi podataka korištene su deskriptivne statističke metode. Za procjenu razlike u sociodemografskim podatcima korišten je hi-kvadrat-test. Za testiranje razlike u koncentraciji serumskih lipida među skupinama korištena je jednosmjerna analiza varijance (ANOVA) i Scheffe-ov *posthoc* test za testiranje razlike među pojedinim skupinama, dok je za kontrolu utjecaja dobi i indeksa tjelesne mase na ispitivane parametre korištena analiza kovarijance (ANCOVA). Distribucija uzorka ispitana je Kolmogorov-Smirnovim testom. Razina vjerojatnosti od $P < 0,05$ je uzeta kao statistički značajna.

Rezultati

U tablici 2. prikazane su koncentracije serumskih lipida u odnosu na tip depresije. Koncentracija LDL-kolesterola je bila značajno niža u ispitanika s atipičnom depresijom nego u ispitanika s distimijom ($F(2,63) = 4,48$; $P = 0,015$, ANOVA; $P = 0,016$, Scheffe-ov test). Razlika je ostala i nakon prilagodbe za dob i BMI ($F(2,61) = 8,57$; $P = 0,001$, ANCOVA). Jednosmjernom analizom varijance nije pronađena statistički značajna razliku u koncentracijama triglicerida, kolesterola i omjera kolesterola/HDL-kolesterola i LDL-kolesterola/HDL-kolesterola među ispitanicima s melancholičnom, distimijom i atipičnom depresijom.

mass index (BMI) was calculated by dividing kilograms by squared height in meters.

Statistical data processing

Data were stored in MS Access 2000 database, and SPSS statistical program (SPSS for Windows 11.0, SPSS, Chicago, IL, USA) was used for statistical analysis. Descriptive statistical methods were used in data processing. Hi-square test was used to assess differences in sociodemographic data. To test differences in serum lipid level between groups, one way analysis of variance (ANOVA) was used. Scheffe posthoc test was applied to examine differences between individual groups, while covariance analysis (ANCOVA) was used to control the effect of age and body mass index on investigated parameters. Sample distribution was tested by Kolmogorov-Smirnov test. $P < 0.05$ probability level was considered statistically significant.

Results

Table 2 shows serum lipid concentrations in relation to the type of depression. LDL-cholesterol level was significantly lower in patients with atypical depression than in dysthymic patients ($F(2.63) = 4.48$, $P = 0.015$, ANOVA; $P = 0.016$, Scheffe test), and this difference persisted after adjustments for age and BMI ($F(2.61) = 8.57$; $P = 0.001$, ANCOVA). One-way analysis of variance revealed no statistically significant difference in the levels of triglycerides, cholesterol, and cholesterol/HDL ratio and LDL-cholesterol/HDL-cholesterol ratio among patients with melancholic and atypical depression and dysthymia. However, after age and BMI adjustments, a statistically significantly lower total cholesterol concentration was found in patients wi-

Tablica 2. Serumski lipidi ($\bar{x} \pm SD$) u pacijenata s depresivnim poremećajem prema podtipu depresije (melankolična, distimija i atipična).

Table 2. Serum lipids (mean ± SD) in patients with depressive disorder according to depression subtype (melancholic, atypical, disthymia).

	Type of depressive disorder			F*	P
	Melancholy	Atypical	Disthymia		
Triglycerides (mmol/L)	1.96 ± 1.12	1.35 ± 0.50	1.76 ± 0.45	1.54	0.168
Cholesterol (mmol/L)	5.99 ± 0.99	6.5 ± 1.25	5.62 ± 0.72	2.47	0.093
HDL-cholesterol (mmol/L)	1.51 ± 0.45	1.58 ± 0.38	1.58 ± 0.48	0.22	0.799
LDL-cholesterol (mmol/L)	3.59 ± 0.97	4.28 ± 0.72	3.24 ± 0.63	4.48	0.015
VLDL-cholesterol (mmol/L)	0.39 ± 0.22	0.27 ± 0.1	0.35 ± 0.09	1.79	0.175
Cholesterol/HDL-cholesterol ratio	4.23 ± 1.14	4.15 ± 0.35	3.81 ± 1.03	0.95	0.393
LDL-cholesterol/HDL-cholesterol ratio	2.56 ± 0.93	2.76 ± 0.34	2.23 ± 0.81	1.35	0.266

