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Elevated Serum Lipids in Veterans with Combat-related Chronic Posttraumatic Stress Disorder

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Aim. To assess possible differences in serum cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, arteriosclerosis index, established risk factor (ERF) of arteriosclerosis, and 10-year risk for coronary disease according to the Adult Treatment Panel III (ATP-III) between veterans with combat-related posttraumatic stress disorder (PTSD) and a control group consisting of patients with major depressive disorder.

Method. We determined serum cholesterol, LDL-C, HDL-C, and triglycerides in the patients with PTSD (n = 103) and patients with major depressive disorder (n = 92), using the enzyme-assay method. AI, ERF, and ATP-III were calculated from cholesterol, LDL-C, and HDL-C levels. The groups were matched in age and body mass index (BMI). Patients with major depressive disorder were chosen as a control group because they do not have changes in serum lipids.

Results. Patients with combat-related PTSD had higher cholesterol (6.2±1.1 mmol/L vs 5.3±0.9 mmol/L; p<0.001), LDL-C (3.9±0.7 mmol/L vs 3.5±1.0 mmol/L; p = 0.005), and triglycerides (2.9±2.3 mmol/L vs 1.5±0.5 mmol/L; p<0.001), and lower HDL-C (1.0±0.3 mmol/L vs 1.3±0.2 mmol/L; p<0.001) than the control group. Arteriosclerosis index (4.2±1.2 vs 3.7±1.7; p = 0.050), ERF (6.4±1.9 vs 5.5±2.4; p = 0.010), and ATP-III (12.1±3.3 vs 10.2±3.8; p<0.001) were higher in PTSD than in the control group.

Conclusion. Elevated concentrations of serum lipids are associated with combat-related PTSD. This may imply that patients with combat-related PTSD are under a higher risk for arteriosclerosis.

Key words: *arteriosclerosis; cholesterol; Croatia; lipoproteins, HDL cholesterol; lipoproteins, LDL cholesterol; stress disorders, post-traumatic; triglycerides; veterans*

Changes in serum lipid concentrations have been studied in many psychiatric disorders (1). Increased concentrations of serum cholesterol and triglycerides have been found in patients with panic disorder, general anxious disorder, aggressive behavior, or antisocial behavior (2-5). Low concentrations of cholesterol have been found in patients with schizophrenia or suicidal behavior (6). In patients with major depressive disorder, no changes in the concentration of serum cholesterol or triglycerides have been detected (7-10). A study that included Vietnam War veterans with chronic combat-related posttraumatic stress disorder (PTSD) found high values of serum cholesterol and triglycerides (11).

PTSD as a diagnostic entity is characterized by four groups of symptoms (12). It is the only psychiatric diagnostic category where a person was exposed to an extreme stress and felt helpless, terrified, or frightened (group A of symptoms). Group B consists of five symptoms associated with continued re-experience of the traumatic event. Group C comprises seven symptoms of avoidance, and group D consists of five symptoms of increased arousal (12,13).

The recent research pointed out the correlation between stress situations and increased concentrations of serum lipids (14,15). The final result of that correlation is increased noradrenergic activity and the activity of hypothalamic-pituitary-adrenal axis, and this changes are often used as biological "stress markers" in persons with PTSD (16-18). Numerous epidemiological studies on Vietnam War veterans showed a high occurrence of cerebrovascular and cardiovascular diseases, especially in veterans suffering from PTSD (19). In Vietnam and Gulf War veterans who died young in extremely stressing situations, the autopsy revealed extraordinarily advanced arteriosclerosis (19,20).

Our aim was to analyze the concentration of serum cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C), and to assess the arteriosclerosis index (AI), established risk factor for arteriosclerosis (ERF), and a 10-year risk for coronary disease accord-

ing to the Adult Treatment Panel III (ATP-III, or the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults) in Croatian war veterans with chronic PTSD.

