

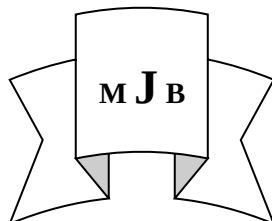
## Serum Testosterone and Prolactin in Posttraumatic Stress Disorder for Iraqi Terror Attack Victims

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### Abstract

**Background:** Abnormal levels of testosterone and prolactin have been reported in various psychiatric disorders and the important roles of in the regulation of many processes in human metabolism have been described.

**Objective:** Investigate the hormonal changes in posttraumatic stress disorder (PTSD) patients and control group.

**Patients and Methods:** Eighty two males witnessed on explosion occurred at 10<sup>th</sup> June 2010 in Hilla city of Iraq, as well as thirty five males apparently healthy persons as a control groups. Participants were grouped to four groups according to PTSD Checklist (PCL) scores. Total testosterone, free testosterone, and prolactin (PRL) were determined using ELISA.

**Results:** Total testosterone, free testosterone, and PRL showed an insignificant decreased in all groups of PTSD patients, when compared to control group. There is negative correlation between each of total testosterone, free testosterone, and PRL with severity of PTSD.

**Conclusion:** Results of present study may indicate that there are inhibition of hypothalamic-pituitary-gonadal (HPG) and hypothalamic-pituitary-prolactin (HPP) axes in PTSD patients.

**Key Word:** PTSD, Testosterone, Prolactin, HPG, HPP

تستوستيرون وبرولاكتين المصل في مرضى اضطراب ما بعد الصدمة لضحايا العمليات  
الارهابية في العراق

### الخلاصة

**الخلفية:** لوحظ في العديد من الامراض النفسية مستويات غير سوية لكل من هرموني التستوستيرون والبرولاكتين ولهما دورا مهما في تنظيم العديد من العمليات الايضية في جسم الانسان.

**الاهداف:** التقصي عن التغيرات الهرمونية في مرضى اضطراب ما بعد الصدمة.

**المرضى والطرق:** شملت الدراسة اثنان وثمانون رجلا ممن شهدوا الانفجار الحاصل في العاشر من حزيران ٢٠١٠ في مدينة الحلة-العراق وخمسة وثلاثون رجلا سليما ظاهريا كمجموعة سيطرة. قسم المشاركون الى اربعة مجموعات طبقا لدرجات لائحة اضطراب ما بعد الصدمة . قدر التستوستيرون الكلي والحر والبرولاكتين بتقنية الاليزا.

**النتائج:** اظهرت النتائج انخفاضا غير معنويا في مستويات كل من التستوستيرون الكلي والحر والبرولاكتين عند مقارنتها مع تلك النتائج المستحصلة لمجموعة السيطرة. ولوحظت علاقة سالبة بين كل من مستويات التستوستيرون الكلي والحر والبرولاكتين شدة المرض.

**الاستنتاج:** تدل نتائج الدراسة على تثبيط كل من المحورين الهرمونيين HPG و HPP عند المرضى باضطراب ما بعد الصدمة.

**الكلمات المفتاحية:** اضطراب ما بعد الصدمة، التستوستيرون ، البرولاكتين ، HPG ، HPP.

## Introduction

**P**osttraumatic stress disorder (PTSD) is classified as an anxiety disorder within Diagnostic and Statistical Manual of Mental Disorders, 4<sup>th</sup> edition (DSM-IV). PTSD is defined as the development of symptoms following exposure to an extreme traumatic event. These symptoms are described as belonging to three distinct but interrelated symptom clusters: (1) re-experiencing, (2) avoidance and numbing, (3) and hyperarousal. Persons diagnosed with PTSD experience significant functional impairment, including increased risk for unemployment, disrupted relationships, and diminished physical health [1].

PTSD prevalence in adult Americans is reported to be 6.8% and the conditional risk for PTSD following trauma exposure ranges from 5 to 31% with interpersonal and combat trauma associated with relatively greater risk [2]. Although there were 75% of the population has experienced a traumatic event, only a minority of those individuals subsequently develop PTSD [3]. This finding suggests that certain persons have an underlying vulnerability to developing PTSD in the aftermath of trauma. Identifying those vulnerable individuals may allow for early and targeted intervention to prevent or reduce the symptoms and functional impairment associated with PTSD [1].

