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Research Article

IS FIBROMYALGIA A SYNDROME OF HORMONAL IMBALANCE?

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ABSTRACT

Objectives: The present study was conducted to estimate cortisol and thyroid-stimulating hormone (TSH) levels in patients with fibromyalgia syndrome (FMS) and to find correlation if any between hormone levels and pain duration in FMS.

Methods: Plasma cortisol and TSH concentration were determined by electro chemiluminescence immunoassay in 89 female patients with FMS and 74 age-matched healthy women.

Results: No significant difference in TSH level was observed between FMS and healthy subjects. Ten patients had higher cortisol levels than the standard reference range, 48 patients with reduced cortisol and 31 patients with normal cortisol levels. No significant correlation was observed between pain duration and levels of cortisol.

Conclusion: The study has confirmed the equivocal data regarding cortisol/hypothalamic-pituitary-adrenal axis related dysfunction in FMS. To the best of our knowledge, it is the first Indian study on FMS which assessed the cortisol and TSH levels and their correlation with pain duration if any.

Keywords: Fibromyalgia syndrome, Cortisol, Thyroid-stimulating hormone.

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INTRODUCTION

Fibromyalgia syndrome (FMS) is characterized by chronic widespread pain and muscle tenderness and often accompanied by fatigue, sleep disturbance, and depressed mood [1,2]. FMS is more prevalent in women than in men (7:1) [3]. FMS patients report high levels of stressful life events [4] and daily nuisance [5,6] and frequently attribute the onset of their illness to stress, emotions, or trauma [7]. A recent study [8] on healthy subjects has also shown that psychological stress of their living state and work-associated stress persuade them toward high levels of stress. Furthermore, an animal study has reported that [9] acute noise stress exposure increases the levels of stress markers and causes changes in various parameters of immune functions. Many studies have implicated the role of hypothalamic-pituitary-adrenal (HPA) axis [10-13] and thyroid [14-19] in FMS. Research on the HPA axis in FMS has shown variations in cortisol levels [20], increased sensitivity to glucocorticoid feedback [21], and increased cortisol release in response to a stressor [22]. Cortisol which is a marker of stress follows a circadian rhythm with its elevated levels in the morning and decreased levels during the night. However, the altered functioning of HPA axis is reported to be an important factor in the perturbation of circadian symptoms of FMS. Studies have shown the blunting of normal diurnal cortisol rhythm, with elevated evening serum cortisol levels in FMS patients [23,24]. However, most of the studies have revealed low 24-h urinary free cortisol excretion, exaggerated adrenocorticotropic hormone (ACTH) release in response to corticotropin-releasing challenge, and abnormal diurnal rhythmicity in the secretion of cortisol [25]. The pattern of difference for basal circadian architecture of HPA axis hormones differs between patients with FMS and chronic fatigue syndrome (CFS) compared to their matched control group. The abnormalities in FMS patients are consistent with loss of HPA axis [26]; depression is due to the disturbance in the HPA axis [27].

Most patients with FM also have abnormal thyroid production [28,29] and utilization [30]. There is a line of collective evidence which indicates that inadequate thyroid hormone regulation, due to hypothyroidism (thyroid hormone deficiency) or peripheral resistance to thyroid hormone, may both be underlying mechanisms causing cellular thyroid deficiency [31]. Both abnormalities cause symptoms such as easy fatigability mainly through inadequate thyroid hormone regulation of gene transcription in the cells of affected tissues. Although the association between depression, anxiety, and thyroid autoimmunity is not fully understood [32-34], chronic emotional or physiologic stress associated with FM can cause significant increases or decreases in cortisol, reductions of T4 transport into cells, and reductions in peripheral conversion of T4 to T3. It has been reported that serum from individuals with significant physiologic stress inhibits the uptake and transport of T4 into the cell while the serum from non-physiological stress has no such effect [35]. Recently, investigators have examined the relationship between stimulating thyroid hormone (TSH) levels and cortisol in a preliminary study of young, healthy adults without known thyroid disease or other underlying health conditions [36]. The positive relationship between serum TSH and an earlier study reported that hypothyroid patients have elevated cortisol levels and suggest that hypercortisolemia in primary hypothyroidism is probably because of decreased metabolic clearance of cortisol and a speculative decrease in negative feedback effect of cortisol on the HP axis [37].

However, a number of conflicting studies have also emerged which fail to find evidence of cortisol and TSH dysregulation in FMS [12]. Altogether, the literature suggests that cortisol release may be abnormal in FMS, but the nature of the pathology remains poorly understood at present. Therefore, the aim of this study was to estimate the plasma cortisol and TSH levels in female patients with FMS and healthy controls and to find correlation if any between cortisol levels and pain duration in FMS.

