SERUM LIPIDS IN PATIENTS WITH POST-TRAUMATIC STRESS DISORDER, PANIC DISORDER, OR GENERALIZED ANXIETY DISORDER

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SUMMARY – The aim of the study was to assess the possible differences in serum cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides among patients with post-traumatic stress disorder, panic disorder or generalized anxiety disorder. The post-traumatic stress disorder, panic disorder or generalized anxiety disorder were diagnosed according to structured clinical interview based on DSM-IV criteria. Serum lipid concentrations were determined by use of enzyme assay. Patients with post-traumatic stress disorder and those with panic disorder had significantly higher concentrations of cholesterol ($F=5.091$, $p<0.009$), triglycerides ($F=4.175$, $p<0.02$) and LDL-C ($F=4.973$, $p<0.001$) than patients with generalized anxiety disorder. In contrast, patients with generalized anxiety disorder showed significantly higher concentrations of HDL-C ($F=4.244$, $p<0.019$) than those with post-traumatic stress disorder or panic disorder. In conclusion, there were no differences in serum lipid concentrations between patients with post-traumatic stress disorder and panic disorder, but they had higher serum lipid concentrations than patients with generalized anxiety disorder.

Key words: *Anxiety disorders – blood; Stress disorders, post traumatic – metabolism; Lipids – blood; Risk factors*

Introduction

Serum lipid concentrations have been studied in different psychiatric disorders. Low concentrations of cholesterol and lipoproteins were found in patients with schizophrenia[1,2], antisocial personality[3], borderline personality disorder, suicidal[4,5] or aggressive[6,7] behavior as well as in a population with criminal history[8]. Studies conducted in patients with major depressive disorder (MDD) produced contradictory results as some of them showed low cholesterol concentrations[9,10], whereas others found no changes in lipid concentrations[11,12]. High cholesterol concentrations were recorded in patients with manic or mixed manic episodes[13]. Studies in patients with anxiety disorders such as panic disorder (PD)[14,15], generalized anxiety disorder (GAD)[16,17], obsessive-compulsive disorder[18] and post-traumatic stress disorder (PTSD)[19,20] report on increased concentrations of serum lipids in these patients.

The aim of the present study was to assess the possible differences in serum cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) among patients with PTSD, PD and GAD.

Patients and Methods

Patients

The study included groups of patients with various psychiatric disorders: (1) 23 male veterans with chronic combat-related PTSD, aged 27-48 years (mean±SD, 43.9±9.7). The length of their combat activity ranged from 1 to 4 years (mean±SD, 2.5±0.9), and number of their war traumas from 2 to 5 (mean±SD, 2.6±0.7). The time elapsed from trauma infliction ranged from 6 to 10 years

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(mean±SD, 6.7±1.1); (2) 21 male patients with PD, aged 25-45 years (mean±SD, 39.3±6.0). The duration of PD symptoms was 1-4 years (mean±SD, 3.2±0.6); and (3) 22 male patients with GAD, aged 27-47 years (mean±SD, 40.9±9.7). The duration of GAD symptoms ranged from 1 to 4 years (mean±SD, 3.2±0.7). None of the study patients suffered from any other psychiatric or medical comorbidity. Prior to entering the study, they had been taking different medications, mostly antidepressants (fluoxetine 8.9%, fluvoxamine 5.2%, paroxetine 25.4%, sertraline 27%, clomipramine 18.7%, trazadone 1.4% and maprotiline 13.4%) and anxiolytics (alprazolam 18.7%, oxazepam 8.6%, diazepam 57.6% and clonazepam 15.1%). Three fourths of the patients used to occasionally take hypnotics during therapy (nitrazepam, funitrazepam or zolpidem). None of the mentioned drugs influences serum lipid concentrations[21]. The patients had negative history of alcohol or other drugs of dependence abuse. An informed consent was obtained from both patients and control subjects after complete and extensive description of the study design.

As lipid concentrations are sensitive to even relatively minor psychosocial influences, our experience suggested it to be important to describe these factors in some detail characterizing PTSD, PD and GAD patients. Descriptive parameters of all patient groups are presented in Table 1. Almost a half of the patients were married (PTSD 77.3%, PD 81.0% and GAD 60.9%), most of them had high-school education (PTSD 86.4%, PD 81.0% and GAD 73.9%) and lived in urban settings (PTSD 54.5%, PD 61.9% and GAD 56.5%). Patients from all three groups were inpatiently treated (i.e. hospitalization or day hospital). During hospitalization, they had an intensive schedule of 30 hours of individual and group therapy *per* week, along with other sociotherapeutic activities. Treatment program was based on therapeutic community.