Testosterone a steroid hormone is the most potent naturally secreted androgen [4]. In normal post pubertal males, testosterone is secreted primarily by the testes with only a small amount derived from peripheral conversion of 4-androstene-3, 17-dione (ASD)[5].

Testosterone is responsible for the development of secondary sex characteristics, such as the accessory sex organs, the prostate seminal

vesicles and the growth of facial, deepening of the voice, increase of muscle mass, libido, pubic and axillary hair [4]. Testosterone measurements have been very helpful in evaluating hypogonadal states. High testosterone levels in males can be found in complete androgen resistance (testicular feminization). Low testosterone levels in males can be found in hypogonadism, orchidectomy, estrogen therapy, Klinefelter's syndrome, hypopituitarism, and hepatic cirrhosis [5].

An abnormal level of androgens has been reported in various psychiatric disorders and the important role of androgens in the regulation of human sexuality; aggression, cognition, emotions and personality have been illustrated [6]. Previous studies in the area of stress and the HPG system in humans indicate that circulating testosterone levels are suppressed by physical and psychological stress [7]. Many studies found low basal plasma testosterone levels in PTSD patients comparable with normal controls [6, 8]. However, other study indicates that basal testosterone levels in PTSD patients may be elevated in comparison with normal subjects, major depressive disorder patients and paranoid schizophrenia patients [6].

Prolactin (PRL) is another hormone plays a role in many biological processes such as reproduction, osmoregulation, growth development, metabolism, brain function and behavior, and immunoregulation. The major known target tissue for PRL is the mammary gland [9].

The regulation of PRL secretion is exclusive amongst the anterior pituitary gland hormones. Unlike many endocrine hormones, the major regulator (dopamine) of PRL secretion acts to suppress rather than to stimulate its release [10]. Any

compound that affects dopaminergic activity in the median eminence of the hypothalamus will also alter PRL secretion [11].

The assay of PRL levels is helpful in diagnosing hypothalamic-pituitary disorders [12]. Microadenomas (small pituitary tumors) may cause hyperprolactinemia, which is sometimes related with male impotence. Elevated PRL levels are commonly associated with galactorrhea and amenorrhea [13].

PRL levels have been shown to be increased by estrogens, TRH, and several drugs affecting dopaminergic mechanisms [14]. PRL levels are raised in renal disease and hypothyroidism, and in some situations of stress, exercise, and hypoglycemia. Additionally, the release of PRL is episodic and demonstrates diurnal variation [15]. Also, many studies were done to investigate PRL levels in psychiatric disorder and show elevated levels in serum PRL in patients with schizophrenia [16], physical or emotional stress [17], and depression [18].

In the present study, we try to study the hormonal changes in male's sex hormones testosterone and stress hormone PRL in patients with PTSD and healthy control group. To our knowledge, no previous study concerning this issue has carried out in Iraqi population.

### **Patients and Methods**

**Patients:** Eighty two males who were witnessed on explosion occurred at 10<sup>th</sup> June 2010 at the exit of public employees in the State Company for Textile Industries in Hilla city of Iraq. All these subjects are employees in the State Company for Textile Industries, as well as thirty five males who are apparently healthy were used as control groups.

Diagnosis of patients was made according to trained psychologist raters

according to the DSM-IV criteria using the Structured Clinical Interview for DSM-IV and the Clinician Administered PTSD Scale (CAPS), and by use PTSD Checklist (PCL) scores self-reported. The PCL is a self-report questionnaire consisting of 17 DSM-IV PTSD symptoms. They are rated on a six-point scale ranging from "not at all" to "extremely." Items are added to obtain a total score. The higher the score, the more symptoms are present. A cutoff score of 50 was used for this analysis to indicate PTSD status [19].

Participants were categorized to four groups according to PCL scores:  $\geq 50$  (A), 26-49 (B),  $\leq 25$  (C), and control group (D).

Five milliliters of overnight fasting blood were drawn at 8:00-8:30 am and allowed to clot for 15 minutes. Serum was obtained by centrifuging for 10 minutes at a relative centrifugal force (RCF) 2000 X g.

**Hormones Analysis:** Total testosterone, free testosterone, and PRL, were determined using ELISA technique according to manufacturer's manuals.

