

*Original Article*

## Relationship between Serum Lipid Concentrations and Posttraumatic Stress Disorder Symptoms in Soldiers with Combat Experiences

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The aim of our study was to assess concentrations of serum cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides in soldiers with combat-related posttraumatic stress disorder (PTSD), in comparison with combat-experienced soldiers without PTSD. The second aim of our study was to explore the relationship between PTSD symptoms such as re-experiencing, avoidance, increased arousal, and serum lipid levels. In 53 soldiers with combat-related PTSD and 49 with combat experiences without PTSD, serum cholesterol, LDL-C, HDL-C, and triglycerides were assayed by an enzyme-assay method. Soldiers with combat-related PTSD were found to have significantly higher concentrations of cholesterol ( $P = 0.001$ ), LDL-C ( $P = 0.002$ ), and triglycerides ( $P = 0.001$ ) than soldiers without current PTSD. HDL-C was statistically lower ( $P < 0.001$ ) in soldiers with combat-related PTSD than in those without PTSD. A positive correlation was found between increased arousal and cholesterol ( $r = 0.464$ ;  $P = 0.039$ ), or LDL-C ( $r = 0.479$ ;  $P = 0.021$ ) concentrations.

**Key words:** cholesterol, low-density lipoproteins, high-density lipoproteins, triglycerides, posttraumatic stress disorder (PTSD)

**P**osttraumatic stress disorder (PTSD) is a relatively new diagnostic category, and the psychological disturbances of Vietnam veterans have aided us in formulating the concept of PTSD [1]. In the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), 3 clusters of PTSD symptoms are listed: trauma re-experiencing, avoidance, and increased arousal [2]. In addition, PTSD is one of the few psychiatric diagnostic categories that fulfills the criterion that a person was exposed to an extreme stress [1, 2]. Furthermore, recent research has found a correlation between stress situations and increased concentrations of serum lipids [3,

4]. Numerous studies, however, have described different biological alterations in patients with PTSD such as increased noradrenergic activity [5] and disturbance of the hypothalamic-pituitary-adrenocortical axis [6–8]. Changes in serum lipids have been analyzed in different psychiatric disorders [9], with increased levels of serum cholesterol and triglycerides having been found in patients with panic disorder, general anxious disorder, aggressive behavior, and antisocial behavior [10–13]. In contrast, low concentrations of cholesterol have been found in patients with schizophrenia and suicidal behavior [14, 15] as well as in those with major depressive disorder who have slight or no changes in their serum lipid levels [16–18]. To our knowledge, there have been only 2 studies in which serum lipid concentrations have been analyzed in chronic combat-related PTSD [19, 20]. One

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of these studies found high values of serum cholesterol and triglycerides [19]. Our previous study indicated increased risk for arteriosclerosis in patients with PTSD [20]. However, those studies had certain limitations; for example, the control group consisted of patients with major depressive disorder or addiction problems, without any combat experience. As such, the main purpose of the present study was to analyze the concentrations of serum cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) in Croatian soldiers with combat-related PTSD as opposed to those of soldiers with combat experience without current PTSD symptoms. The second aim of our study was to analyze the relationship between specific clusters of PTSD symptoms: trauma re-experiencing, avoidance, increased arousal, and lipid levels.

## Materials and Methods

**Subjects.** A total of 53 male patients with combat-related PTSD were recruited from outpatients in the University department of Psychiatry, University Hospital "Sestre milosrdnice". The (mean  $\pm$  SD) age of patients was  $34 \pm 5.4$  (range: 27–45) years. The duration of combat activity was (mean  $\pm$  SD)  $3.5 \pm 0.8$  (range: 1–5) years, and (mean  $\pm$  SD)  $6.2 \pm 0.9$  (range: 4–6) years had elapsed since they had experienced combat trauma. Subjects with PTSD were selected from the total pool of outpatients treated in our department in the year 2002 ( $N = 154$ ). Patients with PTSD comorbid with other psychiatric or medical disorders ( $N = 76$ ), as well as PTSD patients who did not give informed consent ( $N = 25$ ) were excluded from further analysis.

