ORIGINAL ARTICLES

Serum Triiodothyronine Elevation in Israeli Combat Veterans with Posttraumatic Stress Disorder: A Cross-Cultural Study

John Mason, Ronit Weizman, Nathaniel Laor, Sheila Wang, Ayala Schujovitsky, Pnina Abramovitz-Schneider, David Feiler, and Dennis Charney

This study examines the thyroid hormonal profile in Israeli combat veterans with posttraumatic stress disorder (PTSD) and compares it with the previously reported profile in American Vietnam combat veterans with PTSD. Eleven male combat veterans with PTSD were compared with 11 normal subjects. Thyroid function was evaluated by the measurement of serum total triiodothyronine (TT3), free triiodothyronine (FT3), total thyroxine (TT4), free thyroxine (FT4), thyroxine-binding globulin (TBG), and thyroid-stimulating hormone (TSH). The mean total T3 level in the Israeli PTSD patients (160.5 ng/dL) was significantly elevated ($t = 2.53$, $p < .02$) *above that of the comparison group (135.5 ng/dL). Total T3 mean levels were not significantly different between the Israeli PTSD group and two American PTSD groups, but all three PTSD groups had significantly higher total T3 levels than both Israeli and American comparison groups. This preliminary study indicates that T3 elevation in combat-related PTSD may extend across cultures and suggests that further comparison of Israeli and American PTSD and normal groups may be useful in evaluating the significance and implications of the unusual alterations in the thyroid system in PTSD.*

Key Words: PTSD, stress, thyroid, triiodothyronine, thyroxine, TBG, Israel

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Introduction

There is increasing evidence that posttraumatic stress disorder (PTSD) in American Vietnam combat veterans is associated with an unusual pattern of hormonal alterations involving the cortisol, norepinephrine, epinephrine, testosterone, and thyroid systems (Mason et al 1986, 1990a, b, and c, 1994; Kosten et al 1987). Perhaps the most striking and consistent of these hormonal changes are those observed in the thyroid system, particularly the presence of sustained marked elevations of serum total triiodothyronine (T3) levels recently reported in a large sample of 96 PTSD patients (Mason et al 1994). Significant, but less marked elevations were also observed in the levels of free T3, total thyroxine (T4), and thyroid-binding globulin

From Yale University School of Medicine, National Center for PTSD, Clinical Neuroscience Division, VA Medical Center, West Haven, Connecticut (JM, SW, DC); Tel Aviv–Brull CMHC, Center for Trauma and Human Development, and Sackler Faculty of Medicine, Tel Aviv, Israel (RW, NL, AS, PAS, DF); and Yale Child Study Center, New Haven, Connecticut (NL).

Address reprint requests to John W. Mason, MD, VA Medical Center/116A, West Haven, CT 06516.

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(TBG), along with an absence of free T4 elevation, so that the overall thyroid profile suggests that there may be increased peripheral conversion of T4 to T3 and increased thyroid hormone binding in this disorder (Mason et al 1994).

In pursuing the investigation of the clinical significance of these hormonal findings, it appeared that a cross-cultural approach involving a comparison between Israeli and American patients with combat-related PTSD might be useful, not only for testing replicability of the findings in a general way, but also to see if differences in the clinical features of PTSD between the two cultures might be linked to the thyroid hormonal profile. It has been reported, for example, that the absence of alcohol and other substance abuse, or the absence of antisocial behavior, in Israeli PTSD patients are in striking contrast to the prevalence of these features in American Vietnam veterans with PTSD (Lerer et al 1987). As a first step in developing this cross-cultural approach, the present pilot study of Israeli combat veterans with PTSD and Israeli normal subjects was performed to determine if there were any significant alterations in thyroid hormonal profile in the Israeli PTSD sample.

Methods and Materials

Eleven male combat veterans with PTSD and 11 male normal subjects were studied. All patients were recruited from the PTSD unit in the Brull CMHC, three as outpatients and eight as inpatients. Informed consent was obtained after the procedures were fully explained. Diagnosis of PTSD was established on the basis of DSM-III-R criteria, using the Structured Clinical Interview for DSM-III-R (SCID-P) (Spitzer et al 1990). Severity of illness was assessed with the Revised PTSD Inventory, using a rating scale of 1–4 (Solomon et al 1993), and the Impact of Events Scale (IES), using a 1–4 scale (Horowitz et al 1979). The mean ± SD level for the PTSD Inventory sum was 45.3 ± 8.8, and for the IES it was 38.5 ± 9.0. The age range was 27–54 years and all patients had suffered from the disorder for at least 10 years. Six of the patients were medication-free, whereas the remaining five were under phenelzine treatment (45–60 mg) for more than 2 months. The patients were compared to a group of 11 normal male subjects who were closely matched in age and demographic factors. All comparison subjects were interviewed using the SCID-P and exclusion criteria included alcohol use, drug use, and current or past psychopathology. Blood samples were collected between 8 and 9 AM from all patients and comparison subjects, and the serum was divided into three 1.5-mL aliquots and frozen at −20°C until it was transported in dry ice overnight to West Haven, Connecticut, where the assays were performed.

