Changes in Plasma Lipid Concentrations and Risk of Coronary Artery Disease in Army Veterans Suffering from Chronic Posttraumatic Stress Disorder

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Aim To test the differences in serum lipid concentrations between veterans with chronic posttraumatic stress disorder (PTSD) and veterans without PTSD.

Methods We determined plasma lipid parameters and calculated risk factors for 50 veterans in the PTSD group and 50 veterans in the non-PTSD group. Trauma exposure, coping strategies, and quality of life were assessed with Life Stressor List, Manchester Short Assessment of Quality of Life Scale, and Folkman-Lazarus Coping Strategies Questionnaire.

Results There was no difference between the groups in the exposure to combat trauma. PTSD group had significantly lover education than non-PTSD group (10.6 ± 1.8 vs 12.4 ± 2.6 years, $P = 0.007$) and lower monthly income per family member (€67.8 ± 51.3 vs €281.9 ± 208.2, $P < 0.001$). PTSD group had significantly higher levels of all plasma lipid parameters (cholesterol: 6.54 ± 1.24 vs 5.40 ± 1.09 mmol/L, $P < 0.001$; triglycerides: 2.55 ± 0.68 vs 1.73 ± 0.77 mmol/L, $P < 0.001$; very low density lipoprotein-cholesterol: 1.14 ± 0.32 vs 0.78 ± 0.35 mmol/L, $P < 0.001$; low density lipoprotein-cholesterol: 4.49 ± 1.06 vs 3.46 ± 0.93 mmol/L, $P < 0.001$). High-density lipoprotein cholesterol concentration was significantly lower in PTSD group (0.96 ± 0.18 vs 1.15 ± 0.24 mmol/L, $P < 0.001$). Established risk factor for arteriosclerosis (6.96 ± 1.19 vs 4.71 ± 0.88, $P < 0.001$) and Adult Treatment Panel III ten years risk for coronary disease (19.44 ± 7.27% vs 9.74 ± 4.10%, $P < 0.001$) were significantly higher in the PTSD group. Secondary traumatization was significantly more frequent in the PTSD group (3.8 ± 5.7 vs 1.3 ± 4.7 events; $P < 0.001$).

Conclusions Chronic PTSD is associated with dyslipidemia, leading to an increased risk of coronary artery disease. Environmental factors and coping strategies should be considered as important factors for the occurrence and persistence of PTSD.

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"The body keeps the score: memory and the evolving psychobiology of post traumatic stress" by Bessel van der Kolk (1) was published in the *Harvard Review of Psychiatry* in 1994. Although it may not be the first article on neurobiology of posttraumatic stress disorder (PTSD), the strong metaphor contained in the first part of its title summarizes the research results in this field. Studies looking for biological causes of a disorder that is clearly precipitated by environmental or man-made causes were largely outnumbered by studies on the psychosocial nature of the disorder decades after the delayed first recognition of PTSD in the diagnostic manuals – 1980 in Diagnostic and Statistical Manual of Mental Disorders III (DSM III) (2) and 1990 in the International Classification of Diseases-10 (ICD-10) (3). A small number of studies appeared in literature in parallel with the recognition of the disorder, but the number of biological studies since September 11, 2001 has grown 5-fold and keeps growing (4).

Research interest mainly focused on alterations of neuroendocrine regulation (5,6) and neuroanatomical (7) and neuroimmunological alterations (8,9). From the neuroendocrine point of view, in PTSD there is an increased noradrenergic activity in absence of shutdown by serum cortisol that has been found to be decreased in this disorder due to dysregulation of the hypothalamo-pituitary-adrenal axis (10-12). Studies on changes in serum lipid concentrations were based on clinical observations and the results of epidemiological studies indicating increased cerebrovascular and cardiovascular morbidity and mortality in survivors of prolonged traumatic and combat stress (13-17). Kagan's pioneer study (18) of changes in lipid status of Vietnam veterans was published in 1999 and was followed by the work of other researchers who confirmed its results (19-23).

