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Homocysteine and serum lipids concentration in male war veterans with posttraumatic stress disorder

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ABSTRACT

The evidence of increased cardiovascular disease (CVD) risk in posttraumatic stress disorder (PTSD) is accumulating. The present study aimed to determine whether chronic, combat-related PTSD is associated with serum lipid and homocysteine concentrations that could indicate higher CVD risk.

The authors tested 66 war veterans with PTSD, 33 war veterans without PTSD, and 42 healthy volunteers for serum concentrations of homocysteine, total cholesterol, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides. All the subjects were men and the analyses were adjusted for age, body mass index and smoking. Potential influences of depression, anxiety, and psychotic symptoms on the outcome measures were checked by introducing the scores from the Hamilton Depression Rating Scale (HAM-D-17), the Hamilton Anxiety Scale (HAMA), and the Positive and Negative Syndrome Scale (PANSS) into the overall statistical model.

No differences in total cholesterol, LDL-C, HDL-C and triglycerides were found between the groups. Non-smoking PTSD war veterans had higher homocysteine concentrations (mean=10.4 μmol/L, SD=1.7) when compared to non-smoking war veterans without PTSD (mean=8.2 μmol/L, SD=4.0, P=0.014) and both smoking (mean=8.7 μmol/L, SD=2.3, P=0.008) and non-smoking healthy volunteers (mean=8.8 μmol/L, SD=2.2, P=0.021).

The results of our cross-sectional study are possibly confounded by many factors, especially behavioral and life-style related which are difficult to control comprehensively and might have influenced serum lipids and homocysteine concentration in a complex manner.

An increase in the homocysteine concentration observed in the non-smoking PTSD patients needs further investigation with a carefully designed prospective study to confirm associated, possibly enhanced CVD risk.

1. Introduction

Posttraumatic stress disorder (PTSD) has been associated with different psychiatric (Kessler et al., 1995; Kozarić-Kovačić et al., 2000, 2001; Kozarić-Kovačić and Borovečki, 2005; Kozarić-Kovačić and Kocijan-Hercigonja, 2001; Marinić et al., 2007) and somatic comorbidities (Boscarino, 2004). Evidence linking cardiovascular disease (CVD) to PTSD is accumulating (Kubzansky and Koenen, 2007) and is supported by epidemiological (Kang et al., 2006) and prospective studies (Kubzansky et al., 2007).

Among other CVD risk factors, PTSD has been associated with elevated serum lipid levels (Kagan et al., 1999). In addition to hyperlipidemia, elevated serum/plasma homocysteine concentration could be another predictor of CVD because of its prothrombotic and proatherosclerotic effects (Loscalzo, 1996). It has been shown that the CVD risk associated with hyperlipidemia might be further increased through elevated plasma homocysteine (Veerkamp et al., 2003).

Homocysteine is a sulfurated amino acid derived from ingested methionine and its proatherosclerotic effects are mediated primarily through oxidative stress mechanisms (Virdis et al., 2005). High levels of homocysteine may cause endothelial dysfunction, accelerate thrombin formation, inhibit native thrombolysis, promote lipid peroxidation through free radical formation, and induce vascular smooth muscle proliferation and monocyte chemotaxis (Jacobsen

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; BMI, body mass index; CAPS, Clinician Administered PTSD Scale; CVD, cardiovascular disease; FPIA, Fluorescence Polarization Immunoassay; HAMA, Hamilton Anxiety Scale; HAM-D-17, Hamilton Depression Rating Scale; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SCID, Structured Clinical Interview for DSM-IV; SPSS, Statistical Package for the Social Sciences; PANSS, Positive and Negative Syndrome Scale; PTSD, posttraumatic stress disorder.

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et al., 2005; Moat and McDowell, 2005). Epidemiological studies in general population showed that a mild to moderate hyperhomocysteinaemia was associated with elevated risk of CVD (Danesh and Lewington, 1998). Despite such experimental and epidemiologic studies, the current status of homocysteine in CVD risk assessment is equivocal: even if homocysteine is a powerful prognostic marker of mortality and CVD events in patients with preexisting CVD risk factors, some argue if these evidences are sufficient to conclude that moderately increased homocysteine causes CVD (Kothekar, 2007), since among other evidences, a recent meta-analysis demonstrated that lowering of plasma homocysteine did not result in decreasing the risk of coronary heart disease or stroke (Bazzano et al., 2006). Following such results Moat (2008) concluded that it would appear that a mild increase in plasma homocysteine is an indicator but not an instigator of the CVD process.