Medical examination and study design

Three study groups were selected among male patients treated at University Department of Psychiatry, Sestre milosrdnice University Hospital in Zagreb between 2001 and first half of 2003: patients with combat-related PTSD (n=23), PD (n=21) and GAD (n=22). Patients with other psychiatric disorders and those with PTSD and other psychiatric or somatic comorbidity were excluded. Patients who refused to give their informed consent were not included in the study.

A structured clinical interview was conducted by a psychiatrist, who then made the diagnosis on the basis of DSM-IV criteria for PTSD, PD and GAD[22]. A clinical psychologist applied the Clinician Administered PTSD Scale (CAPS) PTSD interview based on DSM-IV criteria to measure the post-traumatic stress reaction[23]. Definitive diagnosis of PTSD was only made in cases where both sets of criteria were met. Diagnostic agreement between the psychiatric and psychological criteria was high (κ=0.96). The alpha coefficient for the CAPS questionnaire was 0.91.

The diagnosis of PD was accepted if the patient met two criteria: an indicative result on the MINI criteria for PD[24] and a sufficient number of symptoms shown on the structural clinical interview based on DSM-IV criteria for PD[22]. Diagnostic balance between the MINI and clinical interview based on DSM-IV criteria for PD was κ=0.98. MINI questionnaire was used for its simplicity and reliability; alpha coefficient was 0.93. Two psychiatrists performed this part of the evaluation independently of each other. The agreement between the two psychiatrists was high (κ=0.97).

The diagnosis of GAD was accepted if the patient fulfilled two criteria: an indicative result on the MINI criteria for GAD[24] and a sufficient number of symptoms shown in the structural clinical interview based on DSM-IV criteria for GAD[22]. Diagnostic balance between the MINI and clinical interview based on DSM-IV criteria for GAD was κ=0.98. MINI questionnaire was used because of its simplicity and reliability; in our study, alpha coefficient was 0.93. Two psychiatrists performed this part of the evaluation independently of each other. The agreement between the two psychiatrists was high (κ=0.97).

The PTSD, PD and GAD patient groups were also compared according to DSM-IV criteria for nicotine dependence[22], because smoking has a strong effect on serum lipid elevation[25].

In addition, body mass index (BMI) was calculated in patient groups, as it correlates well with serum lipid levels[25]. BMI is a ratio of body weight in kilograms divided by square of height in meters (BMI=kg/m^2). Since diet and physical activity can influence examination results, laboratory tests and psychiatric examination were performed between days 14 and 16 of hospital stay. Blood lipid measurements done at this time may be preferable to the values obtained on admission to ensure that all patients had equivalent diet and physical activity levels.

Biochemical testing

Blood samples were collected from forearm vein into glass red-topped vacuum tubes without anticoagulant, in the morning between 8.00 and 9.00 a.m. after overnight

(12 h) fast and 30-min rest prior to sampling. Serum concentrations of cholesterol, HDL and triglycerides were determined immediately upon sampling by enzyme assay using commercial kits (Olympus Diagnostic, GmbH, Hamburg, Germany) on an Olympus AU 600 autoanalyzer. The interassay coefficient of variation in our laboratory was 3.2% for cholesterol, 2.5% for triglycerides, and 3.0% for HDL-C. Serum LDL-C concentrations were calculated by use of the following formula: [LDL-C=cholesterol – (HDL-C – triglycerides/5)][26]. The laboratory reference ranges for these lipids are as follows: cholesterol 3.8-5.7 mmol/L; LDL <4.5 mmol/L; HDL <1.0 mmol/L; and triglycerides 0.6-1.8 mmol/L.

Statistical analysis

The χ^2-test was used to analyze differences in nicotine dependence or sociodemographic and medical variables among the three study groups. Normal distribution was assessed for all measures and for each group by Kolmogorov-Smirnov test. Analysis of variance (ANOVA) and Scheffe's post-hoc analysis for pair-wise comparisons were used to compare patients with PTSD, PD and GAD according to age, BMI, duration of diagnosis (symptoms), and serum levels of cholesterol, triglycerides, LDL-C and HDL-C. Statistical significance was set at $p<0.01$. Statistical analysis was done by use of SPSS software (SPSS for Windows 8.0, SPSS, Chicago, IL, USA).

