

Koncentracija serumskog kolesterola u psihijatrijskih bolesnika

Serum cholesterol concentration in psychiatric patients

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Sažetak

Uvod: Ranije studije pokazale su povezanost niske koncentracije ukupnog kolesterola u krvi i suicidalnog ponašanja. Cilj je istraživanja bio ustanoviti postoje li razlike u koncentraciji serumskog kolesterola među bolesnicima s različitim psihijatrijskim poremećajima.

Materijali i metode: Uzorak se sastojao od 677 psihijatrijskih bolesnika raspoređenih u skupine po dijagnozama prema MKB-10 (F10, F20, F23, F25, F32, F43, F60, X61, X70). Koncentracija ukupnog kolesterola određena je standardnom metodom natašte drugoga dana od primitka na liječenje u Psihijatrijsku bolnicu "Sveti Ivan" u razdoblju od 1. siječnja 2005. do 1. travnja 2005. godine.

Rezultati: Nađena je statistički značajno niža koncentracija kolesterola kod bolesnika s nenasilnim pokušajem suicida u odnosu na bolesnike koji nisu pokušali suicid, a boluju od shizofrenije ($P = 0,039$), shizoafektivnog poremećaja ($P = 0,019$), depresivnog poremećaja ($P = 0,002$), reakcije na stres (akutne i posttraumatske) ($P = 0,019$) i poremećaja ličnosti ($P = 0,011$). Nije utvrđena statistički značajna razlika koncentracije kolesterola između bolesnika sa sindromom ovisnosti ($P = 0,100$) i psihotičnog poremećaja ($P = 0,179$) u odnosu na koncentraciju kolesterola kod bolesnika s nenasilnim pokušajem suicida.

Zaključak: Koncentracije serumskog kolesterola razlikuju se među psihijatrijskim bolesnicima s različitim dijagnozama, a značajno su niže kod bolesnika s nenasilnim pokušajem suicida od bolesnika sa shizofrenijom, shizoafektivnim poremećajem, depresijom, reakcijom na stres te poremećajem ličnosti. Rezultati istraživanja potvrdili su hipotezu o povezanosti niske koncentracije ukupnog kolesterola i suicidalnog ponašanja kod psihijatrijskih bolesnika.

Ključne riječi: kolesterol u krvi, suicid, čimbenici rizika

Abstract

Introduction: Previous studies have demonstrated an association between low total serum cholesterol and suicidal behavior. The aim of the present study was to determine the possible variation in serum cholesterol concentration among patients with different psychiatric disorders.

Material and methods: The study sample consisted of 677 psychiatric patients grouped according to ICD-10 diagnoses (F10, F20, F23, F25, F32, F43, F60, X61 and X70). Fasting total cholesterol concentration was determined by a standard method on the second day of admission to Sveti Ivan Psychiatric Hospital for treatment. The study was conducted from January 1, 2005 till April 1, 2005.

Results: Serum cholesterol concentration was statistically significantly lower in nonviolent suicide attempters than in those without suicidal attempts but suffering from schizophrenia ($P = 0.039$), schizoaffective disorder ($P = 0.019$), depressive disorder ($P = 0.002$), stress reaction (acute and posttraumatic) ($P = 0.019$) and personality disorder ($P = 0.011$). There was no statistically significant difference in cholesterol concentration between patients with dependence syndrome ($P = 0.100$) or psychotic disorder ($P = 0.179$) and nonviolent suicide attempters.

Conclusion: Serum cholesterol concentration varies among psychiatric patients with different diagnoses, and is significantly lower in patients with nonviolent suicidal attempts as compared with patients suffering from schizophrenia, schizoaffective disorder, depression, stress reaction and personality disorder. Study results confirmed the hypothesis on the association of low total cholesterol and suicidal behavior in psychiatric patients.

