Influence of cortisol and DHEA-S on pain and other symptoms in post menopausal women with fibromyalgia

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Abstract. Objective: This study aims to assess cortisol and dehydroepiandrosterone sulfate (DHEA-S) levels in post-menopausal women with FMS and correlate it with pain threshold and tolerance, depression and quality of life.

Methods: We conducted a cross sectional observational study of 17 women with FMS (FMS group), and 19 healthy volunteers (CT group). Algometry, the Beck Depression Index (BDI) and Fibromyalgia Impact Questionnaire (FIQ) were used. Blood samples were collected in the morning (8:00–9:30 am) to determine cortisol and DHEA-S plasmatic levels by chemiluminescence.

Results: Significant differences between groups were recorded for pain threshold and tolerance ($p < 0.0001$), BDI ($p < 0.0001$) and all FIQ parameters ($p < 0.0001$). No significant differences in cortisol levels were found between the two groups ($p = 0.325$). In the FMS group, a tangential effect was observed for DHEA-S ($p = 0.094$) and positive correlations were found between DHEA-S, pain threshold ($p = 0.017$) and pain tolerance ($p = 0.044$). No correlation was observed between cortisol and DHEA-S levels and the variables of depression and quality of life for either group.

Conclusions: There seems to be an influence of the decreased levels of DHEA-S and increased pain sensitivity in post-menopausal women with FMS.

Keywords: Fibromyalgia, cortisol, DHEA-S, pain, depression

1. Introduction

Clinical experience in physical rehabilitation services, associated with findings in the literature, show a history of patients with physical and psychological symptoms related to functional limitation and loss of quality of life. Complementary evaluations show no alteration in muscles, tendons or bone structure and laboratory tests indicate no substantial abnormalities. It is significant that the clinical condition of patients worsens and treatment progress decreases when they report physical or emotional stress. This clinical profile is typical of fibromyalgia syndrome (FMS), a non-inflammatory rheumatic disease of unknown etiology. Symptoms include diffuse and chronic pain and the presence of tender points, mostly in the axial skeleton [1,2].

Among the frequently associated symptoms are fatigue, sleep disturbances, morning stiffness, changes in pain perception, anxiety and depression [2]. When symptoms are present, FMS patients experience diffi-
culty performing physical activities, which negatively affects their quality of life [3–5]. FMS prevalence varies between 0.66% and 4.4% in the general population and is more common among women than men, particularly in the 35- to 60-year age group [6].

Due to the lack of complementary exams describing characteristic alterations, FMS diagnosis is based on clinical criteria. The American College of Rheumatology [1] (ACR) established diagnostic criteria for this syndrome in 1990. These include signs of intense muscle pain in different areas of the body (extensive pain) for at least three months, associated with increased sensitivity to pain in at least 11 of the 18 tender points. Other symptoms such as fatigue, depression, stress and sleep disturbances are also significant, but not essential for diagnosis [1,7].

Staud and Spaeth [8] described an abnormality in the central pain processing system, including temporal summation, as a possible cause for FMS. The persistence of nociceptive receptors in peripheral tissue may provoke plastic alterations in the central nervous system (CNS), causing central sensitization and greater pain sensitivity. Walker and Littlejohn [9] suggest that mental health problems, especially depression, may occur with musculoskeletal disturbances. Reciprocal relationships exist between depression, sleep disturbances, pain and physical incapacity, leading to a vicious cycle of poor mental and physical health.

In addition to pain, fatigue and depression, we found evidence of hormonal changes occurring with alterations in cortisol and adrenal steroid levels, such as dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S). Since this syndrome is highly common in perimenopausal and post-menopausal women, it is important to note the hormonal changes in this reproductive period, with low testosterone, progesterone, DHEA and DHEA-S [10,11]. Hormonal alterations occurring in the fertile, pre- and post-menopausal periods appear to influence FMS symptoms. This suggests that sexual hormones may play an important role in the pathogenesis and deterioration of FMS symptoms [10,12,13].

Pamuk et al. [12] report an increase and worsening of generalized pain, fatigue and other FMS symptoms in post-menopausal women. In the same study, the authors observed that the incidence of early menopause is significantly higher in FMS patients when compared with rheumatoid arthritis patients and healthy controls. The authors propose menopause as one of the contributing factors to FMS deterioration.