The population of Bosnia and Herzegovina suffered massive and prolonged traumatization in the 1992-1995 war (24-26). Increase in the prevalence and incidence of PTSD in comparison with the period before the war, as well as the increase in trauma-related disorders in overall psychiatric morbidity, represents a logical consequence of these events (27). In our work with people suffering from chronic PTSD, we had frequently noticed alterations of serum lipids, associated with an increased risk of cardiovascular diseases. This is consistent with our clinical observation of increased cardiovascular and cerebrovascular morbidity in patients who had been treated in the Unit for Trauma-related Disorders of the Department of Psychiatry of the University Clinical Center in Sarajevo and the literature (13-17). Therefore, we aimed to explore the differences in concentrations of serum cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C), index of arteriosclerosis, established risk factor for arteriosclerosis (ERF), and 10 years-risk for coronary disease according to Adult Treatment Panel III (ATP III) (28) between veterans with the diagnosis of chronic PTSD and veterans without the diagnosis of PTSD. Our second aim was to compare and analyze the differences between the two groups in socio-demographic characteristics, trauma exposure measures, secondary traumatization (after the war), PTSD symptoms, coping strategies, and quality of life, to obtain information on the factors influencing the development and persistence of PTSD in veterans with combat stress exposure.

There are divided opinions in literature whether this disorder develops in individuals with certain predisposing factors or all people have equal chances of developing PTSD (29-32). There is also a question whether biological markers of PTSD are trait markers

or state markers, as well as whether PTSD can be explained by stress-diathesis model as schizophrenia (33). To explore these claims, we also compared socio-demographic characteristics of the sample, trauma events inventory, coping strategies, and quality of life indicators.

Participants and methods

Participants

The study comprised 100 adult men, veterans with combat exposure who met the inclusion criteria for the study and who signed the informed consent. In order to increase the validity of the results, we paid special attention to defining the inclusion and exclusion criteria in a way that would enable better homogenization of both groups of participants in most factors affecting the blood lipid status and coronary artery disease risk. Inclusion criteria were that all participants were male (to exclude possible influence of sexual hormones), aged between 40 and 50, smokers, having a body mass index (BMI) within the reference range, having Mini-Mental State Exam (MMSE) (34) score higher than 25, and did not take any prescription or non-prescription drugs that affected plasma lipid levels or suffered from any somatic condition that affected these levels. Exclusion criteria were all psychiatric co-morbid conditions, except depression.

The participants were divided in two groups – PTSD and control group, each comprising of 50 participants. The participants from the PTSD group were recruited as a consecutive sample from the pool of patients who received out-patient treatment for PTSD in the Unit for Trauma-related Disorders at the Department of Psychiatry of the University Clinical Center Sarajevo in 2006. Out of 160 potential participants, 99 participants were excluded because they did not meet the inclusion criteria – 23 were not veterans, 9 were non-smokers, 18 had too high or too low BMI, 7 were below 40 years of age, 18 were over 50 years of age, 2 had MMSE lower than 25, 15 were taking prescription or non-prescription drugs that affected blood lipid levels (of these, 5 participants also had psychotic symptoms), and 7 were taking lipid lowering drugs. Eleven participants refused to participate in the study.

Control group consisted of 50 men, 40-50 years old, veterans with combat exposure who did not meet the criteria for the diagnosis of chronic PTSD according to DSM IV (35). Participants from the non-PTSD group were also recruited from the community in 2006, using the snowball method (36). Out of 116 potential participants, 52 were excluded – 17 were non-smokers, 12 had too low or too high BMI, 4 were younger than 40 and 14 were older than 50, 1 had MMSE score lower than 25 (due to organic brain disorder), and 4 were taking lipid lowering drugs. Fourteen veterans refused to participate in the study.

Screening and assessment methods

Participants were screened for eligibility by Mini International Neuropsychiatric Interview (MINI), version 5.0.0 (37), Mini mental state examination (MMSE) (32), general health questionnaire, questionnaire on prescription and non-prescription drugs used in the past three months, BMI, psychiatric history and psychiatric examination, screening question on smoking status, and screening question on combat stress exposure. Eligible participants were assessed by the use of the following standardized psychometric instruments: Impact of Events Scale Revised (IES-90 R) (38), Manchester Short assessment of Quality of Life (MANSA) (39), Folkman-Lazarus Coping Strategies Questionnaire (40), and a socio-demographic questionnaire that was designed specifically for this study. Trau-

matic events were recorded by the Life Stressors List (41).

Biochemical analysis

A 5 mL-sample of blood was drawn from the cubital vein and levels of plasma lipids were determined. Blood samples were drawn between 8:00 and 9:00 AM after an overnight fast of 12 hours. Lipid levels were determined by enzymatic test (Dade Behring Inc., Newark, NY, USA) in the Central Laboratory of the University Clinical Center Sarajevo. The following elements of lipid status were determined: total cholesterol, triglycerides, HDL-C, VLDL-C, and LDL-C. All concentrations are shown in mmol/L.