The control group of subjects was recruited consecutively after systematic physical and psychiatric examination of soldiers ( $N = 95$ ) from the outpatient department in our hospital. Patients were at the hospital because they needed to go undergo psychiatry examinations to extend their military work license. Somatic or psychiatric disorders were found in 17 soldiers, and 29 soldiers did not give informed consent. Finally, the control group of subjects consisted of 49 soldiers with combat experience without PTSD or other psychiatric or medical problems, age (mean  $\pm$  SD)  $35 \pm 4.3$  (range: 31–46) years. The duration of their combat activity was (mean  $\pm$  SD)  $3.8 \pm 1.2$  (range: 1–5) years, and (mean  $\pm$  SD)  $5.9 \pm 0.9$  (range: 4–6) years had elapsed since they had experienced combat trauma. The study group as well as the control

group of patients had similar food-intake habits according to anamnestic data. Informed consent of the subjects was obtained after the nature of the procedures had been fully explained. All patients with PTSD have undergone psychopharmacotherapy prior to this study, mostly antidepressants (fluoxetine, paroxetine, sertraline, clomipramine, and maprotiline) and benzodiazepines (alprazolam, oxazepam, diazepam, clonazepam). None of these drugs has been found to influence serum lipid concentrations in prior investigations [18].

**Assessments.** Diagnosis of current PTSD was made according to a structured clinical interview based on DSM IV criteria [2]. Two psychiatrists performed this part of the evaluation, each of them independently examining all the subjects. The agreement between the 2 psychiatrists was high, 0.97. A clinical psychologist carried out a Watson's PTSD interview to measure posttraumatic stress reactions [21]. Watson's PTSD interview consists of four parts. The first part (Section A) relates to the experience of trauma outside the range of usual human experience. The next 17 items closely reflect the PTSD symptoms as described in DSM-III-R PTSD sections B (trauma re-experiencing), C (avoidance), and D (increased arousal). Section E of the interview evaluates the existence of current or life-long PTSD. Evaluation of the psychometric characteristics of this instrument on Croatian samples has confirmed its high reliability [22]. The agreement between psychiatric and psychological criteria was 0.95.

We also compared soldiers with and without PTSD according to DSM IV criteria for Nicotine dependence [2] because there is a strong effect of smoking on the elevation of serum lipids [23]. And finally, the body mass index (BMI) was calculated for the PTSD and the healthy control group because BMI correlates well with serum lipid levels [24]. BMI corresponds to a subject's weight in kilograms divided by the square of the height in square meters ( $BMI = kg/m^2$ ).

**Biochemical Measurements.** Blood samples were collected from the forearm vein in glass, red-topped vacuum tubes without any anticoagulant in the morning between 8:00 and 9:00 AM, after an overnight fast of 12 h and 30 min of rest immediately prior to blood collection. Serum concentrations for cholesterol, HDL, and triglycerides were measured by enzyme assay (EA) immediately after taking the samples with commercial kits (Olympus Diagnostic, GmbH, Hamburg, Germany) on an Olympus AU 600 automatic analyzer. 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 the following formula:  $[\text{LDL-C} = \text{cholesterol} - (\text{HDL-C} \times \text{triglycerides}/5)]$  [25]. Our laboratory's referent intervals for lipids are parameters measured as follow: cholesterol 147–220 mg/dl, LDL lower than 150.0 mg/dl, HDL higher than 42.0 mg/dl, and triglycerides 53–177 mg/dl.

**Statistical Analysis.** We used a Chi-square test to analyze differences in nicotine dependence between the 2 groups. The normal distribution was assessed for all measures and for each group by the Kolmogorov-Smirnov test. The BMI and lipid data were analyzed using the *t*-test for independent samples. Spearman's range of correlation was computed between the lipid data and trauma re-experiencing, avoidance, or increased arousal symptoms. A *P* value of  $< 0.01$  was considered to denote the presence of a statistically significant difference. Statistical analysis was carried out with SPSS software (SPSS for Windows 8.0, SPSS, Chicago, IL, USA).