Results

There were no statistically significant differences among the groups of PTSD, PD and GAD patients either according to marital status, level of education, place of residence, number of previous hospitalizations, and family history of lipid elevation or mental disorders (Table 1), or according to age (Table 2). However, duration of symptoms was longer in PTSD than in PD or GAD patients (Table 2).

DSM-IV criteria for nicotine dependence were met by 95.5% of PTSD, 90.5% of PD and 87.0% of GAD patients ($\chi^2=0.990$, $p=0.610$). There was no significant difference in BMI among PTSD, PD and GAD patients (Table 2).

Patients with combat-related PTSD and those with PD had significantly higher serum concentrations of cho-

Table 1. Sociodemographic and medical characteristics of study patients with post-traumatic stress disorder (PTSD; n=23), panic disorder (PD; n=21) and generalized anxiety disorder (GAD; n=22)

Characteristic	PTSD	PD	GAD	χ^2 (*p* value)
Marital status, n (%)				
Married	17(77.3)	17 (81.0)	14 (60.9)	2.576 (0.276)
Single/divorced/widower	5 (22.7)	4 (19.0)	9 (39.1)	
Level of education, n (%)				
Elementary	1 (4.5)	3 (14.3)	3 (13.0)	2.206 (0.698)
High school	19 (86.4)	17 (81.0)	17 (73.9)	
University	2 (9.1)	1 (4.8)	3 (13.0)	
Place of residence, n (%)				
Urban	12 (54.5)	13 (61.9)	13 (56.5)	0.254 (0.881)
Rural	10 (45.5)	8 (38.1)	10 (43.5)	
Previous hospitalizations, n (%)				
1-2	14 (63.6)	15 (71.4)	15 (65.2)	0.327 (0.849)
3 or more	8 (36.4)	6 (28.6)	8 (34.8)	
Positive family history of lipid elevation, n (%)				
No	17 (77.3)	18 (85.7)	19 (82.6)	0.530 (0.767)
Yes	5 (22.7)	3 (14.3)	4 (17.4)	
Positive family history of mental disorders, n (%)				
No	18 (77.3)	15 (71.4)	17 (73.9)	1.002 (0.606)
Yes	4 (18.2)	6 (28.6)	6 (26.1)	

Table 2. Serum concentrations of cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), age, body mass index (BMI) and duration of diagnosis in patients with post-traumatic stress disorder (PTSD; n=23), panic disorder (PD; n=21) and generalized anxiety disorder (GAD; n=22)

Variable	PTSD	PD	GAD	F value (*p* value)
Age (yrs)	43.1±9.7	39.3±6.0	40.9±9.7	0.995 (>0.375)
BMI	24.9±2.8	24.8±3.0	25.6±2.5	0.563 (>0.572)
Diagnosis duration (yrs)	6.7±1.1**	3.2±0.6	3.2±0.7	5.168 (<0.001)
Cholesterol (mmol/L)	6.1±0.9*	6.3±1.3*	5.4±1.3	5.091 (0.009)
Triglycerides (mmol/L)	3.3±2.0*	3.5±2.5*	1.8±1.5	4.175 (<0.02)
LDL-C (mmol/L)	5.8±0.6*	5.9±1.1*	4.9±1.3	4.973 (<0.001)
HDL-C (mmol/L)	0.9±0.3*	1.0±0.4*	1.3±0.3	4.244 (<0.019)

Values are presented as mean±SD;
* significantly different from GAD group (post-hoc Scheffe test <0.01);
** significantly different from PD and GAD groups (post-hoc Scheffe test <0.01)

lesterol, LDL-C and triglycerides than GAD patients (Table 2). HDL-C was statistically significantly lower in PTSD and PD patients than in those with GAD (Table 2).

Discussion

Study results showed higher serum concentrations of cholesterol and triglycerides in PTSD and PD patients than in those with GAD. The results also pointed to a very high risk of developing arteriosclerosis in PTSD and PD patients but not in GAD patients. The reason for this distinction was the low level of HDL-C and high level of LDL-C. These findings are in accordance with the results reported from the studies in Vietnam and Croatian veterans with chronic PTSD and in patients with PD[19,20]. Unlike previous studies, we compared all study groups according to nicotine dependence, since nicotine dependence increases lipid levels and is associated with a greater risk of arteriosclerosis. In addition, we included data on the family history of lipid metabolism disorders because a positive family history of these impairments increases the possibility of their occurrence also in other family members.