Reference ranges for lipid status parameters in the Central Laboratory of the University Clinical Center in 2006 were the following: cholesterol – 3.1-5 mmol/L; triglycerides – 0.11-1.90 mmol/L; HDLC – 1.06-1.94 mmol/L; VLDL-C – 0.13-0.90 mmol/L; LDLC – 2.00-4.3 mmol/L. Atherogenic index (AI) was calculated according to the following formula: AI = LDL-C/HDL-C (reference values: 1.2-4) and ERF was calculated according to the following formula: ERF = C/HDL-C (normal values lower than 5). Ten-year risk for coronary artery disease according to ATP III guidelines was calculated from the values of total cholesterol, HDL-C expressed in mg/dL, smoking status, and systolic blood pressure. Conversion from SI values to mg/dL was performed according to the following formula: mg/dL 0.0259 = mmol/L. BMI was calculated according to the following formula: BMI = weight in kg/height in squared meters.

The study was approved by the Ethics Committee and the Science and Research Institute of the University Clinical Center Sarajevo. The participants were not reimbursed and they received no other benefit in their treatment in exchange for participation in the study.

Statistical analysis

ANOVA and Mann-Whitney U-value were used to analyze the data and data were presented as means and standard deviations, medians, frequencies, and percentages. The normality of the distribution for the each of the variables was tested with Kolmogorov-Smirnov test. According to the normality of data distribution, ANOVA was used to test differences in blood lipids and Mann-Whitney U test for differences in all other variables. Step-wise multiple analysis (linear regression model) was performed to examine the best prediction model for each of the blood indicators. The predictor variables were the following: years of formal education, monthly income, employment status, exposure to war trauma, exposure to trauma after war, and presence of PTSD, and the dependent variables were the values of plasma lipids indicators. The variable of employment status had three values (1,2, and 3) that represented three possible cases (employed, unemployed, and retired). This variable was divided into three predictor variables by dummy variable coding (values 0 and 1). Each of these dummy variables was entered into the prediction model. The variable "presence of PTSD" was also treated as a dummy variable in these analyses. All other covariates were treated as scale values (results on which mean and standard deviations can be calculated). T-values and their significance levels show the magnitude of the contribution of the predictor variable to a model of prediction. The step-wise method starts with one predictor and continues to enter other predictor variables one by one, and each time the contribution of an entered predictor variable to the overall prediction power is examined. The statistical program used for data analysis was Statistical Package for the Social Sciences for Microsoft Windows, version 13.00 (SPSS Inc,. Chicago, IL, USA).

Results

Quality of life and coping strategies

The PTSD group had significantly fewer years of formal education than the non-PTSD group (Table 1). Also, the PTSD group had significantly lower monthly income per family member than the non-PTSD group (Table 1).

There were no significant differences in the level of exposure to the war trauma between the two groups (Table 1). The level of secondary traumatization (after the war) was significantly higher in the PTSD group (Table 1).

Participants with PTSD had significantly lower satisfaction with all aspects of quality of life than participants without PTSD. Yet, the satisfaction with family life, although lower than in the non-PTSD group, was relatively high in the PTSD group (Table 1).

The PTSD group had significantly higher scores on the maladaptive coping scale, except for the item of positive evaluation, where the scores were higher, although not significantly, in the PTSD group ($P = 0.027$). The scores on adaptive coping strategies were significantly lower in the PTSD group (Table 1).

Plasma lipid indicators

The levels of all plasma lipid indicators, except HDL-C, were significantly higher in the PTSD group (cholesterol – 6.54 ± 1.24 vs 5.4 ± 1.09 mmol/L, $P < 0.001$; triglycerides – 2.55 ± 0.68 vs 1.73 ± 0.77 mmol/L, $P < 0.001$; VLDL-C – 1.14 ± 0.32 vs 0.78 ± 0.35 mmol/L, $P < 0.001$; LDL-C – 4.49 ± 1.06 vs 3.46 ± 0.93 mmol/L, $P < 0.001$). HDL-C plasma lipid levels were significantly lower in the PTSD group (0.96 ± 0.18 vs 1.15 ± 0.24 mmol/L, $P < 0.001$). Decrease in HDL-C was associated with dyslipidemia and increased risk for coronary artery disease. Both AI and the ERF were significantly higher in the PTSD group (AI – 4.67 ± 1.03 vs 2.97 ± 0.73, $P < 0.001$; ERF – 6.96 ± 1.19 vs 4.71 ± 0.88, $P < 0.001$). Ten years-risk for coronary artery disease according to ATP III guidelines was significantly higher