METHODS

Ethical considerations

The protocol was approved by the Institute Ethics Committee, All India Institute of Medical Sciences (AIIMS), New Delhi (Ref No:

IESC/T-251/15.06.2013), and registered on Clinical Trial Registry India (Ref No: CTRI/2013/12/004228). A written informed consent was obtained from each participant before enrolment in the study.

Recruitment of FMS patients and healthy controls

Eighty-nine patients with FMS and 74 age-matched healthy control subjects wre participated in the study. All the study participants were female and inclusion criteria for age was 18-50 years. Patients with FMS were recruited from Rheumatology Clinic of AIIMS, New Delhi. Patients were diagnosed by their physician according to the criteria of the American College of Rheumatology [2]. All patients with FMS were diagnosed with widespread chronic musculoskeletal pain and increased sensitivity to palpation with no medical causes identified. The female control subjects were recruited from patients' relatives and AIIMS staff. Control subjects were not taking any psychiatric or psychotherapeutic treatment and did not suffer from any current chronic disorder or medical illness.

Exclusion criteria

Participants were excluded if they were pregnant or lactating, being treated with steroids, alcohol or drug dependence, current or lifetime psychosis, and bipolar disorder. Women with additional medical illnesses that could explain pain symptoms were also excluded. Patients who were unable to give informed written consent were also excluded from the study. The same exclusionary criteria were applied to the healthy volunteers.

Collection and storage of blood samples

Blood samples were collected in the morning time after overnight fasting and in the mid-luteal phase of the menstrual cycle. After catheterization of a superficial cubital vein with aseptic precautions and a recovery period of 15 min to avoid stress-induced bias, blood samples were directly obtained into heparinized blood collection tubes (Vacuette, Greiner Bio-One, Austria). The plasma was separated and stored at −80°C until further analysis.

Estimation of cortisol and TSH in blood plasma

The concentration of cortisol and TSH was determined utilizing cortisol and TSH assay kits (ELECSYS, Roche Diagnostics, Mannheim, Germany), respectively, by electrochemiluminescence immunoassay method, by utilizing Cobas e 411 immunoassay auto-analyzer (Roche Diagnostics, Germany). It is fully automated system for immunoassay analysis and works on the principle of electrochemiluminescence immunoassay. The protocol involved the use of 20 µL/50 ml of sample for TSH/cortisol, a biotinylated monoclonal TSH/cortisol-specific antibody, and a monoclonal TSH/cortisol-specific antibody labeled with a ruthenium complex reacted to form a sandwich complex. After addition of streptavidin-coated microparticles, the antigen-antibody complex binds to the microparticle solid phase through the interaction of biotin and streptavidin. The reaction mixture was aspirated into the measuring cell where the microparticles were magnetically captured onto the surface of the electrode. Unbound substances were then removed with washing buffer. Application of a voltage to the electrode then induced chemiluminescent emission which was measured by a photomultiplier. Results were determined through a built-in calibration curve provided by the manufacturer.

Statistical analyses

Statistical analyses were performed using GraphPad Prism Software Version 5.0. Statistical significance was tested using unpaired t-test/ Mann–Whitney test. Normality was assessed by Shapiro–Wilk normality tests. Correlation was assessed using Pearson/Spearman correlation test. All statistical tests were two sided and $p<0.05$ was considered to be statistically significant. Numerical variables were reported in terms of mean±standard deviation (SD).

RESULTS

Demographic data are presented in Table 1. There were no statistically significant differences in age, height, and body weight. TSH levels were comparable between healthy controls (2.26±1.82 µ IU/mL; mean±SD) and FMS patients (2.41±1.90 µ IU/mL).

As far as cortisol levels are concerned, higher cortisol levels were observed in ten patients (18.20±6.41µg/dL), while in 48 patients, cortisol levels (6.63±1.68 µg/dL) were lower and 31 patients had normal cortisol levels (11.47±1.35 µg/dL) (Table 2).

A correlation analysis of pain duration (7.06±4.23 years) and plasma cortisol levels showed no significant relationship between these parameters (Table 3 and Fig. 1).

DISCUSSION

In the present study, no significant difference was observed in TSH levels between healthy controls and FMS patients. 11.23% of patients had higher cortisol levels than the standard reference range, 54% of patients with reduced cortisol, and 34.83% of patients with normal cortisol levels. No significant correlation was observed between pain duration and levels of cortisol.

