CONCISE REPORT

Hypothalamic-pituitary-gonadal axis and cortisol in young women with primary fibromyalgia: the potential roles of depression, fatigue, and sleep disturbance in the occurrence of hypocortisolism

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Objectives: To investigate abnormalities of the hypothalamic-pituitary-gonadal (HPG) axis and cortisol concentrations in young women with primary fibromyalgia (FM); and to determine whether depression, fatigue, and sleep disturbance affect these hormones.

Methods: Follicle stimulating hormone (FSH), luteinising hormone (LH), oestradiol, progesterone, prolactin, and cortisol concentrations in 63 women with FM were compared with those in 38 matched healthy controls; all subjects aged <35 years. The depression rate was assessed by the Beck Depression Inventory (BDI) and patients with high and low BDI scores were compared. Additionally, patients were divided according to sleep disturbance and fatigue and compared both with healthy controls and within the group.

Results: No significant differences in FSH, LH, oestradiol, prolactin, and progesterone levels were found between patients with FM and controls, but cortisol levels were significantly lower in patients than in controls ($p<0.05$). Cortisol levels in patients with high BDI scores, fatigue, and sleep disturbance were significantly lower than in controls ($p<0.05$). Correlation between cortisol levels and number of tender points in all patients was significant ($r=-0.32$, $p<0.05$).

Conclusion: Despite low cortisol concentrations in young women with FM, there is no abnormality in HPG axis hormones. Because fatigue, depression rate, sleep disturbance, and mean age of patients affect cortisol levels, these variables should be taken into account in future investigations.

Fibromyalgia (FM) is a clinical entity of unknown aetiology. Although several mechanisms have been proposed for the aetiopathogenesis, these are still obscure. Some current aetiological hypotheses suggest that FM is a rheumatoid-like disease or a disorder of muscular abnormality or repair; that it results from aberrant mechanisms of peripheral pain; that it is a psychoneuroendocrine-immune disorder; a psychomatic disorder; or a psychiatric disorder related to major depression.[1] Additionally, a few studies have examined the inflammatory response system in FM.[2–4]

Although most patients with FM are women, only a few investigations have paid attention to the changes of sex hormones in FM.[5–7] Riedel *et al* investigated female patients with FM and controls who were all in their follicular phase.[5] They found that patients with FM have significantly lower oestrogen levels despite raised follicle stimulating hormone (FSH) levels. Korszun *et al* and Akkus *et al* found no differences in values of FSH and luteinising hormone (LH) in patients with FM.[6 7]

Stress has been shown to inhibit gonadotrophic releasing hormone and LH pulsatile secretion.[8] FM is often viewed as a stress related disorder, and abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis have been found in FM. The central stress axis, the HPA axis, seems to have an important role in FM. Some studies have suggested that patients with FM have decreased function of the HPA. Reduced 24 hour urine free cortisol levels have been reported in subjects with FM compared with healthy controls or subjects with rheumatoid arthritis.[9 10]

In previous studies of FM both axes were not examined in the same patients. As far as we know, this is the first study of both the hypothalamic-pituitary-gonadal (HPG) axis and cortisol, which is the most important hormone of the HPA axis in young women with FM; it evaluates effects of the depression rate, fatigue, and sleep disturbance on both the HPG and HPA axes in the same patients. We aimed at investigating abnormalities of the HPG axis and cortisol concentrations in young women with primary FM; and at determining whether the depression rate, fatigue, and sleep disturbance had any effect on these hormones.

SUBJECTS AND METHODS

A total of 101 subjects participated in this study—38 healthy volunteers and 63 patients with FM, recruited from our department. All subjects were aged <35 years and patients fulfilled the American College of Rheumatology (ACR) criteria for FM. The Human Studies Research Committee of the University of Dicle, Diyarbakır, approved all procedures and written informed consent was obtained from each subject before inclusion in the study.

Major clinical conditions other than FM were excluded by physical examination and laboratory investigations of routine blood cells and differentials, red blood cells, packed cell volume and haemoglobin, baseline thyroid stimulating hormone, and antinuclear autoantibodies.