Subjects and Methods

Subjects

The group of patients with combat-related PTSD included 103 men, with a mean age of 32±4.6 years (range, 28-42 years). The control group consisted of 92 men suffering from major depressive disorder, with a mean age of 33±5.1 years (range, 29-45 years). Patients with major depressive disorder were chosen because such patients show no changes in serum lipids (7-10). The groups were well matched on demographic characteristics, age, and ethnicity.

None of the patients had other psychiatric comorbid disorders or medical problems, and all gave informed consent for the participation in the study. All patients had been taking psychotropic drugs before the study, mostly antidepressants (clomipramine, fluoxetine, maprotiline, paroxetine, trazodone, or amitriptyline) and anxiolytics (alprazolam, diazepam, clonazepam, oxazepam, or nitrazepam). None of these drugs influence serum lipid concentrations (9).

The patients included in the study were selected from the total pool of patients (N = 498) undergoing 30-day inpatient treatment program at the Department of Psychiatry, Sisters of Mercy University Hospital, in 2001. A hospital nutritionist prepared a menu for the patients and they all ate the same hospital food. Patients with other psychiatric disorders (n = 221), and comorbid psychiatric (63 in PTSD group, and 34 in major depressive disorder group) or somatic disorders (2 in PTSP group, and 3 in major depressive disorder group) were excluded from the study (Fig. 1).

Medical Examination

Diagnoses of PTSD or major depressive disorder were based on DSM-IV criteria (12). Two independent psychiatrists examined all the patients included in the study, using a structured clinical interview. The agreement rate between them was 97%. Clinical psychologist applied a Watson's PTSD interview based on DSM-III-R criteria to measure posttraumatic stress disorder (21). The evaluation of the psychometric characteristics of this instrument on a Croatian sample has confirmed its high reliability (22). The agreement rate between psychiatric and psychological criteria was 95%.

We also used DSM-IV criteria to compare the PTSD group and group with major depressive disorder for nicotine dependence (12), because smoking increases serum lipid concentrations (23). In addition, body mass index (BMI) was calculated for both groups, because it has been shown that BMI correlates with serum lipid concentrations (23). BMI equals a person's weight in kilograms divided by height in square meters (BMI = kg/m^2).

Since diet and activity level can influence the results of examinations, laboratory measurements and psychiatric examinations of the patients were carried out between days 14 and 16 of their inpatient stay, after having ensured that all of them had had equivalent diets and activity levels.

Biochemical Measurements

Blood samples from the cubital vein were collected in glass tubes without any anticoagulant, in the morning between 8-9 a.m., after an overnight fast of 12 h and 30 min rest immediately before blood collection.

Serum concentrations for cholesterol, HDL-C, and triglycerides were determined enzymatically, immediately after blood collection. The assays were done with commercial kits (Olympus Diagnostic GmbH, Hamburg, Germany) on Olympus AU 600 automatic analyzer. Serum LDL-C concentrations, AI, and ERF were calculated according to the following formulas: LDL-C = cholesterol – (HDL-C – triglycerides)/5; AI = LDL-C/HDL-C; and ERF = cholesterol/HDL-C (24). ATP-III was calculated from age, cholesterol concentration, smoking status, HDL-C, and systolic blood pressure, as described elsewhere (25).

Our laboratory's referent intervals for biochemical parameters measured are as follows: cholesterol 3.8-5.7 mmol/L, LDL-C < 3.9 mmol/L, HDL-C > 0.9 mmol/L, triglycerides 0.6-2.0 mmol/L, AI < 2.8, and ERF < 4.1 (24).

Statistical Analysis

The difference in nicotine dependence between the two groups was tested by Pearson's chi-square test. The normal distribution of all measured values for each group was assessed by Kolmogorov-Smirinov test. BMI, systolic blood pressure, lipid concentrations, AI, and ERF data were analyzed with t-test for independent samples. We used Hotelling T^2 multivariate test to analyze the differences in mean values between the two groups for multiple dependent variables (26). SPSS software, version 8.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

DSM-IV criteria for nicotine dependence were met by 76.2% of patients with combat-related PTSD and 67.6% of patients with major depressive disorder (chi-square = 0.47; df = 1; p = 0.521).