* One-way ANOVA

lankoličnom i atipičnom depresijom te distimijom. Međutim, nakon prilagodbe za dob i BMI nađena je statistički značajno niža koncentracija ukupnog kolesterola u ispitanika s atipičnom depresijom nego u ispitanika s melankolijom i distimijom (F(2,61) = 4,06; P = 0,022, ANCOVA), nađen je značajno niži omjer kolesterola/HDL-kolesterola u pacijenata s atipičnom depresijom nego u pacijenata s melankolijom i distimijom (F(2,61) = 4,21; P = 0,019, ANCOVA) i nađen je značajno niži omjer LDL-kolesterola/HDL-kolesterola u pacijenata s atipičnom depresijom nego u pacijenata s melankolijom i distimijom (F(2,61) = 5,91; P = 0,005, ANCOVA), (Tablica 3).

Rasprava

Rezultati ovog istraživanja pokazuju značajno nižu koncentraciju LDL-kolesterola, kolesterola, omjera kolesterola/HDL-kolesterola i omjera LDL-kolesterola/HDL-kolesterola u ispitanika s atipičnom depresijom u odnosu na ispitanike s melankolijom i distimijom. Također, prema rezultatima ovog istraživanja proizlazi da nema značajne razlike u serumskim koncentracijama triglicerida, HDL-kolesterola i VLDL-kolesterola između ispitanika s atipičnom depresijom, melankolijom i distimijom. U sličnom istraživanju koje su proveli Huang i Chen 2004. koristeći se analizom kovarijance nakon prilagodbe za dob, govori se da serumske koncentracije triglicerida, VLDL-kolesterola i HDL-kolesterola mogu poslužiti kao biološki biljezi za razlikovanje depresivnih pacijenata s atipičnom depresijom od pacijenata s melankoličnim značajkama (16). Koristeći se istom statističkom analizom nakon prilagodbe za BMI u sličnoj studiji nije nađena nikakva razlika u koncentracijama serumskih lipida između skupina ispitanika s melan-

th atypical depression compared to patients with melancholy and dysthymia (F(2.61) = 4.06; P = 0.022, ANCOVA), a significantly lower cholesterol/HDL-cholesterol ratio in patients with atypical depression than in melancholic and dysthymic patients (F(2.61) = 4.21; P = 0.019, ANCOVA), and finally a significantly lower LDL-cholesterol/HDL-cholesterol ratio in patients with atypical than in patients with melancholic depression and dysthymia (F(2.61) = 5.91; P = 0.005, ANCOVA) (Table 3).

Discussion

Results of this study demonstrated significantly lower values of LDL-cholesterol, cholesterol, cholesterol/HDL-cholesterol ratio, and LDL-cholesterol/HDL-cholesterol ratio in patients with atypical depression compared to patients with melancholy and dysthymia. Also, the results of this investigation indicated no significant difference in the serum levels of triglycerides, HDL-cholesterol and VLDL-cholesterol among patients with atypical depression, melancholy, and dysthymia. A similar study conducted by Huang and Chen in 2004, where covariance analysis was used after age adjustment, suggested that serum concentrations of triglycerides, VLDL-cholesterol and HDL-cholesterol might be used as biological markers to distinguish depressive patients with atypical depression from patients with melancholic characteristics (16). Upon application of the same statistical analysis after adjustment for BMI in a similar study, no difference in serum lipid concentrations was found among subject groups with melancholic and atypical characteristics of depressive disorder (19). After application of the analysis of covariance and age and BMI adjustments, results of our study confirmed the levels of

Tablica 3. Serumski lipidi ($\bar{x}$ (95% CI)) nakon prilagodbe za dob i BMI u pacijenata s depresivnim poremećajem prema podtipu depresije (melankolična, distimija i atipična).