The present study suffered from a number of limitations, e.g., we did not compare study groups according to their dietary history. Also, we compared war veterans with PTSD with civilian PD and GAD patients. In future studies, it will be interesting to investigate serum lipid concentrations in civilian subjects with PTSD. The third limitation was the male sex of all our subjects, because male sex is known to be associated with higher cholesterol, triglyceride and LDL-C concentrations and lower HDL-C concentration than female.

However, previous studies in PTSD and PD patients revealed many biologic alterations such as steroid receptor hypersensitivity[27] and modification of the hypothalamic-pituitary-adrenal/thyroid axis[28,29]. On result interpretation, it is important to note the findings of a high concentration of catecholamines[30], and an increase in the sympathetic nerve system activity, which manifested itself through an intensified heartbeat and blood pressure[31,32]. Therefore, the drugs that increase the activity of the noradrenergic system can induce the PTSD or PD symptomatology[30]. On the other hand, β-adrenergic antagonists are second line drugs for the treatment of PD or PTSD symptoms. Furthermore, a large study of patients with arterial hypertension and other risk factors for arteriosclerosis showed an increased activity of noradrenergic system and a correlation between the increased levels of cholesterol and catecholamines[30,32] These authors state that norepinephrine increases the activity of lipoprotein lipase, which leads to an increase in serum free fatty acids, which in turn can be converted by the liver into cholesterol. Furthermore, a study in PD patients revealed a correlation between the increased activity of lipoprotein lipase, and elevated cholesterol and catecholamine concentrations[14].

In conclusion, the high levels of serum lipids in PTSD and PD appear to be the consequence of the increased activity of the noradrenergic system, as there is a strong correlation between norepinephrine and lipid levels. Therefore, the patients with PTSD and PD are at a risk of many somatic complications, especially cerebro/cardio-

vascular disorders, because the increase in serum lipids is directly related to a higher risk of arteriosclerosis and vascular incidents[33]. Additional studies are needed to investigate the correlation between PTSD, serum lipid levels and catecholamine concentrations. Screening tests for serum lipids should be introduced in routine workup for PTSD patients, along with preventive measures to reduce the risk of atherosclerosis and its sequels in this vulnerable population.

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Sažetak

SERUMSKI LIPIDI U BOLESNIKA S POSTTRAUMATSKIM STRESNIM POREMEĆAJEM, PANIČNIM POREMEĆAJEM ILI GENERALIZIRANIM ANKSIOZNIM POREMEĆAJEM

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Cilj rada bio je ispitati moguće razlike u serumskim koncentracijama kolesterola, kolesterola niske gustoće (LDL-C), kolesterola visoke gustoće (HDL-C) i triglicerida između bolesnika s posttraumatskim stresnim poremećajem, paničnim poremećajem i generaliziranim anksioznim poremećajem. Posttraumatski stresni poremećaj, panični poremećaj ili generalizirani anksiozni poremećaj dijagnosticirani su pomoću strukturiranog kliničkog intervjua zasnovanog na kriterijima DSM-IV. Razina serumskih lipida analizirana je enzimskom metodom. Bolesnici s posttraumatskim stresnim poremećajem i oni s paničnim poremećajem imali su značajno više koncentracije kolesterola ($F=5,091$, $p<0,009$), triglicerida ($F=4,175$, $p<0,02$) i LDL-C ($F=4,973$, $p<0,001$) nego bolesnici s generaliziranim anksioznim poremećajem. Suprotno tome, bolesnici s generaliziranim anksioznim poremećajem imali su značajno višu koncentraciju HDL-C ($F=4,244$, $p<0,019$) u usporedbi s bolesnicima s posttraumatskim stresnim poremećajem ili paničnim poremećajem. Dakle, nije bilo razlike u serumskoj koncentraciji lipida između bolesnika s posttraumatskim stresnim poremećajem i paničnim poremećajem, ali su imali više razine kolesterola, triglicerida i LDL-C nego bolesnici s generaliziranim anksioznim poremećajem.

Ključne riječi: *Anksiozni poremećaji – krv; Stresni poremećaji, posttraumatski – metabolizam; Lipidi – krv; Čimbenici rizika*