## Results

DSM-IV criteria for nicotine dependence were met by 70% of soldiers with combat-related PTSD and 60% of those with combat experience but without PTSD (Chi-square = 1.758; *df* = 1; *P* = 0.185).

The BMI of soldiers with combat-related PTSD was (mean  $\pm$  SD)  $24.3 \pm 2.1$ , and of soldiers with combat experience without PTSD was  $24.8 \pm 1.9$ , (*t* = 0.67; *P* = 0.503).

There was a statistically significant difference between soldiers with combat-related PTSD and those with combat experience without PTSD for all 3 subscale scores on Watson's PTSD interview (Table 1).

Soldiers with combat-related PTSD showed statistically significantly higher cholesterol, LDL-C, and triglyceride concentrations in comparison with soldiers with combat experience without PTSD (Table 2). HDL-C was statistically significantly lower in soldiers with combat-related PTSD in comparison with soldiers without PTSD (Table 2).

In addition, there was a positive correlation between cholesterol, LDL-C, and symptoms of increased arousal in Watson's PTSD questionnaire (Table 3).

## Discussion

Our results showed high concentrations of cholesterol and triglycerides in patients with combat-related chronic PTSD. These findings are in accordance with the results of the 2 prior investigations of veterans with chronic PTSD [19, 20]. However, these previous studies did not include an analysis of the LDL-C and HDL-C, and the correlation between clusters of PTSD symptoms such as re-experiencing, avoidance, and increased arousal and serum lipid concentrations. Further, our results were obtained from a very young population, with 34 years of age as the middle value as opposed to investigations of Vietnam veterans, where the average age has been 44. This observation is important because serum lipid concentrations grow parallel with age [26]. Our results are therefore more significant than previous results because we found very high lipid values of in a young population of patients with PTSD. Also, our new soldiers with combat-related PTSD are without any comorbid conditions, as opposed to our previous study as well as the Vietnam veterans study. We consider this difference to be important because patients with alcohol addiction as well as major depressive disorder, as with most common

Table 1

| Scale item                 | PTSD<br>(N = 53) | Without PTSD<br>(N = 49) | <i>P</i> -value |
|----------------------------|------------------|--------------------------|-----------------|
| Trauma re-experiencing (B) | 28.3 $\pm$ 3.5   | 11.6 $\pm$ 2.7           | < 0.001         |
| Avoidance (C)              | 22.8 $\pm$ 3.7   | 10.8 $\pm$ 1.8           | < 0.001         |
| Increased arousal (D)      | 31.7 $\pm$ 3.1   | 13.7 $\pm$ 2.1           | < 0.001         |

Average scores (mean  $\pm$  SD) of B, C, and D items of the post-traumatic stress disorder (PTSD) interview in soldiers with combat-related PTSD and in combat-experienced soldiers without PTSD.

Table 2

| Serum lipids          | PTSD<br>(N = 53) | Without PTSD<br>(N = 49) | <i>P</i> -value |
|-----------------------|------------------|--------------------------|-----------------|
| Cholesterol (mg/dl)   | 263.7 $\pm$ 48.6 | 226.2 $\pm$ 24.3         | 0.001           |
| LDL-C (mg/dl)         | 168.9 $\pm$ 43.3 | 136.8 $\pm$ 25.1         | 0.002           |
| HDL-C (mg/dl)         | 42.9 $\pm$ 13.5  | 62.2 $\pm$ 18.2          | < 0.001         |
| Triglycerides (mg/dl) | 195.6 $\pm$ 80.5 | 138.1 $\pm$ 36.5         | 0.001           |

Levels (mean  $\pm$  SD) of cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides in soldiers with combat-related posttraumatic stress disorder (PTSD) and in combat-experienced soldiers without PTSD.