Some studies of women suffering from FMS show a correlation between low cortisol levels, pain and depression. This finding points to a relationship between daily variations in the release of cortisol and pain intensity. Women with FMS have low levels of adrenal androgens, changes in pain perception and increasing levels of muscular fatigue [14,15].

There are no previous studies evaluating levels of cortisol and DHEA-S in post-menopausal women with FMS who do not use hormone replacement and engage in physical therapies. Alterations in the production of sex hormones during this reproductive period should be considered. We aim to analyze possible changes in adrenocortical, cortisol and DHEA-S hormones using chemiluminescence, as well as their possible correlation with pain, depression and quality of life in post-menopausal women with FMS.

2. Methods

This is a cross-sectional, observational study. Participants were female volunteers clinically diagnosed with FMS living in the city of Natal, Brazil. All subjects consulted at the Medical Clinic of the Onofre Lopes University Hospital (Federal University of Rio Grande do Norte) and attended the Physiotherapy Teaching Clinic at the Potiguar University. The study was approved by the Research Ethics Committee of the Federal University of Rio Grande do Norte.

2.1. Experimental groups

A total of 17 patients were examined, aged 42–68 years, who met the 1990 ACR [1] criteria for the classification of FMS. The control group (CT) consisted of 19 healthy volunteers chosen randomly from hospital personnel and those accompanying patients.

The reduced number of FMS group subjects is due to the inclusion criteria adopted, namely: (a) medical diagnosis of FMS, (b) ability to understand the study objective and answer the questions, (c) being post-menopausal, (d) not using hormone replacement or other medications that affect the metabolism of sex hormones and cortisol, (e) not participating in physical therapy or rehabilitation programs in the previous month. The CT group met all the inclusion criteria except diagnosis of FMS and absence of both rheumatic and endocrinal disease. Exclusion criteria for both groups were: (a) proven cognitive deficit, such as dementia, (b) physical and/or organic difficulties, when these compromised questionnaire application and analgesic tests; (c) endocrine, rheumatic and/or autoim-
mune diseases including chronic fatigue syndrome, chronic pelvic pain, atypical depression, irritable bowel syndrome, rheumatoid arthritis, gout and lupus; (d) use of corticosteroids, analgesics, anti-inflammatoryatories, psychoactives and antidepressants; (e) history of serious psychiatric disorders, alcohol or stimulant dependence, schizophrenia and personality disorders.

All participants were free of infection, inflammation or allergies for at least two weeks before blood collection. Subjects were also asked if they had suffered any stressful experiences over that period, such as quarrels or receiving bad news, or if they had engaged in intense physical activity.

2.2. Hormonal measurements

Blood samples were collected in the early morning (08:00–09:30 am) after an all night fast (at least 8 hours). Three 15ml blood samples were taken at one-day intervals. Samples were centrifuged to obtain plasma and stored in a freezer at $-20^\circ$C for subsequent analysis of cortisol and DHEA-S concentrations. Hormone levels were determined in duplicate by chemoluminescence, using an Immulite 1000 Immunoassay System® and commercially available kits (Diagnostic Products Corporation – Immunolite Kits® – 2000, USA). Subjects also underwent hematology, lipid, hepatic and renal profiling. Variation coefficients were 2.20% for cortisol and 1.32% for DHEA-S. Evaluations of pain sensitivity, mood and quality of life were conducted on the first day of blood collection.

2.3. Evaluation of pain sensitivity and symptoms of FMS

Algometry was carried out immediately after blood collection to record pain threshold and pain tolerance to pressure. Eighteen tender points were marked with a demographic pencil and assessed while patients were in an orthostatic position, with their feet slightly separated. Pain sensitivity tests were performed on the 18 points identified by ACR in accordance with Okifuji et al. [16]. This was done perpendicular to the skin at 5- to 10- second intervals by the same qualified examiner. A pressure algometer was used (Pain Diagnostics and Thermography®, Great Neck, NY, USA), with a rubber point 1cm in diameter. Pain threshold and tolerance to pressure were quantified in kg/cm$^2$. The examiner positioned the rubber point above the area to be examined and gradually increased the pressure by 1 kg/cm$^2$ per second. The pain threshold was measured when the patient said “I’m starting to feel pain”. To measure tolerance to pain, the patient was asked to bear the maximum amount of pressure from the algometer and use the phrase “Stop, I cannot take anymore” when they were no longer able to do so. Patients were asked to use these exact phrases for total standardization of the test.