Table 1. Thyroid Profile in Israeli PTSD Patients vs. Comparison (Comp) Subjects

	Comp (n = 11)	PTSD (n = 11)	t =	p <
Total T3 (ng/dL)	135.5 ± 15.8	160.5 ± 27.3	2.53	0.02[a]
Free T3 (pg/mL)	3.05 ± 0.51	3.13 ± 0.56	0.36	0.72
Total T4 (μg/mL)	8.64 ± 1.47	9.47 ± 1.26	1.43	0.16
Free T4 (ng/dL)	1.33 ± 0.24	1.46 ± 0.18	1.41	0.17
TBG (μg/mL)	26.6 ± 4.1	28.2 ± 5.1	0.79	0.44
TSH (μIU/mL)	2.28 ± 1.60	1.83 ± 1.35	0.70	0.49
T3/T4 ratio	105.8 ± 22.1	112.3 ± 28.4	0.60	0.56

Units of variance = SD.
[a] Statistically significant.

Serum total T3, total T4, and free T4 levels were measured by radioimmunoassay (RIA) procedures, using kits prepared by the Incstar Corporation, Stillwater, MN. The interassay coefficient of variation in our lab was 6.0% for total T3, 3.7% for total T4, and 4.2% for free T4. Serum free T3 levels were measured by an RIA kit prepared by the Diagnostic Products Corporation, Los Angeles, CA. The interassay coefficient of variation for this procedure in our lab was 2.7%. The serum TBG and thyroid-stimulating hormone (TSH) procedures involved RIA kits from Incstar with interassay coefficients of variation, respectively, of 3.0% and 4.0% in our laboratory.

Results

The mean ± standard deviation of the mean values for all assays in both patient and comparison groups are summarized in Table 1. Analysis with a two-tailed unpaired t test reveals that the mean total T3 value (160.5 ng/dL) of the PTSD patients is significantly elevated over the value (135.5 ng/dL) of the comparison subjects (t = 2.53, p < .02). None of the remaining hormonal measurements shows significant differences between the two groups, although there appears to be a trend toward both total and free T4 also being elevated in the PTSD patients. An analysis of total T3 levels in those PTSD patients on medication (158.5 ± 21.8 ng/dL) versus those off medication (163.0 ± 35.4 ng/dL) revealed no significant difference (t = .25, p < .8). Similar analyses also revealed no significant differences between the medication versus the nonmedication subgroups for any of the other thyroid measures.

Figure 1 shows the raw total T3 data on the two Israeli groups and compares them with previously reported values (Mason et al 1994) in two regionally different American samples of Vietnam veterans with PTSD: group PTSD-2 from Menlo Park, California (n = 24), and group

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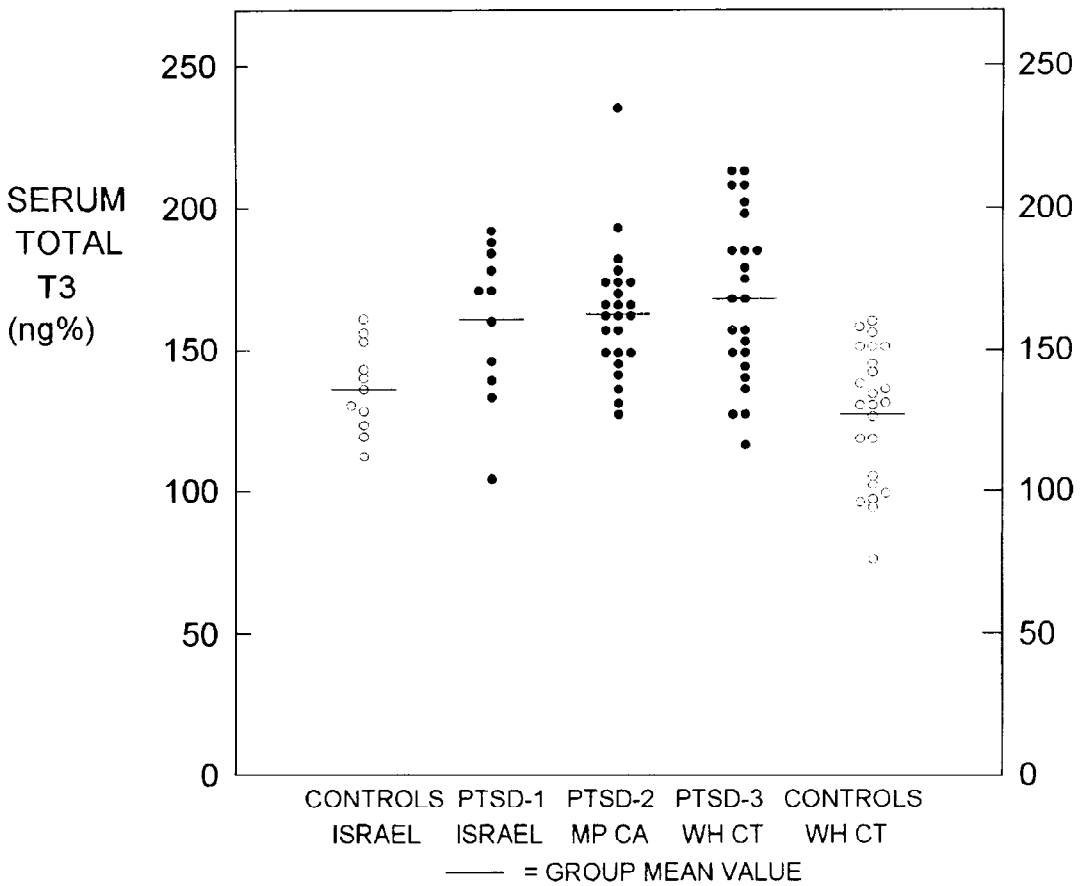

