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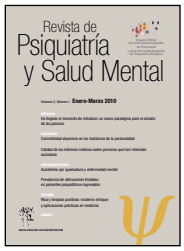

ORIGINAL ARTICLE

Early markers of endothelial dysfunction posttraumatic stress disorder. Role in atherogenesis

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KEYWORDS
Post traumatic stress disorder;
Endothelial dysfunction;
E-Selectin;
V-CAM-1;
S-ICAM-1.

Abstract
There is a strong association between cardiovascular diseases, thromboembolism, and atherosclerosis with endothelial dysfunction. The relationship of the latter with neuropsychiatric diseases such as the post traumatic stress disorder (PTSD) stands as a risk factor for the development of atherosclerotic phenomena.
Objective: To disclose a meaningful association between PTSD and higher values of endothelial dysfunction molecules like e-Selectin, s-ICAM-1 and v-CAM-1, in comparison with healthy subjects without PTSD.
Methods: 24 patients with PTSD and 24 healthy subjects were selected e-Selectin, v-CAM-1 e soluble ICAM-1 levels were measured in plasma. The PTSD severity symptoms scale and the Trauma Symptom Checklist were administered to both samples.
Results: A meaningful and robust correlation between endothelial dysfunction markers e-Selectin, s-ICAM-1 y v-CAM-1 plasma levels and the severity of the PTSD was disclosed.
Conclusion: There is a continual relationship between PTSD symptoms severity and plasmatic levels of endothelial dysfunction markers. This relationship can explain the probability of developing cardiovascular diseases and atherogenesis and traumatic life events which ends up as PTSD at common grounds with inflammatory vascular response.

PALABRAS CLAVE
Trastorno de estrés postraumático;
Disfunción endotelial;
E-Selectina;

Marcadores precoces de disfunción endotelial en trastorno de estrés postraumático. Rol en la aterogénesis

Resumen
La asociación de enfermedades cardiovasculares, tromboembolismo y aterosclerosis se asocia significativamente con disfunción endotelial. La posibilidad de asociación de esta última con enfermedades psiquiátricas como el trastorno por estrés postraumático (TEPT) constituiría un factor de riesgo para el desarrollo de fenómenos de aterosclerosis.

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V-CAM-1;
S-ICAM-1

Objetivo: Detectar una asociación significativa entre el TEPT y mayores valores de moléculas de disfunción endotelial como e-Selectina, s-ICAM-1 y v-CAM-1, en comparación con sujetos sanos sin TEPT.
Métodos: Se seleccionaron 24 pacientes con TEPT y 24 sujetos sanos control sin TEPT y se midieron e-Selectina, v-CAM-1 e ICAM-1 soluble en plasma en ambos grupos. Además se les administró la escala de gravedad de síntomas del trastorno por estrés postraumático y el Trauma Symptom Checklist para evaluación del TEPT.
Resultados: Se comprobó una asociación significativa y robusta entre e-Selectina, s-ICAM-1 y v-CAM-1 y la gravedad del TEPT.
Conclusiones: Hay una relación continua entre la severidad de los síntomas de TEPT y los niveles plasmáticos de marcadores de disfunción endotelial. Este vínculo puede explicar la asociación entre la probabilidad de desarrollar enfermedades cardiovasculares y aterogénesis y los eventos traumáticos conducentes a desarrollar TEPT en el nivel de la respuesta vascular inflamatoria común.