Table 3. Serum lipids (mean (95% CI)) after age and BMI adjustment in patients with depressive disorder according to depression type (melancholic, atypical and dysthymic).

	Type of depressive disorder			F*	P
	Melancholic	Dysthymic	Atypical		
Triglycerides (mmol/L)	1.99 (1.71 – 2.27)	1.56 (0.92 V 2.2)	1.56 (0.24 – 1.08)	1.79	0.176
Cholesterol (mmol/L)	6 (5.69 – 6.31)	6.77 (6.08 – 7.47)	5.43 (4.91 – 5.96)	4.06	0.022
HDL-cholesterol (mmol/L)	1.49 (1.36 – 1.63)	1.48 (1.18 – 1.78)	1.69 (1.46 – 1.92)	1.12	0.334
LDL-cholesterol (mmol/L)	3.62 (3.36 – 3.87)	4.6 (4.02 – 5.18)	2.97 (2.53 – 3.41)	8.57	0.001
VLDL-cholesterol (mmol/L)	0.4 (0.34 – 0.45)	0.31 (0.18 – 0.44)	0.31 (0.22 – 0.41)	1.7	0.191
Cholesterol/HDL-cholesterol ratio	4.28 (3.99 – 4.57)	4.48 (3.83 – 5.14)	3.48 (2.98 – 3.97)	4.21	0.019
LDL-cholesterol/HDL-cholesterol ratio	2.61 (2.38 – 2.83)	3.04 (2.53 – 3.56)	1.94 (1.55 – 2.33)	5.91	0.005

* One-way ANCOVA

količnim i atipičnim značajkama depresivnog poremećaja (19). Uz analizu kovarijance nakon prilagodbe za dob i BMI, rezultati našeg istraživanja govore o koncentracijama kolesterola, LDL-kolesterola, omjera kolesterola/HDL-kolesterola i omjera LDL-kolesterola/HDL-kolesterola kao mogućim biološkim biljezima u razlikovanju pojedinih kliničkih podtipova depresivnog poremećaja.

Rezultati nekih istraživanja pokazuju da omjeri kolesterola/HDL-kolesterola i LDL-kolesterola/HDL-kolesterola (pokazatelji ateroskleroze) imaju značajno veću prediktivnu vrijednost za nastanak koronarne bolesti srca nego koncentracije kolesterola, HDL-kolesterola i LDL-kolesterola (24). Jedan od važnijih rezultata ovog istraživanja je statistički značajna razlika u navedenim pokazateljima u ispitanika s atipičnim, melankoličnim i distimičnim značajkama depresivnog poremećaja, što upućuje na mogućnost postojanja različitog stupnja rizika za razvoj ateroskleroze i posljedične koronarne bolesti srca u pacijenata s različitim kliničkim podtipovima depresivnog poremećaja.

Povišena kao i snižena koncentracija kolesterola može biti povezana sa serotonergičkom disfunkcijom. Primarno sniženje koncentracije kolesterola može različitim mehanizmima, kao što su promjene u koncentraciji 5-hidroksi-triptamina (5-HT), koncentraciji 5-HT- receptora ili aktivnosti 5-HT-transportera, izravno voditi do smanjenja moždane aktivnosti 5-HT. Osim toga, niska koncentracija kolesterola u depresivnih i samoubilačkih bolesnika može biti posljedica poremećene esterifikacije slobodnog kolesterola. Povišenje razine kolesterola može uzrokovati smanjenje senzitivnosti 5-HT-receptora ili smanjenje aktivnosti 5-HT-transportera u depresivnih pacijenata izravno se vezujući na membranske receptore ili molekule transportera ili, neizravno, mijenjajući fluidnost neuronske membrane. Prema dosadašnjim spoznajama koncentracija kolesterola mogla bi imati značajan utjecaj na izgled kliničke slike depresivnog poremećaja kao i na odgovor na psihofarmakološko liječenje. Čini se da su pacijenti s niskom koncentracijom kolesterola (< 4,0 mmol/L) pod povećanim rizikom od samoubojstva, dok pacijenti s povišenom koncentracijom kolesterola (> 5,6 mmol/L) češće pokazuju rezistenciju na liječenje i češće imaju anksiozne poremećaje u komorbiditetu (25).