### **Statistical analysis**

All values were expressed as mean  $\pm$  standard deviation (SD). Student's t-test was used to estimate differences between the groups, and the differences were considered significant when the probability (P) was  $P < 0.05$ .

Analysis of variance (ANOVA) was used to observe the difference among the groups.

The correlation between two variables was determined using Pearson's correlation coefficients with 95% confidence interval.

### **Results**

The ages of patient with PTSD and healthy controls subject to present study are shown in Table 1.

**Table 1** Age of Patients with PTSD and Healthy Controls.

|                         | Group A | Group B | Group C | Group D |
|-------------------------|---------|---------|---------|---------|
| <b>Age Mean (years)</b> | 46.78   | 44.31   | 44      | 43.60   |
| <b>± SD</b>             | 6.28    | 5.64    | 5.16    | 7.28    |
| <b>P</b>                | 0.11    | 0.69    | 0.81    |         |
| <b>CV%</b>              | 13.42   | 12.74   | 11.74   | 16.71   |
| <b>± SE</b>             | 0.27    | 0.17    | 0.13    | 0.17    |
| <b>95% C.I.</b>         | 37-57   | 35-61   | 36-55   | 34-58   |

Where SD = standard deviation, P = probability, CV% = coefficient of variation percentage, and SE = standard error, C.I.= confidence interval.

There are insignificant differences in mean age of patients with PTSD when compared with control group, and ANOVA showed no differences among patients groups.

Table 2 shows the clinical variables of PCL symptoms scores and the four subscales of patients with PTSD.

**Table 2** Clinical variables of PCL symptoms scores and the four subscales of patients with PTSD.

|                            | Group A |      | Group B |      | Group C |      |
|----------------------------|---------|------|---------|------|---------|------|
|                            | Mean    | ±SD  | Mean    | ±SD  | Mean    | ±SD  |
| <b>Total Scores (1-95)</b> | 63.26   | 8.43 | 36.09   | 6.81 | 14.67   | 6.18 |
| <b>Reexperience (0-20)</b> | 14.26   | 3.64 | 8.87    | 3.14 | 3.62    | 2.03 |
| <b>Avoidance (0-35)</b>    | 20.17   | 6.21 | 11.36   | 4.34 | 4.35    | 2.72 |
| <b>Hyperarousal (0-30)</b> | 22.39   | 3.67 | 13.42   | 4.87 | 6.02    | 4.59 |
| <b>Duration (0-10)</b>     | 6.72    | 2.74 | 2.42    | 1.88 | 0.69    | 1.01 |

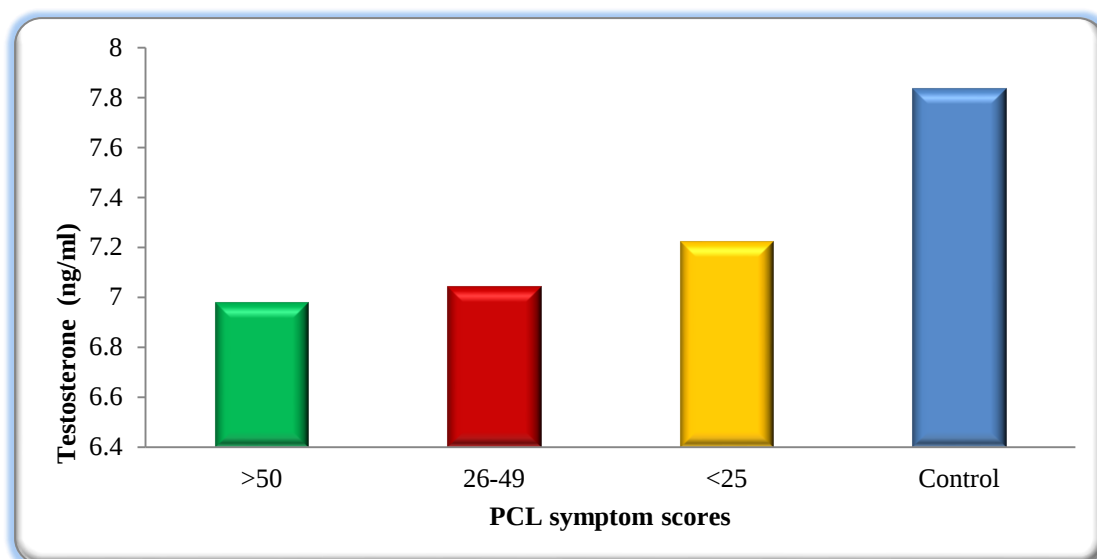
ANOVA shows highly significant difference in PCL symptoms scores with ( $P<0.000$ ) between group A and both of groups B and C in each of clinical variables of symptoms: reexperience, avoidance, hyperarousal and duration.