The purpose of the exam and instructions for responding were first explained to the patients. Mood evaluation was carried out individually with no interference from the examiner; however doubts were clarified when necessary.

Participant depression levels were assessed using the Beck Depression Inventory (BDI) [17], a self-reporting tool composed of 21 questions related to cognitive symptoms and attitudes. For each question, patients must choose one or more phrases that best describe how they felt in the previous week. The maximum score is 63 points and high scores indicate severe depression. Beck et al. [18] suggest the following quantifications scores for depression: a score of less than 10 indicates minimal or no depression; 10 to 18 signifies mild to moderate depression, 19–29 moderate to severe depression and from 30 to 63 severe depression.

Quality of life was evaluated using the Brazilian version of the Fibromyalgia Impact Questionnaire (FIQ) [3]. The FIQ is a brief 10-item, self-administered instrument that measures physical function, work status, depression, anxiety, sleep, pain, stiffness, fatigue, and well being. All the scales vary from 1 to 10, with high scores indicating negative impact and greater impairment. The total FIQ score is graded from 1 to 100 points. Higher scores are related to greater impact of the disease on the patients’ functionality and a corresponding reduction in their quality of life [3,19].

2.4. Statistical analysis

Statistical analyses were developed using R® software, with public access at http://www.r-project.org/, as well as GraphPad Prism 5 (GraphPad Software Inc. 2009). Quantitative parameters were statistically described by mean (Mn) and standard deviation (SD).

The first step of statistical analysis was to test the normal patterns of all parameters using the Shapiro-Wilk test. One-way Analysis of Variance (ANOVA) was used for intragroup analyses to determine hormonal variations between the three blood samples, in addition to the unpaired Student’s t-test for intergroup parametric analysis. The Mann-Whitney U-test was applied to compare intergroup nonparametric means. A general-
Table 1
Mean values (± SD) for measured variables in the fibromyalgia and control groups and P-values for the comparison between both groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fibromyalgia (N = 17)</th>
<th>Control (N = 19)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53 ± 7.98</td>
<td>53.32 ± 6.46</td>
<td>0.8965</td>
</tr>
<tr>
<td>Age at menopause</td>
<td>45.53 ± 4.78</td>
<td>46.50 ± 4.13</td>
<td>0.5385</td>
</tr>
<tr>
<td>Quality of life</td>
<td>68.43 ± 17.38</td>
<td>18.44 ± 12.82</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Depression</td>
<td>17.94 ± 7.36</td>
<td>7.52 ± 5.13</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Pain threshold</td>
<td>1.63 ± 0.57</td>
<td>3.56 ± 1.23</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Pain tolerance</td>
<td>2.35 ± 0.65</td>
<td>4.4 ± 1.42</td>
<td>&lt; 0.0001*</td>
</tr>
<tr>
<td>Cortisol</td>
<td>8.99 ± 1.62</td>
<td>7.92 ± 1.19</td>
<td>0.325</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>60.12 ± 16.09</td>
<td>78.95 ± 16.53</td>
<td>0.094</td>
</tr>
</tbody>
</table>

*Significant at 5%. aCalculated with the unpaired t test. bCalculated using the Mann-Whitney nonparametric test. Pressure pain threshold and pain tolerance in kg/cm².
Cortisol and DHEA-S (dehydroepiandrosterone sulfate) in ug/dL.

3. Results

Clinical characteristics of the study groups are reported in Table 1. There was no difference in age or onset of menopause between the groups. Depression was significantly higher (p < 0.0001) in the FMS group (17.94 ± 7.37) when compared to the CT group (7.53 ± 5.14). The mean score of the FMS group was classified between mild and moderate depression and the CT group as having minimal or no depression (Table 1). A significant difference was recorded between the two groups on analysis of FIQ scores (p < 0.0001) (Table 1). The FMS group showed a decrease in pain threshold and tolerance to pressure, with greater pain sensitivity. There was a significant difference between the means for pain threshold (FMS = 1.71 ± 0.58; CT = 3.63 ± 1.29) and pain tolerance (FMS = 2.33 ± 0.72; CT = 4.49 ± 1.47) between the groups (p < 0.0001) (Table 1).