Table 1: General body parameters of healthy subjects and FMS patients

S. No	Parameters	Healthy subjects (n=74)	FMS patients (n=89)	p
1	Age (y)	38.61±8.01	40.39±7.99	0.15
2	Body weight (kg)	156.6±5.8	157.7±4.38	0.19
3	Height (cm)	62.0±7.98	63.62±7.63	0.21
4	Pain duration (y)	N/A	7.06±4.23	

Data are presented as mean±SD. FMS: Fibromyalgia syndrome, SD: Standard deviation

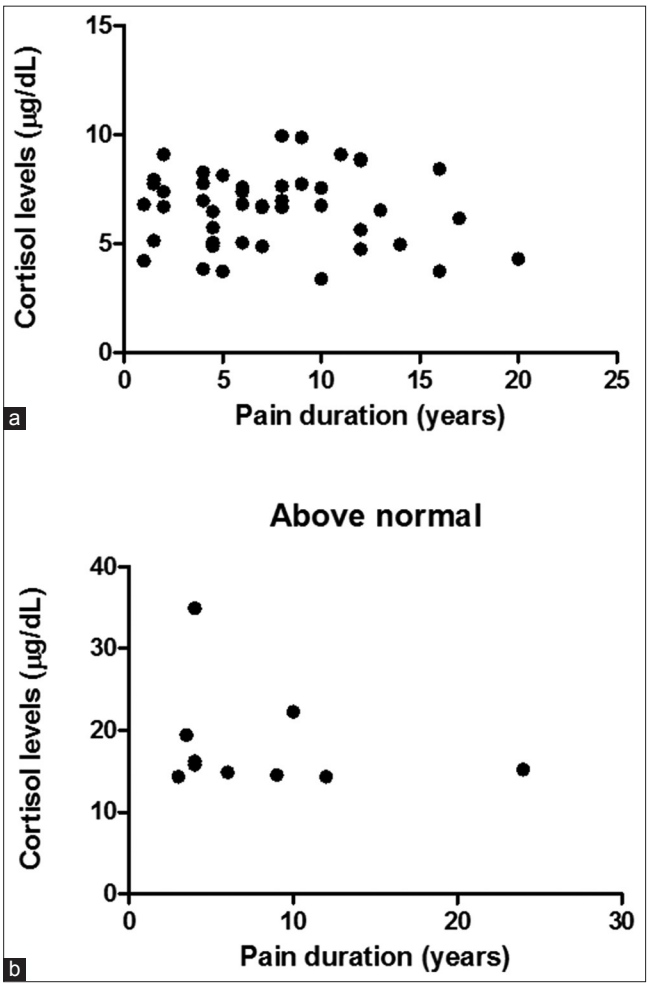

Fig. 1: Correlation between cortisol levels (a) below normal and (b) above normal and pain duration in FM syndrome patients

Table 2: Plasma cortisol and TSH levels of healthy subjects and FMS patients

Sr. No	Hormones	Range	Healthy subjects	FMS patients	p
1	TSH (μ IU/mL)		2.26±1.82 (n=79)	2.41±1.90 (n=89)	0.53
2	Cortisol (μg/dL)	Below normal	7.93±1.45 (n=13)	6.63±1.68 (n=48)	0.01
		Normal	11.86±1.16 (n=51)	11.47±1.35 (n=31)	0.17
		Above normal	19.96±6.07 (n=10)	18.20±6.41 (n=10)	0.36

Data are presented as mean±SD. TSH: Thyroid-stimulating hormone, FMS: Fibromyalgia syndrome, SD: Standard deviation

Table 3: The correlation between plasma cortisol levels and pain duration in patients with FMS

Sr. No	Pain duration versus cortisol levels	R	p
1	Below normal	−0.072	0.62
2	Normal	−0.179	0.33
3	Above normal	−0.15	0.68

FMS: Fibromyalgia syndrome

TSH level in FMS

Investigations of the HPA axis in FMS patients have revealed evidence of primary adrenal insufficiency. Altered pituitary releasing patterns of ACTH, TSH, growth hormone (GH), and subsequent abnormalities in hormone levels may contribute to the variety of symptoms seen in patients [38]. Thyroid hormonal profiles could be relevant for drug-dosage optimization. Its alteration may lead to malfunction in the physiological performance and associated with bad psychological effects [39].

In the present study, no significant difference was observed in TSH levels between healthy controls and FMS patients. Our results are in partial agreement with a recent study [40] which found no significant difference in the TSH concentration among 82% of FMS patients while only 18% FMS patients were found with elevated level of TSH which was probably due to the misdiagnosis of subclinical hypothyroidism as FM [40]. It has been found that the levels of thyroid hormones are usually in normal range even if the patients show some symptoms of hypothyroidism [41].