Key words: serum cholesterol, suicide risk factors

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Uvod

U suvremenoj medicini dugo postoji znatno zanimanje za istraživanje povezanosti koncentracije kolesterola u serumu i suicida, koji predstavlja velik problem u liječenju

Introduction

In modern medicine, interest has long been focused on the association between serum cholesterol concentration and suicide, the latter posing a major problem in the ma-

psihijatrijskih bolesnika. Uočena je povećana učestalost smrti suicidom kod osoba koje su sudjelovale u kliničkim ispitivanjima lijekova za snižavanje koncentracije kolesterola u krvi (1). Tako je serumski kolesterol slučajno postao predmetom ispitivanja kao mogući biološki čimbenik rizika kod osoba koje su umrle neprirodnom smrću. Mnoge kasnije studije su doista pokazale da nizak serumski kolesterol predstavlja čimbenik rizika za suicid (2-4). Druge pak studije nisu uspjele potvrditi tu tezu (5,6). Istraživao se i neurobiološki aspekt suicida. Kolesterol je prisutan u središnjem živčanom sustavu (oko 20%), a važan je i u smislu stanične strukture i njene funkcije. Način na koji niska koncentracija kolesterola može biti povezana s funkcijom mozga još nije razjašnjena. Postoje brojne hipoteze, a jedna od najcitiranijih je Engelberg-ova (1992.) koja kaže da se niska koncentracija kolesterola u serumu odražava smanjenjem koncentracije kolesterola u mozgu te time snižava sadržaj kolesterola u moždanim stanicama (glija stanice, neuroni, astrociti). Pretpostavlja se da nizak kolesterol može smanjiti aktivnost serotoninskih receptora i serotoninskog transportera zbog smanjene lipidne mikroviskoznosti neuronske membrane, jer povećava fluidnost membrane neuronskih stanica (7). Međutim, nisu sve studije pokazale takve promjene povezane s niskom koncentracijom kolesterola. Nasuprot tome, pokazana je povećana aktivnost serotoninskog transportera, te s tim povezano povećano preuzimanje serotonina (8). Proučavani su i drugi mogući mehanizmi kao što je modulacija funkcije serotoninskog receptora te sudjelovanje kolesterola u formiranju sinapse (9-11). Prema tome, može se zaključiti kako kolesterol ima razne uloge u sinaptičkom prijenosu u različitim smjerovima, tj. preko modulacije neurotransmeterskog sustava promjenom membranske fluidnosti, izravnom molekularnom interakcijom ili reguliranjem sinaptogeneze.

Obzirom na veliko zanimanje za utvrđivanje veze između serumskog kolesterola i suicidalnog ponašanja prisutno u literaturi, te na kontraverzne dokaze, cilj ovoga rada bio je ispitati postoji li razlika u koncentraciji kolesterola u krvi među bolesnicima s različitim psihijatrijskim dijagnozama.

Materijali i metode

Ispitanici

Uključeni su svi bolesnici primljeni na liječenje u Psihijatrijsku bolnicu „Sveti Ivan“ u razdoblju od 1. siječnja 2005. do 1. travnja 2005. godine. Bolesnici s psihijatrijskim dijagnozama niske učestalosti nisu bili uključeni u istraživanje. Od ostalih ukupno 677 bolesnika krv je uzeta tijekom rutinske obrade natašte drugog dana od prijma. Bolesnici su podijeljeni po dijagnozama prema Međunarodnoj klasifikaciji bolesti i srodnih zdravstvenih problema MKB-10 (12)

management of psychiatric patients. An increased incidence of suicidal deaths was recorded in subjects included in clinical trials of cholesterol lowering drugs (1). Serum cholesterol has thus incidentally become a topic of research as a biological risk factor in individuals dying a violent death. Indeed, many subsequent studies found low serum cholesterol to be a risk factor for suicide (2-4), while others failed to confirm the hypothesis (5,6). The neurobiological aspect of suicide has also been extensively investigated. Cholesterol is found in the central nervous system (about 20%) and is also involved in cell structure and its function. The mechanism by which low cholesterol concentration might be associated with cerebral function has not yet been clarified. There are numerous hypotheses, one of the most frequently cited ones being that proposed by Engelberg (1992), that low serum cholesterol concentration leads to a decreased cerebral concentration of cholesterol, thus reducing the cholesterol content in brain cells (glial cells, neurons, astrocytes). Low cholesterol has been postulated to reduce the activity of serotonin receptors and serotonin transporter due to a decreased lipid microviscosity of neuronal membrane because it increases the neuronal cell membrane fluidity (7). However, not all studies demonstrated such changes associated with low cholesterol concentration. The more so, an enhanced activity of serotonin transporter and a consequentially increased serotonin uptake have been reported (8). Other possible mechanisms have also been studied, e.g., modulation of the serotonin receptor function and cholesterol involvement in the synapse formation (9-11). Accordingly, it is concluded that cholesterol has different roles in different directions of synaptic transmission, i.e. *via* neurotransmitter system modulation by change in membrane fluidity, or direct molecular interaction or regulation of synaptogenesis.