Figure 1. Total T3 elevations in three diverse regional samples of PTSD patients. The three PTSD patient groups do not differ significantly from each other, but all are significantly elevated above both comparison groups (F = 11.39, df = 4,89, $p < .0001$). MP CA = Menlo Park, California; WH CT = West Haven, Connecticut.

PTSD-3 from West Haven, Connecticut (n = 24), along with a healthy comparison group from West Haven (n = 24). A one-way analysis of variance (ANOVA) and Duncan test reveal that all three PTSD groups are significantly elevated above both of the normal comparison groups (F = 11.39, df = 4,89, $p < .0001$; COMPAR-Israel = COMPAR-WH < PTSD-1 = PTSD-2 = PTSD-3).

Discussion

The results of this preliminary study indicate that the elevation of total T3 levels in patients with combat-related PTSD may extend across cultures and not be restricted only to American veterans of the Vietnam war. In the interpretation of the findings of the present study, it is of interest that there are some differences in the thyroid profile between the two comparison groups, even though the somewhat higher total T3 mean level of the Israeli comparison group shown in Figure 1 is not significantly elevated over that of the American comparison group. In particular, the total T4 level in the Israeli comparison group (8.64 ± 1.47 μg/dL) is significantly elevated (t = 3.68, $p < .001$) above that of the American comparison group (6.75 ± 0.28 μg/dL). This observation suggests the possibility that the Israeli comparison subjects, who were personnel at the mental health center, may have been experiencing a greater degree of stress exposure than the American comparison subjects.

A further observation lending support to this possibility is that a comparison of the Israeli PTSD group with the American healthy comparison group reveals significant elevations in the PTSD group not only in the levels of total T3 (t = 3.71, $p < .001$), but also of free T3 (t = 2.62, $p < .01$), of total T4 (t = 5.57, $p < .0001$), of TBG (t = 4.89, $p < .0001$), and of the total T3/free T4 ratio (t = 2.51, $p < .02$), but *not* of free T4 (t = .68, $p < .5$). This overall profile of thyroid alterations is exactly the same as that previously reported in the large American sample of PTSD patients and appears to support the hypothesis that

there is both an increased conversion of T4 to T3 and an increase in thyroid hormone binding in this disorder (Mason et al 1994).

In this preliminary study, it was not possible to obtain 24-hour urine samples to determine if the Israeli PTSD patients show elevations in catecholamine levels similar to those reported in American PTSD patients (Kosten et al 1987). This is an important consideration since elevated peripheral catecholamine levels are believed to promote increased conversion of T4 to T3 (Mason et al 1994), and demonstration of elevated catecholamine levels would provide further support for the increased conversion hypothesis in relation to the Israeli PTSD sample. The present findings provide some encouragement for further cross-cultural comparison of Israeli and American PTSD patient samples, with future studies involving larger samples of both Israeli PTSD patients and normal subjects, the addition of catecholamine, cortisol, and testosterone assays for a broader view of hormonal profile, and the assessment of psychological and clinical features of PTSD patients and comparison subjects, which may differ between the two cultures, and which, in turn, may relate to possible differing qualitative or quantitative features in hormonal profile.

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