Total and free testosterone concentrations in the present study found to be insignificantly decreased in patients groups with PTSD when

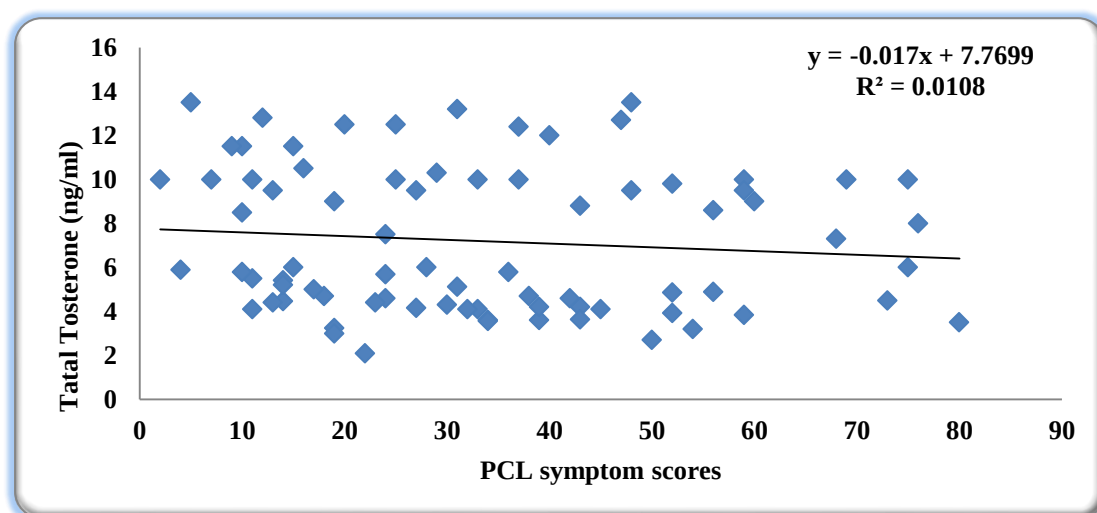
compared with those of healthy control group as shown in Table 3 and Table 4, respectively. ANOVA showed no differences among patients groups. Male's total and free testosterone concentrations were decreased with severity of PTSD, and there are negative correlation among total and free testosterone levels and severity of PTSD, as shown in figures 1 and 2, 3 and 4.

**Table 3** Total testosterone concentration in PTSD patients and healthy control.

|                                        | Group A   | Group B   | Group C   | Group D   |
|----------------------------------------|-----------|-----------|-----------|-----------|
| <b>Mean Total Testosterone (ng/ml)</b> | 6.98      | 7.04      | 7.23      | 7.84      |
| <b>± SD</b>                            | 2.62      | 3.52      | 3.44      | 3.12      |
| <b>P</b>                               | 0.32      | 0.36      | 0.45      |           |
| <b>CV%</b>                             | 37.57     | 49.91     | 47.63     | 39.76     |
| <b>± SE</b>                            | 0.11      | 0.11      | 0.09      | 0.07      |
| <b>95% C.I.</b>                        | 5.63-8.31 | 5.68-8.40 | 6.02-8.42 | 6.89-9.13 |