The mean BMI was 27.2±2.9 for the PTSD group, and 26.9±2.6 for patients with major depressive disorder (t = 0.67; p = 0.503). The mean systolic blood pressure in the PTSD group was 126.8±10.9 mm Hg, and 127.7±11.6 mm Hg in the group with major depressive disorder (t = 0.472; p = 0.638).

Patients with combat-related PTSD showed significantly higher cholesterol, LDL-C, and triglyceride

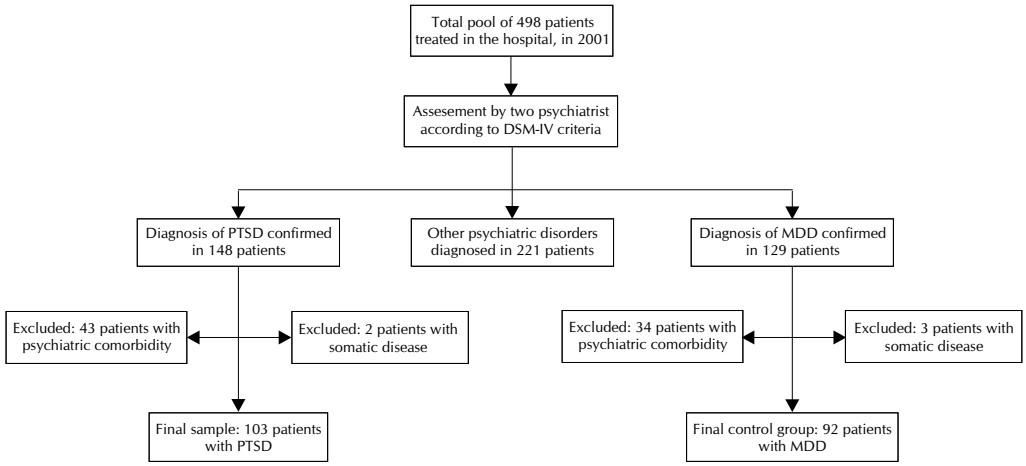

Figure 1. Profile of the study. PTSD – posttraumatic stress disorder; MDD – major depressive disorder.

Table 1. Concentrations (mean ± SD) of cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides, and arteriosclerosis index (AI), established risk factor for arteriosclerosis (ERF), and 10-year risk for coronary disease[a] in veterans with combat-related posttraumatic stress disorder (PTSD), and control group with major depressive disorder (MDD)

Parameter	PTSD (n = 103)	MDD (n = 92)	t-ratio	p[b]
Cholesterol (mmol/L)	6.2 ± 1.1	5.3 ± 0.9	5.18	< 0.001
LDL-C (mmol/L)	3.9 ± 0.7	3.5 ± 1.0	2.85	0.005
HDL-C (mmol/L)	1.0 ± 0.3	1.3 ± 0.2	5.47	< 0.001
Triglycerides (mmol/L)	2.9 ± 2.3	1.5 ± 0.5	4.99	< 0.001
AI	4.2 ± 1.2	3.7 ± 1.7	1.94	0.050
ERF	6.4 ± 1.9	5.5 ± 2.4	2.62	0.010
ATP-III	12.1 ± 3.3	10.2 ± 3.8	3.61	< 0.001

[a]According to the Adult Treatment Panel III (ATP-III, or the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults).
[b]Hotteling $T^2 = 208.35$; $F = 29.14$; $p<0.001$.

concentrations then patients with major depressive disorder (Table 1). Also, AI, ERF, and ATP-III were significantly higher in patients with combat-related PTSD than in the group with major depressive disorder (Table 1). On the other hand, HDL-C concetrations were significantly lower ($p < 0.001$) in the PTSD group.