Introduction

The clinical picture for post-traumatic stress disorder (PTSD) is characterised by 3 types of different symptoms (DSM IV): recurrent experience of the traumatic event, avoidance of signals or clues related to it and hyperarousal (American Psychiatric Association, 1994). The prevalence of PTSD is 7.8% in the general adult population, and twice as high in women (10.4%) as in men (5%). The most frequently experienced traumas are witnessing someone seriously injured or killed; being involved in shootings, floods or natural disasters; or in a life-threatening accident. The majority experience more than one type of trauma, with 10% of men and 6% of women reporting up to four or more during their lives.[1] The incidence of the disorder doubles in patients who have suffered acute myocardial infarction (AMI).[2] In addition, patients with PTSD are at increased risk of thromboembolic disease[3,4] and cardiovascular mortality.[5-8] Patients with AMI and PTSD as a comorbidity have higher rates of relapse. PTSD and depression may be associated with atherosclerosis through a proinflammatory state and endothelial dysfunction.[9,10] Endothelial dysfunction can be assessed by quantifying circulating endothelium-derived proteins. Various research studies indicate a number of substances, such as cytokines IL-1, IL-6 and TNF-α; E-selectin (ES), endothelin-1 (E-1), intercellular adhesion molecule-1, 2 and 3 (ICAM-1, ICAM-2, ICAM-3), vascular cell adhesion molecule (VCAM-1), von Willebrand factor antigen (vWFag), plasminogen activator inhibitor types 1 and 2 (PAI-1 and PAI-2), soluble thrombomodulin, soluble tissue factor (STF), soluble intercellular adhesion molecule-1 (sICAM-1);[11-24] tissue activation inhibitor factor (TAIF),[25,26] C-reactive protein (CRP), asymmetric dimethylarginine (ADMA).[27,28] The proposed mechanism is that endothelial cells express STF, sICAM-1 and VCAM on the cell surface at the site of inflammation and injury (Fig. 1).

Although the exact role of each of the above factors is not known with precision, they are all involved in the inflammatory responses and coagulation preceding atherogenic phenomena.[29] In response to proinflammatory stimuli, ICAM-1 mediates endothelial adhesion and leukocyte migration, takes on coronary plaque macrophages and induces fibrosis and plaque instability. ICAM-1, VCAM-1, and CRP are found in a higher concentration in healthy subjects about to have an acute myocardial infarction (AMI). They anticipate the development of carotid atherosclerosis with ES, are found in a higher concentration in patients who have had an AMI and are associated with cardiovascular risk factors, anxiety, minor depression and health habits, which in turn increase endothelial dysfunction.[30,31] The latter is the result of several stages, including increased IL-1, IL-6, TNF-α and interferon; leukocyte adhesion to endothelial cells by ICAM-1, VCAM-1 and ES; transendothelial migration, increased vWFAg, activation of the thrombotic cascade and atheromatous formation.[32] The expression of ICAM, VCAM-1 and ES is increased in atherosclerotic plaques[33] while the soluble forms increase in plasma under inflammatory conditions such as coronary artery disease, carotid sclerosis, peripheral vascular disease, metabolic syndrome, diabetes, hypertension and dyslipidaemia.[34-37] VCAM-1 belongs to the integrin β1 family and mediates adhesion of lymphocytes, monocytes, eosinophils and basophils to vascular endothelium, and is involved in signal

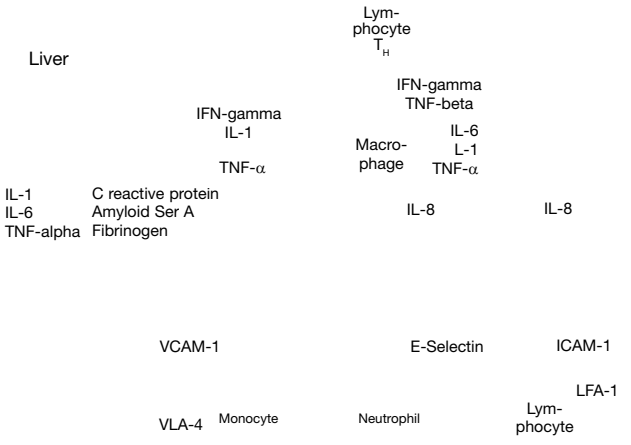

Figure 1 Proposed mechanism.

transduction and the development of atherosclerosis and rheumatoid arthritis. Tumour necrosis factor-alpha (TNF-α) and the interleukins 1 and 4 (IL-1, IL-4) regulate it when it increases.[38] CD54 (ICAM-1) is a transmembrane protein of the Ig superfamily which is strongly glycosylated and associated with the endothelium and leukocytes. It is involved in stabilising intercellular interactions and endothelial transmigration, the transduction of immune signals, production of proinflammatory effects and recruitment of kinases such as p56lyn.[39] E-Selectin (ES) belongs to a family of transmembrane glycoprotein type cell adhesion molecules and is expressed in endothelial cells in response to inflammatory cytokines such as interleukin-1ß (IL-1ß) and/or TNF-α. It has been suggested that increased levels of the soluble form of ES (sES) could be specific and early markers for vascular endothelial damage.[40]

Objectives

To detect a significant association between PTSD and higher values of molecules associated with endothelial dysfunction, such as ES, sICAM-1 and VCAM-1, compared with healthy subjects without PTSD as a control group. To do so, a number of possible correlations between endothelial function and PTSD using various statistical tests were evaluated.