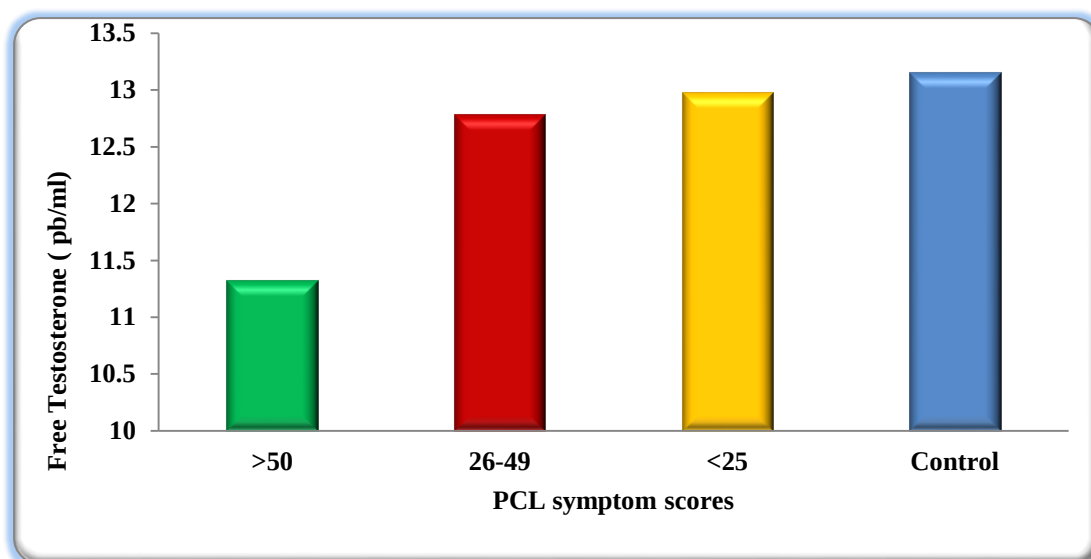
**Figure 1** Total testosterone concentration in PTSD patients and healthy control.



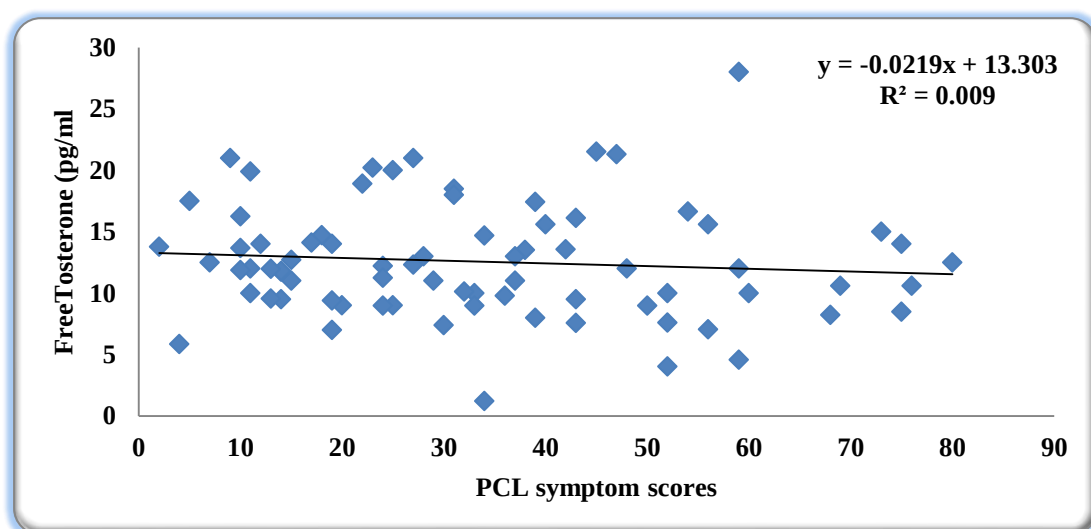
**Figures 2** Correlation between PCL symptom scores and total testosterone level ( $r = -0.1039$ ) ( $P = 0.365$ )

**Table 4** Free concentration in PTSD patients and healthy control.

|                                | Group A    | Group B     | Group C     | Group D     |
|--------------------------------|------------|-------------|-------------|-------------|
| Mean Free Testosterone (pg/ml) | 11.33      | 12.78       | 12.98       | 13.16       |
| ± SD (pg/ml)                   | 5.30       | 4.82        | 3.94        | 4.40        |
| P                              | 0.24       | 0.76        | 0.87        |             |
| CV%                            | 46.80      | 37.74       | 30.35       | 33.48       |
| ± SE                           | 0.23       | 0.15        | 0.11        | 0.10        |
| 95% C.I.                       | 8.61-14.03 | 10.87-14.68 | 11.56-14.40 | 11.51-14.80 |