Discussion

Our results showed higher concentrations of cholesterol and triglycerides in patients with combat-related chronic PTSD than in patients with major depressive disorder. Also, patients with combat-related PTSD seemed to be under a very high risk of developing arteriosclerosis, because of the low concentration of HDL-C, high concentration of LDL-C, and presence of high risk factors (AI, ERF, and ATP-III) (24,25,27).

These findings are in accordance with the results of Kagan et al (11), who studied blood lipid concentrations in Vietnam veterans with chronic PTSD. However, Kagan's group did not analyze the LDL-C and HDL-C cholesterol in their subjects, and did not assess the arteriosclerosis risk factors, such as AI, ERF, and ATP-III. Furthermore, we studied a very young population, with a mean age of 31 years, as opposed to their group of Vietnam veterans, whose mean age was 44 years. This is important to note because serum lipid concentrations increase with age (27). It is significant that we found very high values of lipid concentrations in much younger patients with PTSD.

Former research revealed many biological alterations in the patients with PTSD, such as hypersensitivity of steroid receptors (28) and alterations in hypothalamic-pituitary-adrenal axis (14,29). Studies that focused on high concentration of catecholamines (30) and increased sympathetic nerve system activity, which manifested itself through an intensified heartbeat and increased blood pressure (31,32), implied that ß–adrenergic antagonists could be important drugs in the pharmacotherapy of PTSD (33,34). Other research also showed that the drugs increasing the activity of noradrenergic system can induce the symptomatology of PTSD (35). On the other hand, investigating patients with arterial hypertension and other risk factors for developing arteriosclerosis, researchers found increased activity of noradrenergic system, and a correlation between the increased levels of cholesterol and catecholamines (36,37). The increase in serum lipid concentrations was found to be directly related to the higher risk of arteriosclerosis and vascular incidents (38).

Our results also confirmed the association of the stress and arteriosclerosis. Moreover, they indicated higher possibility and frequency of cerebrovascular and cardiovascular diseases in Croatian veterans with PTSD, and the necessity of taking preventive measures for stopping further disablement. Higher prevalence of hemorrhagic insult was recorded in Jerusalem during the Gulf War (39), whereas in Sarajevo (Bosnia and Herzegovina, ref. 40) and Split (Croatia, ref. 41), higher prevalence of cerebrovascular incidents during the bombardment was detected. In Croatian refugees with prolonged stress, there has been higher incidence of arterial hypertension and increased vasospasm, especially in younger age groups (42). These somatic consequences are based on a unique pathophysiologic mechanism caused by psychotrauma. The sensitivity of the locus coeruleus, the main noradrenergic nucleus located in the medulla oblongata, significantly increases after a perception of a life-threatening situation (31). Furthermore, the hypothalamic center located in the paraventricular nucleus of the diencephalon is responsible for the discharge of corticotropins (14,15). Corticotropins and noradrenalin induce a series of neuronal activities that result in stress response, including the increased heart beat and blood pressure, inhibition of vegetative parasympathetic function, increase of vasoreactivity, and finally, increase in the serum lipid concentrations (33-37).

Our study has several limitations. It included only men, who had higher lipid concentrations and arteriosclerosis index than women. Moreover, we did not analyze the concentrations of cortisol, corticotropin, and catecholamine as "stress markers" (14,15). In the further research, it would be interesting to compare cortisol, corticotropin, catecholamines, and lipid concentrations.

High levels of serum lipids in PTSD are probably the consequence of the increased activity of the noradrenergic system, because there is a strong correlation between the concentrations of noradrenalin and lipids (36,37). Therefore, the population with PTSD is at risk of numerous somatic complications, especially cerebrovascular and cardiovascular disor-

ders, which can additionally induce and/or complicate invalidity. More research is needed to investigate the correlation between the specific symptoms of PTSD, such as hyperarousal, and the level of the serum lipid concentrations, because this symptomatology is directly related to the increase of catecholamines (35).

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