Methods

At the start of the study, a 10cm^3 sample of antecubital venous blood was taken from each subject between 8am – 9am in the morning after fasting for at least 12h. The samples were placed in tubes containing 3.8% sodium citrate and centrifuged at 2,000g for 20min at 4°C. The plasma, serum and buffy coat fractions were then separated and stored at -80°C. Subsequently, an aliquot was processed for determination of glucose and lipid profile using an enzymatic colorimetric method (BTS-330® BioSystems, Barcelona, Spain). The concentrations of sICAM-1 (soluble intercellular adhesion molecule-1) were determined by enzyme immunoassay (ELISA, enzyme-linked immunosorbent assay, Human Parameter sICAM-1 Immunoassay; R&D Systems, Minneapolis, USA). The assay sensitivity was 0.35ng/ml, with values ranging from 2.73 to 49.55ng/ml and intra-analytical and inter-analytical variability between 4.8% and 10.1%. The sVCAM-1 (soluble vascular cell adhesion molecule 1) content was measured by ELISA using a monoclonal antibody specific for sVCAM-1 (Quantikine Human sVCAM-1 Immunoassay; R & D Systems, Minneapolis, USA). The lower limit of detection was 0.17-1.26ng/ml with a range of 0-200ng/ml. The intra-assay variation coefficients ranged from 2.3% to 3.6% with inter-assay variation coefficients of 5.5% to 7.8% sES was measured using a high sensitivity quantitative enzyme panel (Human Parameter sE-Selectin Immunoassay; R & D Systems, Minneapolis, USA). The minimum detectable level of ES was <0.1ng/ml and the assay range was 0.47 to 10.52mg/ml. The intra- and inter-assay variation coefficients ranged from 4.7% to 5.0% and 5.7% to 8.8%, respectively. Samples from patients and controls were randomly distributed over different vials in different assays to prevent systematic measurement errors. PTSD was assessed using the post-traumatic stress disorder symptom scale.[41] This scale consists of 17 DSM IV diagnostic criteria items and evaluates the symptoms of this syndrome in victims of traumatic events. The items are grouped into three domains: re-experiencing (cluster A, DSM IV), avoidance (cluster B) and hyperarousal (cluster C). Symptoms are measured on a Likert scale (0 to 3) according to the frequency and intensity of the symptoms. Re-experiencing consists of 5 items, avoidance has 7 and hyperarousal has 5. There is an additional subscale of somatic anxiety manifestations with the same structure, consisting of 13 items (range: 0 to 39), which may help in differentiating between different types of victims and guiding the choice of therapeutic strategies. The test-retest reliability coefficient was 0.89 and the alpha coefficient 0.90. To meet the PTSD criteria, at least 1 symptom of re-experiencing, 3 of avoidance and 2 of hyperarousal were required. Moreover, these symptoms had to have lasted more than 1 month and caused clinically significant distress or impairment in social, occupational or other important areas of daily life of the individual. The content validity of this scale, covering 100% of the DSM IV diagnostic criteria, can be considered entirely satisfactory. The Trauma Symptom Checklist[42] was used to assess anxiety and depression, as the latter is often found as a comorbidity in people with PTSD. The psychometric properties are satisfactory, with a Cronbach's α index of 0.86 for anxiety and depression scales. Both scales contained 9 items whose response is assessed on a 4-point Likert scale from 0 (never) to 3 (very often), with an overall result of 0 to 27.

Subjects

A number of patients (24) diagnosed with PTSD, complying with the DSM-IV diagnosis criteria, were selected from an outpatient psychiatric department and day workshop. A control group of 24 subjects, matched for age and sex, with no psychiatric pathology, were recruited from self-referred visits at a kinesiology and rehabilitation unit at the hospital. The sample size was calculated for a Pearson correlation coefficient between samples of 0.8 with a (1-ß) power of 99%, a two-sided, type 1 α-error probability of 0.01 and size effect of 0.7 for an f value of 0.35.[43] Among the traumatic events triggering PTSD, the most common was to have been in an accident. There were also references found to accidents among the controls, but in these, they did not lead to the development of the condition. Both patients and controls were subjected to a thorough clinical assessment by two clinics not involved in the study, and no patients had any health problems for exclusion from the study. Exclusion criteria were a history of heart, liver, renal or systemic disease; accidents or major surgery in the month preceding the study; respiratory, urinary or gastrointestinal infections; fever in the previous week; pulmonary embolism or use of oral anticoagulants within the last 3 months; use of aspirin in the last 10 days; pregnancy or hormone therapy. Since antidepressants can modify the levels of endothelial markers, patients medicated with the latter were subjected to a washout period of 1 month.[44] MINI 5.0[45] was used to