**Figure 3** Free testosterone concentration in PTSD patients and healthy control.



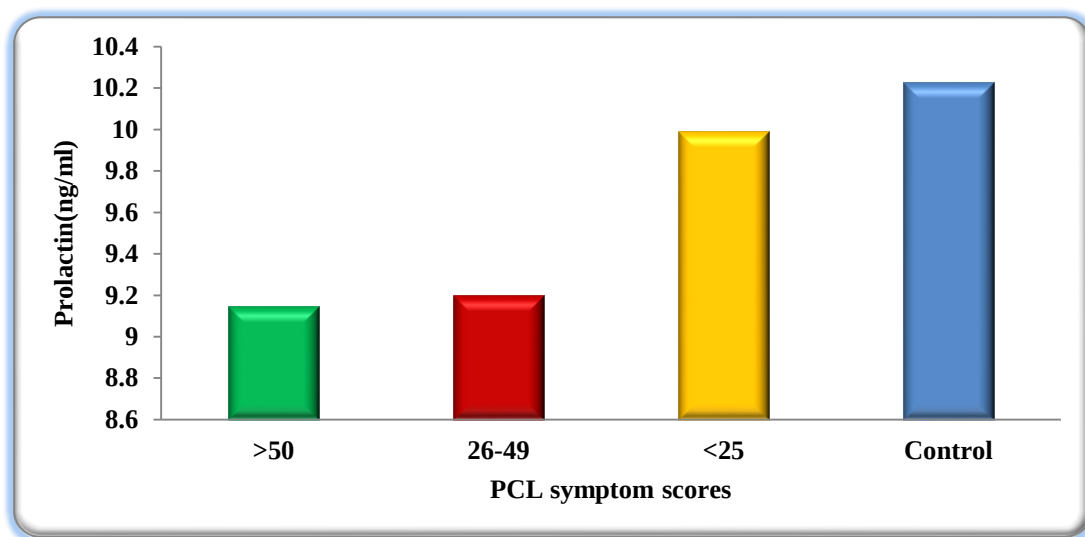
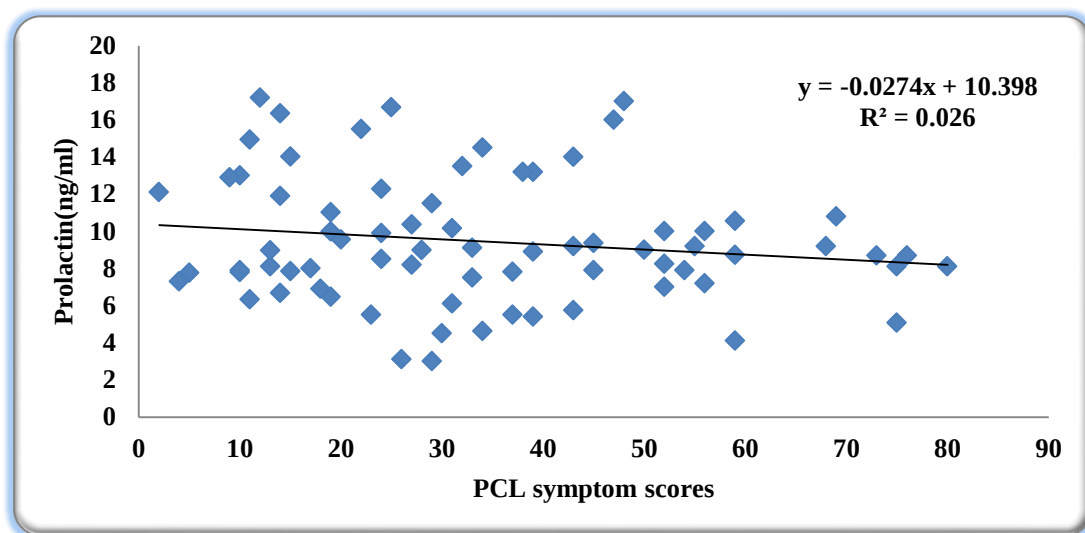
**Figures 4** Correlation between PCL symptom scores and free testosterone level ( $r = -0.09486$ ) ( $P = 0.415$ )

PRL concentration in the present study found to be insignificantly decreased in patients groups with PTSD when compared with those of healthy control group, Table 5. ANOVA showed no

differences among patients groups. PRL concentration was decreased with severity of PTSD, and there are negative correlation between PRL level and severity of PTSD, as shown in figure 5 and 6.