The considerable interest in the postulated association between serum cholesterol and suicidal attempts, and the controversial evidence found in the literature stimulated the present study aimed at assessing the possible variation in serum cholesterol concentration among patients with different psychiatric diagnoses.

Materials and methods

Patients

All patients admitted to Sveti Ivan Psychiatric Hospital from January 1, 2005 till April 1, 2005, were included in the study. Patients with psychiatric diagnoses of low prevalence were not included. In a total of 677 patients, fasting blood samples were collected during routine work-up on the second day of admission. Patients were divided into nine groups according to the International Classification of Diseases and Related Health Problems, Tenth Revi-

u 9 skupina: F10 sindrom ovisnosti (alkoholizam, droge, lijekovi), F20 shizofrenija, F23 psihotični poremećaj, F25 shizoafektivni poremećaj, F32 depresivni poremećaj, F43 reakcija na stres (akutna, posttraumatska), F60 poremećaj ličnosti (paranoidni, disocijativni, emotivni), X61 nenasilni pokušaj suicida (otrovanje lijekovima) i X70 nasilni pokušaj suicida (vješanjem, davljenjem, oštrim predmetom). Skupina bolesnika sastojala se od 262 žene i 415 muškaraca u dobi od 17 do 89 godina. Krv za analizu uzimana je nakon psihijatrijskog pregleda prema standardiziranom postupku i u skladu s etičkim načelima (uz odobrenje bolničkog Etičkog povjerenstva).

Metode

Koncentracija ukupnog kolesterola u serumu određena je standardnom metodom CHOD-PAP na biokemijskom analizatoru Cobas Integra 400 tvrtke Roche Diagnostics s reagensima istoga proizvođača.

Statistička analiza

Prikupljanje podataka za statističku analizu učinjeno je u programu Excel 2000 programskog paketa Microsoft Office (Microsoft, SAD). Za sve analizirane varijable napravljena je deskriptivna statistika. Homogenost varijance ispitana je Bartlettovim testom. Normalost distribucije kolesterola po skupinama testirana je Kolmogorov-Smirnovljevim testom. Budući je test homogenosti varijance zadovoljen za testiranje razlika između koncentracije kolesterola po skupinama rabili smo test ANalize VARijance (ANOVA). Da bismo utvrdili koje skupine točno čine tu razliku rabili smo višestruki LSD *post hoc* test. Za sve analize je razina statističke značajnosti utvđena na 5%. Analize i grafički prikaz napravljeni su u statističkom paketu STATISTICA 7.1.

Rezultati

Rezultati ispitivanja koncentracije kolesterola u serumu bolesnika s različitim psihijatrijskim poremećajima, doista su pokazali razlike među pojedinim skupinama. Općenito, ispitanici koji su pokušali suicid imali su nižu koncentraciju kolesterola u odnosu na druge bolesnike, a među njima, oni s dijagnozom nenasilnog pokušaja suicida (X61) imali su najniže vrijednosti. Razlike u koncentraciji kolesterola među skupinama s određenim dijagnozama testirali smo ANOVA testom, budući da je test homogenosti varijance pokazao da nema statistički značajnih razlika varijance ($P = 0,19$). Analiza varijance pokazala je kako postoji statistički značajna razlika između skupina bolesnika s različitim dijagnozama ($P = 0,012$). Višestrukim *post hoc* testom (LSD) utvrđeno je da se skupina ispitanika s dijagnozom X61 statistički značajno razlikuje od skupina ispitanika s dijagnozama shizofrenije (F20) ($P = 0,039$), shizoafektivnog poremećaja (F25) ($P = 0,019$), depresivnog