Zaključno, rezultati našeg istraživanja ukazuju da bi se serumske koncentracije kolesterola i LDL-kolesterola te omjeri kolesterola/HDL-kolesterola i LDL-kolesterola/HDL-kolesterola mogli koristiti kao biološki biljezi u razlikovanju kliničkih podtipova depresivnog poremećaja. Nedostatci ovog istraživanja su mali uzorak i nedostatak kontrolne skupine zdravih ispitanika. Također nismo uzeli u obzir razlike u prehrambenim navikama naših ispitanika, konzumiranju alkohola i pušenju. U sljedećim istraživanjima biti će potrebno uključiti veće uzorke ispitanika uz zdravu kontrolnu skupinu. Također je u budućim istraživanjima potrebno istražiti prediktivne vrijednosti omjera kolesterol, LDL-cholesterol, cholesterol/HDL-cholesterol ratio, and LDL-cholesterol/HDL-cholesterol ratio as possible biological markers for differentiation between certain clinical subtypes of depressive disorder.

Results of some studies demonstrated cholesterol/HDL-cholesterol ratio and LDL-cholesterol/HDL-cholesterol ratio (indication of atherosclerosis) to be of a significantly higher predictive value for the onset of coronary heart disease than cholesterol, HDL-cholesterol, and LDL-cholesterol concentrations (23). One of the relevant results of this study is the statistically significant difference in the above indices in patients with atypical, melancholic and dysthymic characteristics of depressive disorder, which indicates the possible existence of various degrees of risk for atherosclerosis progression and consequent coronary heart disease in patients with different clinical subtypes of depressive disorder.

Both elevated and decreased cholesterol levels may be related to serotonergic dysfunction. Primary decline in cholesterol level may lead directly to reduction in cerebral 5-HT activity by various mechanisms like changes in concentrations of 5-hydroxy triptamine (5-HT), of 5-HT receptor, and in 5-HT transporter activity. Moreover, low cholesterol level in depressive and suicidal individuals may be a consequence of disturbed free cholesterol esterification. A rise in cholesterol level may cause a decrease in 5-HT receptor sensitivity or in 5-HT transporter activity in depressive patients by direct binding to membrane receptors or transporter molecules, or indirectly by altering fluidity of the neuronal membrane. Based on past information, the cholesterol level could exert a considerable effect on the appearance of the clinical picture of depressive disorder, and on the response to psychofarmacological treatment. It seems that patients with low cholesterol level (< 4.0 mmol/L) are at an increased risk of suicide, while patients with elevated cholesterol level (> 5.6 mmol/L) more often exhibit resistance to treatment and more frequently have comorbid anxiety disorders (24).

In conclusion, the results of our study suggest that serum cholesterol- and LDL-cholesterol concentrations and cholesterol/HDL-cholesterol- and LDL-cholesterol/HDL-cholesterol ratios could serve as biological markers to distinguish between clinical subtypes of depressive disorder, implicating diagnostics, specifical psychofarmacological approach, and improved prevention of suicide. Drawbacks of this study are a small patient sample and the lack of a control group of healthy subjects. Also, we did not consider differences in dietary and smoking habits and alcohol consumption of our patients. It will be necessary to include larger subject samples in the healthy control group in further studies. Future studies will also require investigation of predictive values of cholesterol/HDL-cholesterol- and LDL-cholesterol/HDL-cholesterol ratios for the development of coronary heart disease in depressive patients according to different clinical subtypes.

rola/HDL-kolesterola i LDL-kolesterola/HDL-kolesterola za rizik razvoja koronarne bolesti srca u depresivnih pacijenta po različitim kliničkim podtipovima.

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