Table 1. Education level, monthly income, scores on MANSA quality of life-scale, and Lasarus-Folkman's coping strategy rating (mean±SD) in war veterans with (n = 50) or without posttraumatic stress disorder (PTSD) (n = 50) in Bosnia and Herzegovina

Variable	Group		*P**
	PTSD	non-PTSD	
Years of formal education	10.66 ± 1.83	12.36 ± 2.64	0.007
Monthly income per household member (€)	67.78 ± 51.28	281.27 ± 208.23	<0.001
Trauma exposure:			
exposure to war trauma (frequency of traumatic events of any kind)	244.80 ± 64.85	248.36 ± 75.99	0.687
exposure to secondary trauma after the war	3.82 ± 5.66	1.28 ± 4.67	<0.001
MANSA QOL scale: †			
satisfaction wit financial situation	2.74 ± 1.04	5.44 ± 1.05	<0.001
satisfaction with social life and functioning	3.27 ± 0.98	5.48 ± 0.99	<0.001
satisfaction with family life	4.76 ± 1.30	5.49 ± 0.75	<0.001
satisfaction with sexual life	3.86 ± 1.44	6.22 ± 1.13	<0.001
satisfaction with health	3.18 ± 1.06	6.22 ± 0.89	<0.001
general satisfaction with life	3.38 ± 0.76	5.82 ± 0.74	<0.001
Maladaptive coping strategies:‡			
distancing	2.03 ± 0.72	0.49 ± 0.47	<0.001
self-control	1.50 ± 1.50	1.02 ± 0.65	0.002
taking responsibility	1.92 ± 0.60	0.44 ± 0.58	<0.001
avoidance	1.89 ± 0.78	0.07 ± 0.18	<0.001
positive evaluation	0.83 ± 0.96	0.38 ± 0.61	0.027
Adaptive coping strategies:‡			
distancing	0.65 ± 0.83	2.46 ± 0.63	<0.001
social support	0.66 ± 0.94	2.2 ± 0.70	<0.001
taking responsibility	2.24 ± 0.69	1.96 ± 0.49	<0.001
planning (problem solving)	0.80 ± 0.77	2.10 ± 0.50	<0.001
positive evaluation	0.67 ± 0.77	2.42 ± 0.62	<0.001

*Mann-Whitney U statistics.
†Manchester Short Assessment of Quality of Life (39) – Likert-type scale with scores from 1 to 7; a higher score is reflecting a higher quality of life.
‡Folkman-Lazarus Coping Strategies Scale (40) – Likert type scale with scores from 0 to 3; a higher score reflecting the higher frequency of the use of coping strategies.

in the PTSD group (19.44 ± 7.27 vs 9.74 ± 4.1, $P < 0.001$), indicating that nearly 20% of the PTSD patients would develop coronary artery disease in the following 10 years, according to the Framingham Tables (27)

PTSD group had higher mean values of almost all plasma lipid indicators, except for HDL-C (Table 2).

Table 2. Lipid parameters (mean ± standard deviation) in war veterans with (n = 50) or without posttraumatic stress disorder (PTSD) (n = 50) in Bosnia and Herzegovina

	Group†	
Variable*	PTSD	non-PTSD
Cholesterol	6.54 ± 1.24	5.40 ± 1.09
Triglycerides	2.55 ± 0.68	1.73 ± 0.77
HDL-C	0.96 ± 0.18	1.15 ± 0.24
VLDL-C	1.14 ± 0.32	0.78 ± 0.35
LDL-C	4.49 ± 1.06	3.46 ± 0.93
AI	4.67 ± 1.03	2.97 ± 0.73
ERF	6.96 ± 1.19	4.71 ± 0.88
ATP III	19.44 ± 7.27	9.74 ± 4.1

*Abbreviations: HDL-C – high density lipoprotein cholesterol; VLDL-C – very low density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; AI – atherogenic index; ERF – established risk factor for atherosclerosis; ATP III – Adult Treatment Plan III.
†*P* values for F-ratios in this table were all significant at 0.01 level, ANOVA.

Prediction models for plasma lipid alterations

Step-wise multiple regression analysis (linear regression model) was performed for the following predictor variables: years of formal education, monthly income, employment status, exposure to war trauma, exposure to trauma after war, and presence of PTSD, and the dependent variables were the values of plasma lipids indicators. Models in Table 3 represent a specific set of predictor variables that proved to be significant in predicting of plasma lipid alterations. The variable "presence of PTSD" entered each of the models that showed to be significant in the prediction of plasma lipids indicators. "Exposure to war trauma" and "employment" contributed to the prediction power of the models, including some of plasma lipids indicators but not all of them. Other predictor variables showed no significance in each of the models in the table.