sion (ICD-10) (12): F10 dependence syndrome (alcoholism, illicit drugs, drugs); F20 schizophrenia; F23 psychotic disorder; F25 schizoaffective disorder; F32 depressive disorder; F43 stress reaction (acute, posttraumatic); F60 personality disorder (paranoid, dissociative, emotional); X61 nonviolent suicidal attempt (drug poisoning); and X70 violent suicidal attempt (hanging, suffocation, sharp object). There were 262 female and 415 male patients aged 17-89. Blood samples were collected after psychiatric examination, according to standardized procedure and in line with ethical principles (with approval issued by the Hospital Ethics Committee).

Methods

Total serum cholesterol concentration was determined by the standard CHOD-PAP method on a Roche Diagnostics Cobas Integra 400 biochemistry analyzer and reagents from the same manufacturer.

Statistical analysis

Collection of data for statistical analysis was performed by use of the Microsoft Office Excel 2000 software (Microsoft, USA). Descriptive statistics was performed for all the variables analyzed. Variance homogeneity was tested by Bartlett test and cholesterol distribution normality according to groups by Kolmogorov-Smirnov test. As the test of variance homogeneity proved satisfactory, between-group differences in cholesterol concentration were tested by the ANalysis Of VARiance (ANOVA) test, while multiple LSD *post hoc* test was employed to identify the groups yielding this difference. In all analyses, the level of significance was set at 5%. All analyses and graphic presentation were done by use of STATISTICA 7.1 statistical package.

Results

Study results showed the concentration of serum cholesterol to vary among the groups of patients with different psychiatric disorders. Generally, patients with a history of attempted suicide had a lower level of serum cholesterol than other patient groups, with the lowest level measured in patients with the diagnosis of nonviolent suicidal attempt (X61). Differences in serum cholesterol concentration among patient groups with particular diagnoses were estimated by ANOVA because the test of variance homogeneity showed no statistically significant variance differences ($P = 0.19$). Analysis of variance yielded a statistically significant difference among the groups of patients with different diagnoses ($P = 0.012$). Multiple *post hoc* test (LSD) revealed the group of patients diagnosed with X61 to differ statistically significantly from the groups of patients diagnosed with schizophrenia (F20) ($P = 0.039$), schizoaffective disorder (F25) ($P = 0.019$), depressive disorder

TABLICA 1. Koncentracija ukupnog kolesterola u serumu bolesnika svrstanih u 9 skupina s dijagnozama prema MKB-10 (ANOVA, $P=0,012$)**TABLE 1.** Total serum cholesterol concentration in nine patient groups according to ICD-10 classification (ANOVA, $P=0.012$)

Group	ICD-10 Diagnosis	n	Age (yrs; median, range)	Sex, female (%)	Cholesterol (mmol/L; $\bar{x} \pm SD$)	P (group vs. other 8 groups)
1	F10 Dependence syndrome (alcoholism, illicit drugs, drugs)	150	58 (25-89)	14	5.12 \pm 1.34	0.100
2	F20 Schizophrenia	136	46 (26-84)	43	5.27 \pm 1.30	0.039
3	F23 Psychotic disorders	47	42 (21-57)	40	5.07 \pm 1.48	0.179
4	F25 Schizoaffective disorder	64	47 (23-76)	76	5.42 \pm 1.31	0.019
5	F32 Depressive disorder	117	48 (20-74)	68	5.63 \pm 1.33	0.002
6	F43 Stress reaction (acute, posttraumatic)	65	44 (30-57)	12	5.42 \pm 1.30	0.019
7	F60 Personality disorders (paranoid, dissociative, emotional)	67	41 (20-73)	19	5.48 \pm 1.39	0.011
8	X61 Nonviolent suicidal attempt (drug poisoning)	17	37 (17-61)	53	4.56 \pm 1.47	
9	X70 Violent suicidal attempt (hanging, suffocation, sharp object)	14	48 (21-84)	29	4.91 \pm 0.63	0.485

poremećaja (F32) ($P = 0,002$), reakcijom na stres (F43) ($P = 0,019$) i poremećajem ličnosti (F60) ($P = 0,011$), čije su koncentracije kolesterola bile više (tablica 1.).