Exclusion criteria for patients with FM and healthy controls were (*a*) recent or past history of psychiatric disorders—for example, major depressive disorder, alcohol dependence, substance abuse, schizophrenic or paranoid disorder, personality disorder, and somatoform disorder; (*b*) immunocompromised subjects; (*c*) subjects with neurological, inflammatory, endocrine or clinically significant chronic

Abbreviations: ACR, American College of Rheumatology; BDI, Beck Depression Inventory; FM, fibromyalgia, FSH, follicle stimulating hormone; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; LH, luteinising hormone

Table 1 Serum hormones, tender points, and age in healthy volunteers (HV) and patients with fibromyalgia (FM) with (+D) and without (−D) a Beck Depression Inventory Scale score ⩾17

	All FM (n = 63)	FM−D (n = 31)	FM+D (n = 32)	HV (n = 38)
Age (years)	29.1 (7.6)	28.3 (8.1)	29.8 (7.2)	29.5 (7.3)
BDI score	22.9 (12.5)*	12.9 (4.8)	33.0 (9.3)*	13.7 (5.3)
Tender points (n)	12.3 (1.6)*	11.6 (0.8)*†	13.1 (1.8)*	1.5 (1.6)
Luteinising hormone (IU/l)	9 (9)	12 (11)*†	6 (5)	7 (5)
Follicle stimulating hormone (IU/l)	6 (3)	6 (4)	6 (3)	6 (7)
Progesterone (nmol/l)	14 (20)	14 (16)	14 (26)	10 (12)
Oestradiol (pmol/l)	430 (310)	470 (270)	390 (350)	310 (180)
Prolactin (μg/l)	25 (27)	32 (37)	18 (8)	18 (10)
Cortisol (nmol/l)	300 (140)*	330 (150)	280 (140)*	380 (180)

Values are shown as mean (SD).
*Significantly different from HV ($p<0.05$); † significantly different from patients with FM+D ($p<0.05$).

disease, such as diabetes mellitus, rheumatoid arthritis, inflammatory bowel disease, and organic brain disorders; (*d*) abnormal liver function tests, such as serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and γ-glutamyltranspeptidase; and (*e*) pregnant women. All subjects and controls had normal menstrual cycles and were not taking the contraceptive pill.

All subjects were free of infection, inflammatory or allergic reactions for at least 2 weeks before blood sampling and free of drugs known to affect immune or endocrine functions and of hormonal preparations. None of the 38 healthy volunteers fulfilled ACR criteria for FM and none was a regular drinker or had ever taken psychotropic drugs. Each patient had normal findings on radiography of the chest, hands, feet, and sacroiliac joints.

Blood samples were collected in the early morning (8 30–10 30 am) after an all night fast and plasma was separated immediately by centrifugation; the serum samples obtained were stored at −20℃ until required for hormonal assaying. All hormones were assayed by the ''Electro Chemil Luminescence Immunoassay (ECLIA)'' (Roche, 1010/1020 Elecsys Systems Immunoassay) method.

Clinical assessments were carried out on the same morning as the blood collections. The depression rate was assessed by the Beck Depression Inventory (BDI) in all patients and controls. Patients with FM were divided into two groups according to a BDI score ⩾17 or <17. Additionally, patients were divided according to sleep disturbance and fatigue and compared with both healthy controls and within group.

Statistical analyses

Statistical significance was tested using one way analysis of variance and post hoc Bonferroni test for multiple group comparisons. Pearson's correlation test was used for correlation analysis. All statistical tests were two sided; $p<0.05$ was considered to be significant. Results are expressed as the mean (SD).

RESULTS

Mean ages of patients and controls were 29.1 (7.6) and 29.5 (7.3), respectively. In this study, high BDI scores (⩾17), fatigue, and sleep disturbance were detected in 32 (51%), 35 (56%), and 37 (59%) young women with FM, respectively. There were no significant differences in FSH, LH, oestradiol, prolactin, and progesterone levels between patients with FM and healthy controls, whereas cortisol levels were significantly lower in patients than in controls ($p<0.05$) (table 1).

When compared according to the depression rate, cortisol levels in patients with high depression scores were significantly lower than in controls ($p<0.05$). LH levels in patients with low depression scores were significantly higher than those both of patients with high depression scores and controls ($p<0.05$). Cortisol levels in patients with high depression scores were significantly lower than in controls ($p<0.05$) (table 1).

Cortisol levels in patients who had fatigue were significantly lower than in controls ($p<0.05$) The number of tender point and BDI scores in patients without fatigue were significantly higher than those of both patients with fatigue and controls ($p<0.05$). In patients who had sleep disturbance, cortisol levels were significantly lower and LH levels were significantly higher than in controls ($p<0.05$) (table 2).

A significant correlation between the number of tender points and cortisol levels ($r = -0.32$, $p<0.05$) and FSH levels ($r = 0.24$, $p<0.05$) was found in all patients.