exclude psychiatric disorders in controls. All participants gave their informed consent. Cardiovascular risk factors and lifestyle as potential correlates of endothelial markers were assessed. Subjects were required to give information about smoking, hypertension, diabetes, blood glucose levels and any history of diabetes or dyslipidaemia for the assessment. The body mass index (BMI) was calculated as the ratio between weight in kilograms and the square of the height in metres. Hypertension was considered to occur with blood pressure values for systolic (SBP) >140mm Hg and/or diastolic (DBP) >90mm Hg, when calculated as the average of 3 sphygmomanometric measurements with the subject sitting. Information on exercise habits, alcohol and coffee consumption was also requested.

Statistical analysis

The statistical package SPSS 14.0 (Chicago, USA) was used for the analysis. The significance level was set at $P \leq .05$, and all tests were two-tailed. To avoid bias due to a non-normal distribution, values were normalised by z-transformation before being submitted for statistical analysis. This procedure replaced each original value with the corresponding z value, and the scalar distances between ranges were adjusted for a normal distribution. Patients and controls were compared using a paired case-control design using two-tailed t-tests for continuous variables and Wilcoxon signed-rank tests for categorical variables. The association between variables was estimated by the Pearson correlation analysis. We used logistic regression analysis to determine whether the relationship between PTSD disease status (1=PTSD, 0=control) and plasma levels of endothelial markers would be affected by adjustment of covariates that were significantly associated with endothelial markers in correlation analysis. To identify PTSD symptom clusters significantly associated with endothelial markers, with and without adjustment for covariates of endothelial markers, a hierarchical linear regression analysis was used for the sample of patients and controls separately and jointly. The significance of the difference for patients and controls in the correlation coefficients between the PTSD scale and endothelial markers was also determined, with and without adjustment for covariates.

Results

There were no significant differences in demographic and clinical data between patients and controls (Table 1). There was no significant history of systemic, kidney, liver or heart diseases. The average time between the traumatic event and the development of PTSD was 18(15 (range 9-37) months.

The t-test was used for paired samples and the Wilcoxon signed-rank test for case controls.

Patients with PTSD had higher levels of symptoms, anxiety and depression than the controls (Table 2).

The analysis used a two-tailed t-test for paired case-control.

In all subjects, s-ICAM, VICAM and E-selectin correlated with anxiety symptoms (r=0.56, p=0.014) and depression (0.58, $P=.006$). Anxiety and depression scales were highly correlated (r=0.75, $P < .001$). The time between the traumatic event and the onset of symptoms was not significantly associated with endothelial markers in patients ($P = .47$). Endothelial dysfunction markers reached higher values in PTSD with a significant size effect (Cohen's d=0.81). The highest values of s-ICAM in patients compared to controls showed a moderate size effect (d=0.65), as did E-selectin (d=0.54). Adjustment of s-ICAM, VICAM and E-selectin for age and exercise showed no significant differences between groups (Table 3).

Values are expressed as means and interquartile ranges. The t-test was applied for paired samples and logistic regression in case-control pairs for comparison adjusted for covariates (age and exercise).

Table 1 Demographic and medical data for PTSD and control groups, mean(SD)

	PTSD (n=24)	Control (n=24)	*P* value
Sex	M/W (12/12)	M/W (12/12)	1.00
Age	45(10)	44(11)	0.773
BMI (kg/m^2)	24,3(2.5)	25,2(3.7)	0.845
SBP (mm Hg)	129(12)	130(11)	0.572
DBP (mm Hg)	83(11)	84(10)	0.769
Smoking (y/n)	15/9	14/10	0.677
Diabetes (y/n)	1/23	2/22	0.854
Dyslipidaemia (y/n)	2/22	3/21	0.749
Exercise (y/n)	16/8	17/7	0.834
Alcohol (y/n)	10/14	9/15	0.837
Glucose (mmol/l)	3.7(0.40)	3.8(0.50)	0.745
Cholesterol total (mmol/l)	4.3(1.3)	4.2(1.5)	0.893
HDL-cholesterol (mmol/l)	1.3(0.4)	1.2(0.2)	0.956
Triglycerides (mmol/l)	0.67(0.23)	0.75(0.26)	0.859