Models in the table show that the variable "presence of PTSD" alone suffices the prediction of the values of the blood lipids indicators even if the co-variability of this predictor with other predictors in the set has been removed (all Models I).

Table 3. Regression coefficients of the predictor variables entering models of prediction of the blood serum lipids in Bosnia and Herzegovina war veterans (n = 100)

Dependent variable*	Model (R^2)	Predictors in the model	Standardized β-coefficients
Cholesterol	I (0.196)	PTSD	0.443†
	II (0.246)	PTSD	0.437†
		exposure to war trauma	-0.224‡
Triglycerides	I (0.247)	PTSD	0.497†
HDLC	I (0.163)	PTSD	-0.404†
VLDLC	I (0.233)	PTSD	0.483†
LDLC	I (0.216)	PTSD	0.464†
	II (0.271)	PTSD	0.458†
		exposure to war trauma	-0.235†
	III (0.308)	PTSD	0.269‡
		exposure to war trauma	-0.241†
		unemployment	-0.271‡
AI	I (0.480)	PTSD	0.693†
	II (0.503)	PTSD	0.547†
		unemployment	-0.209†
ERF	I (0.541)	PTSD	0.736†
ATP III	I (0.408)	PTSD	0.639†
	II (0.443)	PTSD	0.634†
		exposure to war trauma	-0.188‡
	III (0.449)	PTSD	0.487†
		exposure to war trauma	-0.192‡
		unemployment	-0.210‡

*Abbreviations: PTSD – posttraumatic stress disorder; HDL-C – high density lipoprotein cholesterol; VLDL-C – very low density lipoprotein cholesterol; LDL-C – low density lipoprotein cholesterol; AI – atherogenic index; ERF – established risk factor for atherosclerosis; ATP III – Adult Treatment Plan III.
†$P < 0.01$
‡$P < 0.05$

Discussion

This study showed significant increase in plasma lipid concentration and associated risk factors for atherosclerosis and coronary artery disease in a sample of veterans suffering from chronic PTSD. This finding probably justifies not only routine screening of plasma lipids in this group of patients but also a different organization and provision of health and mental health services for this population. Also, in a top-down approach, it may justify screening for PTSD in patients suffering form coronary artery disease or recovering from myocardial infarction (42,43).

The comparison of the two groups according to socio-economic parameters, coping

strategies, and quality of life assessments indicated the importance of the environment for the occurrence and persistence of PTSD.

Contrary to the data from the literature (27,44), the magnitude of exposure to traumatic events during the war did not affect the persistence of PTSD for the participants in our study. Yet, there was a significant difference between the groups in the number, duration, and frequency of traumatic events that were experienced after the war. Most frequently recorded traumatic events in this period were loss of employment and temporary housing, indicating the importance of societal factors for the prevention of development of chronic sequelae of traumatization.

It seems that the repertoire of coping strategies on the individual level plays an important role in persistence of PTSD. Obviously, maladaptive coping strategies were significantly more often present in the PTSD group, while adaptive coping strategies were significantly more often present in the non-PTSD group. This is of particular importance when thinking about psychotherapeutic treatment strategies, particularly cognitive-behavioral interventions. Our results may be of use in assessing the risk and protective factors for the occurrence and persistence of PTSD.

Our study has several limitations. The first is that it is difficult to draw any conclusions on causality between the analyzed variables. The second limitation is that the participants included in the study were not randomized. Also, since the participants were either from an outpatient sample or community sample, they did not have uniform diet in the period before blood samples were taken.

Previous research has identified a number of biological changes in patients with chronic PTSD (5-12), including plasma lipid concentrations (18-20). Depression co-morbid with PTSD has been reported to have similar effect on blood lipids as PTSD alone, but not unipolar depression without PTSD (21). This is very interesting since epidemiological studies showed 70% prevalence of co-morbid depression in participants with chronic PTSD (45). For this reason, we did not exclude participants with depressive co-morbidity (84% in the PTSD group) from our study.

In many people who have undergone severe stress, posttraumatic sequelae lose their intensity over time (46). Yet, in others, they tend to persist and become chronic, producing mental and somatic disability and leading to decreased quality of life. The role of research is to point out to the preventable complications and identify efficient services (health, mental health, and social services) that can adequately address the needs of those patients. Further research is needed to confirm our results and better identify factors of resilience and vulnerability for PTSD.

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