**Table 5** PRL concentration in PTSD patients and healthy control.

|                  | Group A    | Group B    | Group C    | Group D    |
|------------------|------------|------------|------------|------------|
| Mean PRL (ng/ml) | 9.14       | 9.20       | 9.99       | 10.22      |
| ± SD (ng/ml)     | 2.83       | 3.88       | 3.70       | 3.81       |
| P                | 0.24       | 0.30       | 0.80       |            |
| CV%              | 30.94      | 42.22      | 37.07      | 37.26      |
| ± SE             | 0.12       | 0.12       | 0.10       | 0.09       |
| 95% C.I.         | 7.78-10.50 | 7.66-10.73 | 8.63-11.35 | 8.95-11.63 |

**Figure 5** PRL concentrations in PTSD patients and healthy control.**Figure 6** Correlation between PCL symptom scores and PRL level ( $r=-0.1612$ ) ( $P=0.108$ )

### Discussion

Results of present study is in agreement with results of Kreuz *et al.* who found reduced plasma testosterone levels in young soldiers in

Officer Candidate School during the early stressful part of the course as compared with the senior or relaxed phase, and attributed their finding to possibility of reflection an acute stress

response of the HPG axis [20]. Also, results of present study in concordance with results of Spivak *et al.* who correlate the decrease in serum testosterone with the avoidance symptoms of PTSD [8].

Earlier studies in the field of stress and the HPG system in humans indicate that circulating testosterone levels are suppressed by physical and psychological stress [7]. Other study in agreement with present study that were found low basal plasma testosterone levels in PTSD patients comparable with normal controls [8]. However, another study was not in agreement with present study and indicates that basal testosterone levels in PTSD patients may be elevated in comparison with normal subjects, major depressive disorder patients and paranoid schizophrenia patients [6].

Other clinical and epidemiological investigations were reported that PTSD often associates with other psychiatric disorders [21]. Those investigations showed that about 80% of PTSD patients met criteria for at least one other psychiatric disorder. Major depressive disorder and alcohol dependence are example of the most common comorbid conditions in PTSD patients [22], which is characterized by reduced levels of serum testosterone [23, 24]. This may explain the insignificant decrease in total and free testosterone levels in the present study.

Other study not in concordance with present study investigated soldiers with PTSD and without considering comorbid conditions, did not show any difference in testosterone levels in comparison to the controls. However, when they divided the same PTSD sample based on comorbid conditions, they showed that pure PTSD have significantly higher serum testosterone levels in comparison to PTSD comorbid with major depressive disorder, comorbid with alcohol dependence, or controls[25].

It is not expected to find one of stress hormones levels such as PRL to be decrease in a stressful disorder like PTSD. This result is agreed with Olff *et al.* study [26] which proposes that low PRL levels may give some indication that these are associated with a sensitized negative feedback system. Result of PRL in the present study is not consistent with other studies [27].

PRL is one of the components of HPA axis functioning, which has been shown to be altered in PTSD, Davis *et al.* report a decreased PRL response to a serotonin challenge in patients with PTSD compared to healthy controls. They also found a significant inverse correlation between the PRL response and PTSD symptomatology, especially the re-experiencing symptoms [28]. Activation of the HPA axis is a crucial event in the stress response and, through its complex interactions with other systems, particularly the immune system, and the HPA axis acts to maintain homeostasis. Stress-related disturbances in glucocorticoid signaling may interrupt the complex communication with the immune system, resulting in impaired immune regulation with opposing results such as chronic low-grade inflammation. PRL, which is immunostimulatory has been proposed to act as a glucocorticoid antagonist [29].

On the other hand, and contrasting to other endocrine hormones, the major regulator of PRL secretion is dopamine which acts to suppress rather than to stimulate its release [10]. Furthermore PRL level shows to be increased by estrogens, TRH, and several drugs affecting dopaminergic mechanisms [14]. The present study might explain the reason of prolactin depletion in PTSD patients in that the regulation of the axis includes the hypothalamus inhibitory effect mediated by dopamine [14].

Clinical results that support a role for dopamine in the stress response and in PTSD involve the high rates of psychotic symptoms observed among individuals with PTSD [30].

Also, present study may attribute the insignificant decrease of PRL level in PTSD patients to the inhibitory effect of dopamine that may proposed to exceed the stimulatory effect of TRH.

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