Table 2 Psychometric data for PTSD and control groups, mean(SD)

	PTSD (n=24)	Control (n=24)	P value
Re-experiencing	12(1.3)	3.2(1.1)	<0.001
Avoidance	18.2(2.1)	10.1(1.6)	<0.001
Hyperarousal	11.2(2.3)	3.2(1.5)	<0.001
TSC			
Anxiety	22.4(1.3)	9.2(3.1)	<0.001
Depression	17.1(3.4)	9.2(3.1)	<0.001

The analysis used a two-tailed t-test for paired case-control.

Table 3 Endothelial dysfunction markers in PTSD and control groups

	PTSD	Control	P adjusted	P
sICAM-1 (µg/l)	259.4 (211.1-289.2)	132.3 (110.3-143.7)	0.002	<0.001
VCAM-1(µg/l)	592.7 (518.2-603.5)	422.1 (408.5-449.5)	0.011	<0.001
E-Selectin (µg/l)	54.2 (43.6-58.6)	31.8 (26.4-37-9)	0.003	<0.001

Values are expressed as means and interquartile ranges. The t-test was applied for paired samples and logistic regression in case-control pairs for comparison adjusted for covariates (age and exercise).

Table 4 Regression Model for E-selectin

Symptoms	Model 1			Model 2		
	Total (F1,46)	PTSD (F1,23)	Control (F1,23)	Total (F2,45)	PTSD (F2,22)	Control (F2,22)
Re-experiencing	0.49*	0.56**	0.23	0.44*	0.52**	0.31
Avoidance	0.57**	0.76***	0.33	0.47*	0.69**	0.30
Hyperarousal	0.71***	0.79***	0.37	0.54*	0.62**	0.27
Total	0.68**	0.75***	0.34	0.52*	0.61**	0.30

Model 1: no adjustment for covariates; Model 2: adjusted for age and physical activity. Significance levels are *P<.10, **P<.05, ***P<.001. The values indicate ß coefficients (slope). The columns indicate subjects and df.

All PTSD symptoms were associated with E-selectin in patients with PTSD (Table 4), particularly hyperarousal and avoidance, but not in controls (model 1). However, the significance of association decreases statistically when the data are corrected for covariates such as age and physical activity, although the slopes remain.

Model 1: no adjustment for covariates; Model 2: adjusted for age and physical activity. Significance levels are *P<.10, **P<.05, ***P<.001. The values indicate ß coefficients (slope). The columns indicate subjects and df.

The relationship between E-selectin and PTSD re-experiencing, avoidance and hyperarousal symptoms, as well as totals in controls and patients plotted as transformed data (z) show a significant association between the severity of PTSD symptoms and the concentrations of E-selectin (Fig. 2).

Discussion

From the results, the existence of a significant association between endothelial dysfunction and PTSD can be assumed, when compared with control subjects without PTSD. The patients had higher levels of E-selectin, sICAM-1 and VCAM-1, even controlling for covariates such as physical activity and age, which may change endothelin values. A significant association was also observed between depression and anxiety results and endothelial marker values, which is not surprising given the prevalence of these symptoms in PTSD. However, PTSD symptoms made a greater contribution to the endothelial marker increases than depression and anxiety separately. Avoidance and hyperarousal symptoms were robustly associated with endothelins, especially E-selectin when compared with controls. These findings are consistent with other studies that found an association between PTSD and AMI signs, even after adjusting for depression and anxiety.[46] The positive relationship between PTSD and sICAM-1 levels was robust even after correcting for age, suggesting a continuing relationship between these variables, even with moderate PTSD symptoms. In other words, there is a direct association between intensity and severity of PTSD symptoms and levels of endothelial dysfunction markers, even in the lower level severity range of symptoms. There seems to be evidence in favour of a continuous endothelial inflammatory atherogenic response associated with increasing levels of intensity in PTSD stressor responses.[47] The markers E-selectin, sICAM-1 and VCAM-1 were elevated regardless of the time of development