In addition to CVD, an increase in homocysteine levels has also been associated with neurodegenerative and psychiatric disorders. It has been linked to schizophrenia (Levine et al., 2006), depression (Tiemeier et al., 2002; Bottiglieri et al., 2000) and age-related cognitive impairments (Troen and Rosenberg, 2005) such as Alzheimer's disease (Morris, 2005; Sachdev, 2005; Seshadri, 2006). The most convincing evidence showing association of psychiatric disorders with increased serum levels of homocysteine comes from the research in depression (reviewed in (Bottiglieri, 2005; Folstein et al., 2007). Anxiety disorders, including PTSD (Kozarić-Kovačić et al., 2001; O'Donnell et al., 2004) commonly occur simultaneously with depression (Levine et al., 2001). Although only a weak, nonsignificant relationship between plasma homocysteine levels and anxiety symptoms has been reported in a large Hordaland Homocysteine Study cohort (Bjelland et al., 2003), the increased levels of homocysteine have been found in patients with obsessive–compulsive disorder (Atmaca et al., 2005). Moreover, studies showed elevation in plasma homocysteine during acute psychological stress (de Souza et al., 2006; Stoney, 1999), together with rise in blood pressure and heart rate (Sawai et al., 2008) suggesting important role of neurotransmitters and hormones involved in stress-response in regulation of homocysteine metabolism. Thus, it is plausible to hypothesize that patients who developed PTSD after war trauma may exhibit high serum homocysteine levels.

Since homocysteine and serum lipids play an important role in the development of CVD and have been associated with various psychiatric disorders, the present study aimed to examine whether there is a relationship between homocysteine levels together with serum lipids and war trauma exposure. Serum lipids and homocysteine concentrations, as well as other CVD risk factors, were examined in war veterans with PTSD and compared to a group of subjects exposed to war trauma without PTSD as well as healthy volunteers who didn't experience war trauma.

2. Methods

2.1. Subjects

The study subjects were war veterans who developed PTSD after being exposed to trauma (N=66), war veterans who didn't develop PTSD after trauma exposure (N=33), and healthy volunteers with no exposure to war or other extreme traumas (N=42). War veterans participated in the war in Croatia from 1991 to 1995. All subjects were males, Caucasians, and their other basic characteristics are shown in Table 1. They were recruited through the inpatient and outpatient unit

Table 1
Demographic, biological and psychometric characteristics of war veterans with and without posttraumatic stress disorder (PTSD) and healthy volunteers

Characteristic	War veterans with PTSD (n=66)		War veterans without PTSD (n=33)		Healthy volunteers (n=42)		Data analysis	
	Mean	(SD)	Mean	(SD)	Mean	(SD)	F (df=2, 138)[a]	P
Age (years)	37.6	(4.7)	37.4	(4.2)	37.0	(7.2)	0.19	0.832
Body mass index (kg/m^2)	26.9	(3.5)	27.0	(2.4)	27.3	(3.8)	0.23	0.798
Number of cigarettes smoked per day	19.0	(15.0)	7.9	(12.7)	8.6	(10.4)	11.53	<0.001
	Mean	(SD)	Mean	(SD)	Mean	(SD)	F (df=2, 133)[b]	P
Triglycerides (mmol/L)[c]	2.24	(1.44)	1.92	(1.35)	1.86	(1.23)	0.87	0.424
Total cholesterol (mmol/L)	5.57	(1.20)	5.66	(1.12)	5.52	(0.94)	0.13	0.881
Low-density lipoprotein cholesterol (mmol/L)	3.40	(1.05)	3.50	(1.03)	3.45	(0.83)	0.11	0.893
High-density lipoprotein cholesterol (mmol/L)[c]	1.18	(0.17)	1.31	(0.26)	1.22	(0.22)	2.00	0.136
Homocysteine (μmol/L)[d]	10.09	(4.10)	9.06	(4.30)	8.75	(2.22)	4.51	0.013
	Mean	(SD)	Mean	(SD)			t (df=97)[e]	P
Clinician Administered PTSD scale scores								
Total	61.1	(13.8)	19.0	(12.0)			14.96	<0.001
Re-experiencing symptoms	17.2	(4.2)	4.6	(3.5)			14.86	<0.001
Avoidance and numbing symptoms	24.8	(6.7)	6.5	(4.2)			14.96	<0.001
Symptoms of increased arousal	19.1	(4.6)	8.0	(4.7)			11.37	<0.001
Hamilton anxiety scale score	23.6	(3.1)	8.8	(0.8)			41.69	<0.001
Hamilton depression rating scale score	24.4	(3.9)	8.9	(1.0)			34.49	<0.001
Positive and negative syndrome scale scores								
Total[d]	67.7	(19.1)	36.0	(15.0)			15.98	<0.001
	Median	(Range)	Median	(Range)			Mann Whitney U[f]	P
Positive symptoms	7	(6–28)	7	(7–8)			1005	0.495
Negative symptoms	10	(7–22)	7	(7–8)			216	<0.001
General psychopathology	35	(27–60)	18	(17–19)			0	<0.001
Supplement	8	(5–13)	3	(3–4)			0	<0.001

[a] One-way analysis of variance.
[b] Effect of group after two-way analysis of covariance for the effect of group and smoking with age and BMI as covariates.
[c] Analyses were performed with transformed variables (logarithm to the base 10) while the data are presented by the initial values.
[d] Analyses were performed with the rank transformed variables, while the data are presented by the initial values.
[e] Independent sample t-test.
[f] Mann Whitney U test.