Table 2 Measurements of serum hormones, tender points, and age in healthy volunteers (HV) and patients with fibromyalgia (FM) with (+F) and without (−F) fatigue, and FM with (+S) and without (−S) sleep disturbance

	FM−F (n = 28)	FM+F (n = 35)	FM−S (n = 26)	FM+S (n = 37)	HV (n = 38)
Age (years)	30.1 (9.6)	28.9 (8.8)	30.0 (9.4)	28.4 (9.3)	29.5 (7.3)
BDI score	31.5 (9.2)*†	20.4 (10.5)*	19.6 (10.3)*	25.7 (11.4)*‡	13.7 (5.3)
Tender points (n)	13.6 (2.1)*†	12.2 (1.1)*	11.8 (1.1)*	13.0 (1.9)*‡	1.5 (1.6)
Luteinising hormone (IU/l)	8 (8)	10 (12)	8 (7)	11 (13)*	7 (5)
Follicle stimulating hormone (IU/l)	7 (5)	7 (7)	5 (3)	8 (8)	6 (7)
Progesterone (nmol/l)	14 (20)	16 (24)	16 (26)	14 (22)	10 (12)
Oestradiol (pmol/l)	340 (240)	450 (490)	290 (210)	500 (460)	310 (180)
Prolactin (μg/l)	16 (7)	27 (29)	30 (35)	18 (12)	18 (10)
Cortisol (nmol/l)	330 (260)	290 (150)*	330 (140)	290 (130)*	380 (180)

Values are shown as mean (SD).
*Significantly different from HV ($p<0.05$); †Significantly different from patients with FM+F ($p<0.05$); ‡Significantly different from patients with FM+S ($p<0.05$).

DISCUSSION

Previous studies have suggested that the HPA axis is perturbed in FM,[10–12] and hyperreactive response to different stimuli of adrenocorticotrophic hormone and growth hormone was detected, whereas in the cortisol response a decrease occurred.[9 11] Crofford *et al* reported raised serum levels of 24 hour free cortisol, resulting in a loss of normal diurnal cortisol fluctuation, and with stimulation a brisk but lesser increase in cortisol level in FM.[9] A previous study by Griep *et al* had shown that neither basal levels nor stimulated levels of cortisol differed between the groups.[11] In a later study by the same group, mild hypocortisolaemia was seen.[12] Differences in methodology and sample characteristics may explain the difference between the results.

In our study, levels of reproductive HPG axis hormones did not differ significantly between young women with FM and controls. These findings are in agreement with those of Korszun *et al*, who reported data from nine patients with FM and eight with chronic fatigue syndrome.[8] However, LH levels in patients with low depression scores were significantly higher than those of patients with high depression scores and those of controls. In patients who had sleep disturbance, LH levels were significantly higher than in controls. These findings suggest that fatigue, depression rate, and sleep disturbance may have an effect on LH levels.

It is known that most patients with FM also have depressive symptoms and depressed patients with pain are not uncommon. Some investigators have therefore suggested a possible connection between FM and depression. Similarities between patients with FM and those with depression raise the possibility of a neuroendocrine relationship between these two disorders. It is unclear whether the depression develops as a reaction to the chronic pain or is an independent disease within the FM.[13]

In our study, in contrast with high BDI scores of patients with FM, circulating cortisol levels were significantly lower. This is in contrast with the hypercortisolism of classic major depression. In recent years, however, it has become increasingly apparent that depression is a heterogeneous condition from both a psychological and a physiological perspective.[14] Moreover, decreased HPA axis activity has been reported in some stress related states such as chronic fatigue syndrome, atypical and seasonal depression.[15] These results suggest that the depression which is seen in FM may be different from classic depression. Forms of depressive illness dominated by reduced energy, a reactive mood, and a reversal of the typical pattern of vegetative features seen in classic depression have been described.[14] There may be overlapping between symptoms of FM and those depressive subtypes or reactive form of depression in FM. This condition may explain hypocortisolism in patients with FM in this study.

In conclusion, our study suggests that in young women with FM, despite a low cortisol concentration, HPG axis hormones are normal, except for LH levels in patients with high depression rate and with sleep disturbance. Fatigue, depression rate, sleep disturbance, and mean age of the study group may have an effect on cortisol levels, or hypocortisolism may be a biological factor that contributes fatigue chronicity, a depressive state, and sleep disturbance. So, these variables should be taken into account in future investigations.

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