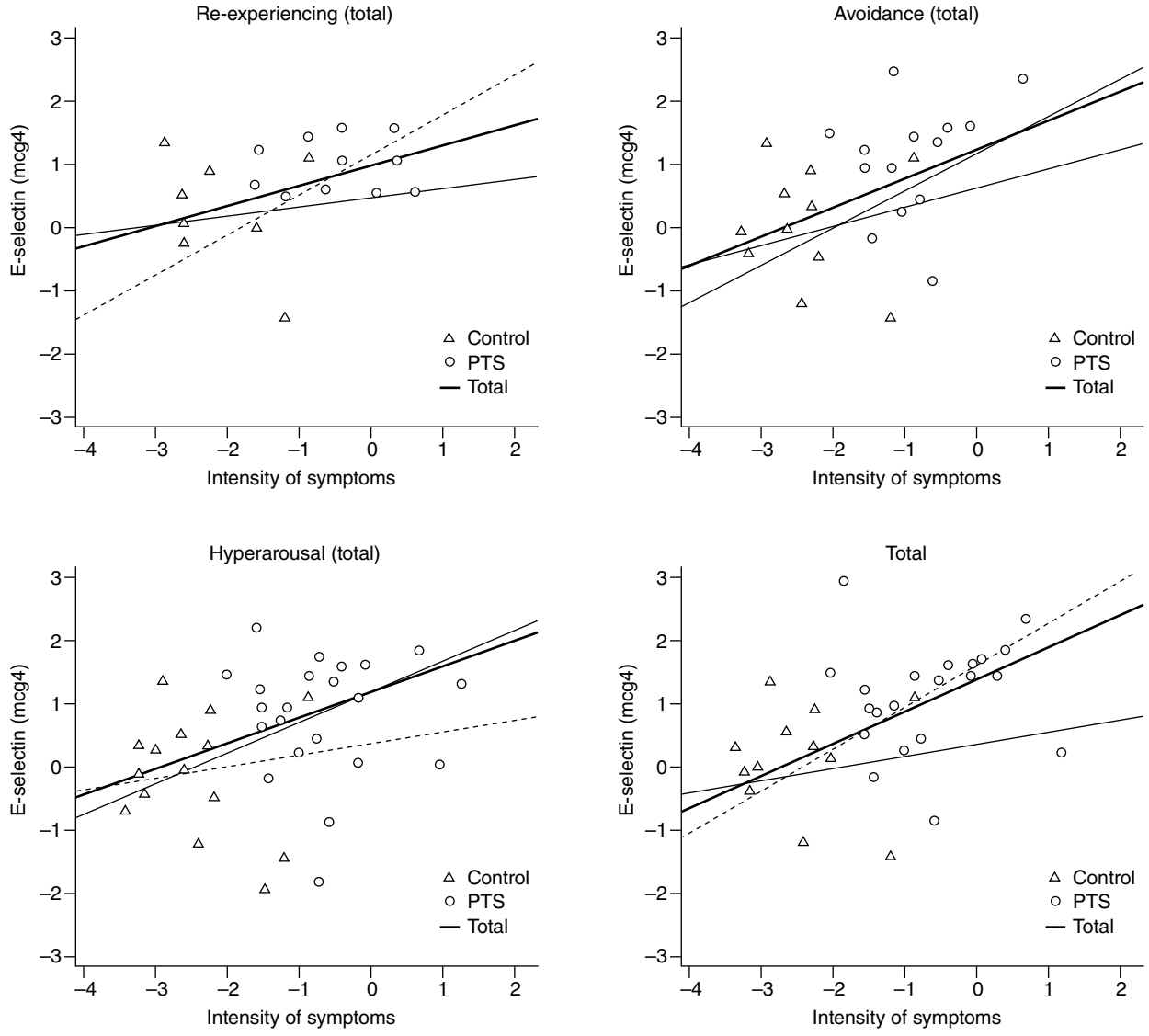

Figure 2 Association of E-selectin with PTSD symptoms (z values)