One-way Analysis of Variance (ANOVA) showed no significant variation in these hormones between the first, second and third blood collections. All three samples were included for hormone analysis. There were no significant differences in cortisol (p = 0.325) and DHEA-S (p = 0.094) between the FMS and CT groups (Fig. 1). Plots of DHEA-S values for FMS and CT groups at each time point are shown in Fig. 2. A significant positive correlation was observed between DHEA-S levels and pain threshold (p = 0.017) and pain tolerance (p = 0.044). No association was found between cortisol levels and pain threshold or tolerance (FIQ and BDI). Although there was a significant difference between the groups, FIQ and BDI displayed no correlation with cortisol or DHEA-S levels (Table 2).

4. Discussion

There was no difference in plasma cortisol levels between FMS patients and healthy individuals in the present study, composed of post-menopausal women who do not use hormone replacement.

Similar patterns of age, sex, postmenopausal period, control of hormonal medication and exclusion of other painful syndromes such as chronic fatigue (CFS) were controlled in this sample, since they may directly influence cortisol levels. There are no previous studies with
Table 2

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Cortisol Coef.</th>
<th>SE Coef.</th>
<th>P-value</th>
<th>DHEA-S Coef.</th>
<th>SE Coef.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain threshold</td>
<td>−0.015</td>
<td>0.036</td>
<td>0.670</td>
<td>0.008</td>
<td>0.003</td>
<td>0.017*</td>
</tr>
<tr>
<td>Pain tolerance</td>
<td>0.010</td>
<td>0.043</td>
<td>0.811</td>
<td>0.008</td>
<td>0.003</td>
<td>0.044*</td>
</tr>
<tr>
<td>Quality of life</td>
<td>−0.939</td>
<td>0.912</td>
<td>0.311</td>
<td>0.086</td>
<td>0.079</td>
<td>0.281</td>
</tr>
<tr>
<td>Depression</td>
<td>0.227</td>
<td>0.387</td>
<td>0.562</td>
<td>0.026</td>
<td>0.033</td>
<td>0.443</td>
</tr>
</tbody>
</table>

*Significant at 5%. Dehydroepiandrosterone sulfate (DHEA-S).

This experimental protocol and controlled use of hormone replacement and corticosteroids by participants. Klerman et al. [20] used a protocol that strictly controlled variables that may affect circadian markers. They found no abnormalities in circadian rhythm or cortisol secretion when women with FMS were compared with healthy females. Riedel et al. [21] analyzed the cortisol release response caused by the corticotropin-releasing hormone (CRH) in 13 female patients with FMS and 13 controls. They determined that the increase in the adrenocorticotropic hormone (ACTH) and cortisol after CRH injection was not significantly different between FMS patients and controls. No significant differences were recorded in levels of plasma cortisol and ACTH between the two groups. The results support evidence that cortisol secretion in FMS patients is mainly caused by stimulation in CRH secretion, possibly in response to chronic pain and stress.

In a comparative study of adrenal function in groups of women with FMS, CFS and a group of healthy volunteers, Crofford et al. [22], using a sample composed of premenopausal and postmenopausal women with and without hormone replacement, found no significant mean hormone differences between patients and controls in relation to ACTH and cortisol during the entire 24-hour period or over any time frame. However, a variation in cortisol levels was observed when the correlation of sex hormones in women was considered. The premenopausal group showed lower cortisol levels independently of the FMS, CFS or control groups, whereas the postmenopausal women using estrogen replacement exhibited higher levels. The authors emphasize that there are similarities and differences between FMS patients whose main complaint is pain and CFS patients complaining primarily of chronic fatigue [22, 23].

Several studies [20–22] corroborate our findings in that they describe no significant alterations in cortisol levels, even when induced by use of corticotropin [21], or when analyzed throughout the period of wakefulness [20]. MacLean et al. [27] studied the function of the HPA axis in 20 patients with FMS through salivary cortisol levels, conducting 5 collections over 2 consecutive days. There were no differences in daytime levels and variations of cortisol when compared to the control group.

However, findings from other studies show different results. Gur et al. [24] studied 63 female FMS sufferers and 38 healthy controls, with a mean age of 29 years, and found significantly lower cortisol levels in patients than controls. The authors also report that cortisol levels are lower in patients with high levels of depression and fatigue than controls. In a study of 53 women with FMS aged between 29 and 64 years (mean age of 53), Izquierdo-Álvarez et al. [25] observed that women in the FMS group had significantly lower urinary cortisol levels than those of healthy women. Most of the FMS patients displayed lower than normal urinary cortisol levels, indicating less adrenal cortisol production. Previous research found a normal range of free cortisol levels in patients with FMS [20,21], or substantially below the normal lower limit [24,26].