Table 3

| Serum lipids  | Trauma re-experiencing |       | PTSD symptoms<br>Avoidance |       | Increased arousal |       |
|---------------|------------------------|-------|----------------------------|-------|-------------------|-------|
|               | r                      | P     | r                          | P     | r                 | P     |
| Cholesterol   | -0.111                 | 0.640 | 0.137                      | 0.565 | 0.464             | 0.039 |
| LDL-C         | -0.088                 | 0.713 | 0.148                      | 0.532 | 0.479             | 0.021 |
| HDL-C         | 0.006                  | 0.981 | -0.226                     | 0.339 | -0.252            | 0.284 |
| Triglycerides | -0.177                 | 0.454 | 0.182                      | 0.442 | 0.422             | 0.064 |

Correlation coefficients between the serum cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides with avoidance, intrusive, and increased arousal on Watson's questionnaire for posttraumatic stress disorder (PTSD) in soldiers with combat-related PTSD.

comorbid conditions in patients with PTSD, have some serum lipid changes [18, 10–13, 27].

Further, contrary to the our former study in which the control group consisted of patients with major depressive disorder [20], or the former Vietnam veterans study in which the control group consisted of patients with addiction problems [19], we used as a control group soldiers with combat experience but without current PTSD symptoms. We believe that using this population as a control group is necessary because, first, we eliminate any other disorders from the control sample that can change serum lipid concentrations. Second, serum lipid levels are extremely sensitive to a variety of psychosocial and environment changes. As such, it may be that war and combat-related factors have some influence on serum lipid levels. Using a control group of soldiers with combat experience but without PTSD was necessary to exclude those influences. In addition, this study was conducted with a new group of soldiers with chronic PTSD, and once again we confirmed high concentrations of cholesterol and LDL-C in soldiers with chronic combat-related PTSD.

Our results may also imply a very high risk of developing arteriosclerosis in patients with combat-related PTSD. The reason for this risk is that with low levels of HDL-C, there are high levels of LDL-C [24]. Increases in these serum lipoproteins are directly related to a higher risk of arteriosclerosis and vascular incidents [26]. Former epidemiological studies of Vietnam veterans have shown a high occurrence of cerebro/cardio-vascular disease, especially in those patients with PTSD [28–30].

However, in addition to the increased lipid concentrations in PTSD, there are many other biological disturbances such as alterations in cortisol, thyroid hormones, and immunology [6, 8, 31]. In particular, changes in catecholamine concentrations, in view of our results,

need special attention [32].

We found, in patients with PTSD, enhanced sympathetic nervous system activity, which manifested itself through an intensified heartbeat and blood pressure [33]. Therefore,  $\beta$ -adrenergic antagonists appear to be effective drugs in psychopharmacotherapy of PTSD [33, 34], and the drugs that increase the activity of the noradrenergic system can induce symptoms of PTSD, especially symptoms of increased arousal [35]. On the other hand, in a large investigation of patients with arterial hypertension and other risk factors for developing arteriosclerosis, increased activity of the noradrenergic system has also been found, along with a correlation between increased levels of cholesterol and catecholamine [36]. Increased catecholamine levels can activate lipoprotein lipase, which subsequently increases the concentrations of free fatty acids in the serum, and in the liver these fat acids are transformed into cholesterol and triglycerides [35]. It therefore seems logical that increased values of serum lipids in patients with PTSD were found.

The second principal finding of our research is a correlation between increased arousal symptoms, cholesterol, and LDL-C concentrations. A possible explanation of this relationship could be the formerly mentioned connection between the noradrenergic system and increased arousal symptoms as well as the connection between increased cholesterol levels and noradrenergic activity. Our study does, however, have some limitations. First, our research is limited by the use of a one-time serum lipid measurement. Also, the correlation analyses do not imply any causality. In addition, although our study sample (N = 53) is reasonably large, it should be emphasized that our results can only be regarded as preliminary and need replication in further studies, especially those studying the connections between serum lipids, serotonin, and catecholamine levels as well as the

connection between these biological variables with symptoms clusters of PTSD.

In conclusion, we found increased concentrations of cholesterol, triglycerides, and LDL-C in soldiers with PTSD; in addition, increased concentrations of cholesterol and LDL-C appear to be correlated with increased arousal symptoms of PTSD.

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