of the symptoms, suggesting a common basis for the atherogenic and cardiovascular effects of acute and acute PTSD, although a causal chain cannot be deduced from the study. The primary objective of this study was to investigate the relationship between endothelial dysfunction markers and PTSD, generating a hypothetical basis for linking the disorder with cardiovascular diseases. While this is a cross-sectional study and a longitudinal hypothesis on the long-term changes of endothelial markers cannot be reflected, some mental and emotional states particular to PTSD that influence their expression are known,[48] which in turn modify the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SS).[49] PTSD patients have lower plasma cortisol levels, increased catecholamine levels in plasma and urine at 24h,[50] endothelial cell activation,[51] cytokine hyperactivity,[52] IL-6, selectins and adhesion factors.[53] The TNF-α activates the nuclear transcription factors AP-1, COUP-TF1, NFκB, STAT, which stimulate the production of IL-6 and adhesion factors,[54] whereas glucocorticoids exert their effect by two mechanisms, genomic and nongenomic. Included in the former are negative feedbacks on TNF-α, which are increased in PTSD[55] and activation and transcription factors. Nongenomic mechanisms generate insensitivity to genome transcription inhibitors, modifying ion channels and membrane-associated proteins, and inhibiting the intracellular signalling of ICAM-1 and VCAM1, as well as the cytoskeletal reorganisation required for cellular mobilisation and adhesion.[56] From the noradrenaline produced at the A1/A2 centres of the locus coeruleus and in the central autonomic nervous system, SS stimulates noradrenergic β2 endothelial receptors[57] which, in PTSD, increase levels of MCP-1, MIP-1α, M-CSF, TNF-α, IL-1, IL-1ra, IFN-γ and IL-6, and decrease levels of IL-4 and IL-10. This increases the expression of neutrophils, monocytes, $CD8^+$, $CD2^+$, $DC26^+$,$CD2^+$, T cells HLA-DR^+ and B cells $CD19^+$, E-selectin, ICAM-1 and VCAM1.[58] In addition, they induce

a change in immune response from T_H1 (cellular) to T_H2 (humoral).[59] An increase in the values of ICAM-1 and VCAM-1 has been observed in adults with cardiovascular events over a long period[60] while increased levels of E-selectin, but not ICAM-1 or VCAM-1, are associated independently and robustly with cardiovascular risk factors and aortic atherosclerosis.[61] This indicates that E-selectin is related to the initial phase, and ICAM-1 and VCAM-1 with the final phase of atherosclerosis, replacing the cascade of events triggered by E-selectin and VCAM-1 by a single step involving ICAM-1.[62] E-selectin appears to be prevalent in chronic stress situations, while it is added to ICAM-1 and VCAM-1 in acute stress situations, suggesting different temporal modes of regulation. The initial events in atherosclerosis are associated with the expression of adhesion molecules on the surface of endothelial cells, which in turn are inhibited by activation of peroxisome proliferator receptors, limiting the chronic inflammation mediated by VCAM-1 and ICAM-1, without affecting the acute inflammation phenomena mediated by E-selectin and the leukocyte agglutination.[63] The same phenomenon of high levels of E-selectin is associated with chronic stress.[64] Because these modifications can respond to multiple triggers, such as cardiovascular risk factors, rheumatoid arthritis, endocrine and metabolic disorders,[65] including health habits such as smoking, physical inactivity, alcohol consumption and obesity, in addition to age and sex,[66] the pairing of the clinical sample for age and gender with healthy controls was taken into account. Limitations of the study arise from the relatively small sample size, the lack of assessment of endothelial function through more precise methods,[67] the lack of longitudinal follow-up and omission of potentially confounding factors arising from risk behaviours not assessed in the study (e.g., the number of cigarettes smoked or intake of foods with high fat or salt content), which might be associated with the onset of PTSD symptoms.

Conclusions

There is a continuing relationship between the severity of PTSD symptoms and plasma levels of endothelial dysfunction markers. This link may explain the association between the probability of developing cardiovascular disease and atherosclerosis and the traumatic events leading to developing PTSD at the level of the common inflammatory vascular response. More longitudinal studies are needed to assess the possible role of the traumatic event history and PTSD in the development of cardiovascular disease, as well as to investigate the relationship between the neuro-hormonal changes, such as adrenal sympathetic hyperactivity, hypothalamic-pituitary-adrenal axis dysfunction and hypercortisolaemia in the endothelial dysfunction of PTSD patients, as these neuroendocrine factors could directly or indirectly affect endothelial function.

Conflict of interest

The authors declare they have no conflict of interest.

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