Rasprava

Ovim smo istraživanjem pokazali kako postoji statistički značajna razlika između bolesnika koji su pokušali nenasilni suicid i koji su imali niže koncentracije kolesterola ($4,56 \pm 1,47$ mmol/L) u krvi, u odnosu na ostale psihijatrijske bolesnike s dijagnozama F20, F25, F32, F43, F60. Pritom se skupina bolesnika koja je pokušala nasilni suicid, iako oni imaju općenito nešto niže koncentracije kolesterola u krvi, nije statistički značajno razlikovala od skupine bolesnika koji su pokušali nenasilni suicid ($P = 0,485$). Takvi rezultati ne slažu se s rezultatima drugih istraživanja gdje su upravo agresivni, impulzivni te bolesnici koji su pokušali nasilni suicid imali značajno nižu koncentraciju kolesterola u krvi od onih koji su pokušali nenasilni suicid (4,13,14). Mogući razlog nepostojanju razlike u koncentraciji kolesterola između nasilnih i nenasilnih pokušaja suicida je u malom broju takvih ispitanika (17 nenasilnih, 14 nasilnih pokušaja suicida). Uz to, postoje pretpostavke koje ukazuju na to da način suicida određuje dostupnost određenih vanjskih čimbenika za počinjenje takvog tipa suicida (15). Takvo tumačenje umanjuje potencijalnu važnost biološkog čimbenika te može objasniti nepostojanjem razlike u koncentraciji kolesterola među našim bolesnicima skupina s nasilnim i nenasilnim pokušajem suicida. Zanimlji-

der (F32) ($P = 0.002$), stress reaction (F43) ($P = 0.019$) and personality disorder (F60) ($P = 0.011$), which all had higher serum cholesterol levels (Table 1).

Discussion

The present study demonstrated statistically significant differences in serum cholesterol between nonviolent suicide attempters and all other psychiatric patients diagnosed with F20, F25, F32, F43 and F60. Serum cholesterol concentration was lower in the former (4.56 ± 1.47 mmol/L). The group of violent suicide attempters also had lower serum cholesterol, however, the difference from the group of nonviolent suicide attempters did not reach statistical significance ($P = 0.485$). These results are in contrast to those reported from other studies where violent suicide attempters were found to have a statistically significantly lower serum cholesterol in comparison to nonviolent suicide attempters (4,13,14). The absence of significant difference in serum cholesterol between the violent and nonviolent suicide attempters in our study may have been due to the small number of these patients (17 nonviolent and 14 violent suicide attempts). In addition, the mode of attempting suicide has been presumed to be determined by the availability of some external factors for the particular type of suicide (15). This concept would decrease the potential role of biological factor and may explain the lack of difference in cholesterol level between our patient groups of violent and nonviolent suicide attempters. Inte-

vi su i rezultati za skupinu s depresivnim poremećajem, gdje su vrijednosti kolesterola ($5,63 \pm 1,33$ mmol/L) najviše od svih ispitivanih skupina, što se ne slaže s istraživanjima drugih autora koji nalaze jaku povezanost depresije i niže koncentracije kolesterola u krvi (16-18) i time sklonost takvih bolesnika suicidu.