Cortisol abnormalities in FMS

Stress-related diseases are a significant cause of disorders in modern times, perhaps contributing to 75% of illness [42]. In the present study, we found lower cortisol levels in 54% of FMS patients. This seems to be consistent with other studies [43] which investigated abnormalities of hypothalamic-pituitary-gonadal axis hormones and cortisol concentrations in premenopausal women with CFS and find the effects of depression rate on these hormones. There are reports of significantly lower cortisol levels in FMS patients compared to controls [20]. Low levels of urinary free cortisol and a diminished cortisol response to corticotropin-releasing hormone (CRH) suggest an abnormal HPA axis [44]. Hypocortisolism is characterized by a blunted cortisol secretion, compromised HPA resilience and a triad of pain, fatigue, and stress sensitivity [45]. In support of this idea, women with FMS have lower urinary [10] and salivary cortisol levels [20] than healthy controls and less diurnal variability in comparison to individuals with rheumatoid arthritis (RA) [24]. In addition, core features of FMS, such as fatigue, pain, and psychological stress, have been associated with lower morning cortisol levels and blunted diurnal slopes [46-48]. Previous studies have suggested that HPA axis is perturbed in FMS [24,49,50] and hyperreactive response to different stimuli of ACTH and GH was detected, whereas in the cortisol response, a decrease observed [23,49]. The results of one earlier study also indicated lower 24-h urinary free cortisol and total plasma cortisol, but no differences were found between FMS patients and controls in plasma free cortisol [50]. Another report has shown raised serum levels of 24 h free cortisol, resulting in a loss of normal diurnal cortisol fluctuation, and with stimulation a rapid but lesser increase in cortisol level in FMS but reduced 24 h urine free cortisol levels have been reported in subjects with FM compared with healthy controls or subjects with RA [23,24]. A previous study had shown that neither basal levels nor stimulated levels of cortisol differed between both FMS patients and healthy controls [49]. FM patients also have an inability to suppress plasma cortisol levels in dexamethasone suppression tests [24,51] and adrenal hyporeactivity to CRH stimulation [49].

Differences in methodology and sample characteristics may explain the difference between our findings and results earlier studies. Notwithstanding the variability in cortisol sampling procedures and findings, it is accepted that there is a dysregulation of HPA functioning in patients with FM [22], resulting in alterations in levels of cortisol, CRH, GH, and thyroid hormones, which may have secondary effects on pain, fatigue, immune function, mood, and sleep [52].

Recent research indicates that FM patients exhibit hypocortisolism, particularly as an attenuated cortisol awakening response [53]. In the present study, 11% of FMS patients were having higher levels of cortisol hormone, while in 10 controls also, cortisol level was higher. In an earlier research [54], authors compared cortisol levels, diurnal cycles of cortisol, and reactivity of cortisol to psychological stress in FMS and RA patients. They found that FMS and RA patients had higher average cortisol levels than controls; however, there were no differences between the groups in diurnal cycles of cortisol or reactivity to psychological stress. The research on HPA functioning and cortisol levels in FMS patients is ambiguous [49]. There are a number of variables which complicates an accurate portrayal of HPA function, but variations in the methods used to collect cortisol samples, such as time of cortisol measurement (morning, afternoon, and evening), number of measurements per day (1–8, or continuous readings), and source (salivary, plasma, serum, or urinary) of cortisol, make it particularly difficult to derive a clear picture of HPA activity in FMS patients [27].

In the present study, we tried to systematically explore any possible correlation between pain duration and cortisol levels, but no significant correlation was found between pain duration and either lower or higher cortisol. HPA axis dysfunction has also been associated with psychological dysfunction, such as depression, and stress but not with pain in patients with FMS [27], indicating that the relationship between HPA function, pain, and psychological distress in FMS needs further examination.

There are some limitations of the present study that should be considered when interpreting the results. Although no significant correlation between cortisol and pain duration emerged, the duration of chronic pain of FMS patients may have affected the cortisol findings. We cannot completely rule out the possibility that unidentified differences between the studies are responsible for the observed difference in levels of cortisol. In this study, we examined the cortisol day profile only at single time point, which is also a limitation.

CONCLUSION

To the best of our literature search, it is the first Indian study on FMS which assessed the cortisol and TSH levels and their correlation with pain duration if any.

In our study, no significant difference in TSH was found between patients and healthy controls. No specific trend was observed for cortisol levels. The study has confirmed the equivocal data regarding cortisol/HPA axis related dysfunction in FMS. This might be one explanation for ambiguous findings in the literature. Future research should examine

the correlates of individual differences in cortisol rhythms, including social, psychological, genetic, and biological factors. More research is required for a better understanding of the pathophysiology of complex and stress-related disease as here mentioned. More research is needed to better understand cortisol diurnal rhythm in larger subgroups of FMS patients with distinct psychoendocrine patterns as this may help in better understanding the role of variation in symptoms of FMS and underlying pathophysiology.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest concerning the work reported in this paper.

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