Moguća ograničenja ovoga istraživanja vjerojatno su u tome što nije ispitana moguća psihijatrijska povijest ispitanika koji su pokušali suicid, te stoga nismo imali podatke o njihovim drugim psihijatrijskim dijagnozama. Tako bismo doista mogli utvrditi koji su bolesnici skloniji suicidu i koje su to koncentracije serumskog kolesterola koje bi mogle poslužiti kao biokemijski pokazatelji sklonosti suicidu. Svjesni smo ograničenja ovoga istraživanja zbog nedostatka podataka o indeksu tjelesne mase (BMI, engl. *body mass index*), čijim se povećanjem smanjuje rizik od suicida (19). Može se pretpostaviti povećana sklonost suicidnom ponašanju kod bolesnika sa sindromom ovisnosti (alkoholizam, droge, lijekovi) (F10) i psihotičnog poremećaja (F23), budući da nije dobivena statistički značajna razlika u koncentraciji kolesterola u odnosu na bolesnike s nenasilnim pokušajem suicida (koncentracije kolesterola kod tih skupina bolesnika bile su podjednake). Kako je ovisnost o alkoholu rizik za suicid (20), koncentracija serumskog kolesterola već se istraživala kod ovisnika o alkoholu, no nije nađena jasna veza između suicida i koncentracije kolesterola u krvi (21). Naši se rezultati slažu i s utvrđenom sniženom koncentracijom kolesterola kod ovisnika o kokainu, koje su u literaturi pokazane kao prediktivne za relaps kokainske ovisnosti (22).

Kako je nađena statistički značajna razlika u koncentraciji kolesterola između bolesnika koji su pripadali skupini s dijagnozom nenasilnog pokušaja suicida i skupina bolesnika s dijagnozama F20, F25, F43, F60 a koje su bile statistički značajno više, može se pretpostaviti da bi sniženje koncentracije kolesterola u krvi kod takvih bolesnika moglo upućivati na rizik od suicidnog ponašanja.

Buduća bi se istraživanja trebala baviti praćenjem koncentracije kolesterola kod svih psihijatrijskih bolesnika kroz duže razdoblje. To bi bilo na tragu drugih istraživanja koja su kroz dugo razdoblje praćenja zdravih ispitanika u studiji čimbenika rizika za koronarne bolesti utvrdila da su niske koncentracije kolesterola kao i koncentracije koje su kroz godine padale povezane s povećanim rizikom za smrt od suicida (23). Koncentracije kolesterola mogle bi tako poslužiti kao čimbenik predispozicije za suicidno ponašanje, te tako doprinijeti prevenciji suicida kod psihijatrijskih bolesnika.

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resting results were observed in the group of patients with depressive disorder, where the highest serum cholesterol level was measured (5.63 ± 1.33 mmol/L). This finding was inconsistent with other literature reports on a strong correlation between depression and low serum cholesterol (16-18), implying suicidal behavior in these patients.

The present study probably suffered from some limitations because we did not explore the potential psychiatric history of suicide attempters, which may have revealed coexistence of some other psychiatric disorders. In this way, the information on suicidal behavior and on the cholesterol level indicative of such behavior would be by far more exact. We are also aware of the study limitation due to the lack of data on body mass index (BMI), as the increase in BMI has been demonstrated to reduce the risk of suicide (19). An increased suicidal behavior could be assumed in patients with dependence syndrome (alcoholism, illicit drugs, drugs) (F10) and psychotic disorder (F23), since there was no statistically significant difference in serum cholesterol in comparison with nonviolent suicide attempters (in these groups, serum cholesterol concentrations were quite comparable). As alcohol dependence poses a risk of suicide (20), serum cholesterol concentration has already been investigated in subjects suffering from this psychiatric disorder; however, no overt association was found between serum cholesterol and suicide attempts (21). Our results are consistent with the lower cholesterol level recorded in cocaine abusers, demonstrated to be predictive of cocaine dependence relapse (22).

The statistically significant difference in serum cholesterol levels between the group of nonviolent suicide attempters and groups of patients diagnosed with F20, F25, F43 and F60, which showed statistically significantly higher serum cholesterol, appears to suggest that lowering serum cholesterol may imply the risk of suicidal behavior in these patients.

Additional studies should include serum cholesterol monitoring over a longer period in all groups of psychiatric patients, on the model of long-term follow up studies of risk factors for coronary disease conducted in healthy subjects, which found a low cholesterol concentration and cholesterol concentration declining over years to be associated with an increased risk of death from suicide (23). Accordingly, cholesterol concentration could be used as a factor of predisposition for suicidal behavior, thus contributing to the prevention of suicide in psychiatric patients.

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