The present study found no significant difference in cortisol levels when the two groups were compared, even though the FMS group exhibited a higher mean than that of the CT group. Moreover, there was no...
important correlation between cortisol and the symptoms of pain, depression and quality of life in the FMS group.

FMS is predominant among women and its prevalence increases with age. This suggests the role of sex steroids in its etiopathology, indicating a relationship between other neuroendocrine changes and symptoms of the syndrome. The adrenal gland is the main source of testosterone in women and is directly responsible for its production through DHEA and DHEA-S. Levels of these androgens decrease in pre and postmenopause and are inversely related to perceptions of stress and cortisol levels. This causes antagonistic physiological effects with regard to corticosteroids [28–32].

Dessein et al. [32] studied 56 women with FMS in preand postmenopause and a group of healthy volunteers. They found a correlation between decreased DHEA and pain perception. Several variables may affect this relationship, including age, menopausal state, body mass, use of oral contraceptives and recent use of glucocorticoids. Our investigation observed a tendency towards reduction in DHEA-S levels (\( p = 0.094 \)) in the FMS group, suggesting a positive correlation between this hormone and the pressure pain threshold (\( p = 0.017 \)) and tolerance (\( p = 0.044 \)).

There is indirect evidence that FMS may be a consequence of a decline in androgens since many of its antianabolic symptoms, such as muscular pain and fatigue, are typically associated with androgen deficiencies. Our data corroborate the theory that androgens are associated with FMS symptoms and are significant to pain perception [26, 32].

In addition to relationship with reduced DHEA-S, the present study found that FMS significantly affects quality of life, indicated by high FIQ scores. Many studies show a decline in functional capacity in FMS patients, especially among women, with pain and fatigue as the main causes [3,5,7]. Mood disturbances and chronic depression are also related to functional loss. Depression may worsen with physical or mental stress as described in previous research [31,33,34].

All patients in the FMS group suffered from light to moderate or moderate to serious depression. There is an obvious connection between FMS and depression; however, its trigger mechanism is still uncertain. Depression in FMS is independent of the characteristics and severity of pain, but contributes to a decline in quality of life and performance of daily activities [34]. Berber et al. [35] studied the prevalence of depression and its relationship with quality of life in 70 FMS patients. They observed a prevalence of 32.9% for mild depression, 21.4% for moderate depression and 12.9% for severe depression. The authors found that depression was responsible for a statistically significant decrease in quality of life scores, physical condition, physical functionality, pain perception, social, mental and emotional health and general health perception [35,36]. Pae et al. [37] observed significant similarities between clinical signs of FMS, such as serious depression, neuroendocrinial abnormalities, psychological characteristics, and physical symptoms. However, current findings do not support the theory that serious depression and FMS have the same etiologies; in other words, that one pathology supports the other.

In most FMS patients generalized pain is preceded by chronic pain at the site of the initial painful stimulus. This nociceptive change is likely caused by alterations in neural plasticity due to constant neural stimuli by pain impulses in the spine, transmitted by A-Delta and C fibers. Tonic activity in C and A-Delta fibers can maintain central sensitivity [38–40]. Staud and Spaeth [8] refer to hyperexcitability in the spinal dorsal horn neurons as underlying the central sensitivity occurring in FMS patients. This causes nociceptive stimulus in the brain. As a result, small stimulations of the skin or muscle tissue highly stimulate the brain, intensifying pain sensitivity. A significant portion of the substantial pain variance in FMS patients can be explained by psychological factors and disturbances in the autonomic nervous system and HPA axis, owing to their high degree of correlation [39].

In conclusion, this study shows that postmenopausal women with FMS that do not use hormone replacement exhibit higher pain sensitivity, depression and lower quality of life than healthy women. There was no significant difference in cortisol levels between FMS and CT groups, but positive correlations were found between DHEA-S, pain threshold and pain tolerance. We suggest that reduced DHEA-S seems to influence the symptoms of increased sensitivity to pain at this post-reproductive phase.

Although the present study had some limitations, such as the small sample size and only three cortisol samples per subject, our findings provide new information for clinical management in decreasing FMS symptoms and improving the physical and psychological well-being of patients. However, prospective longitudinal studies are needed to determine whether adrenocortical parameters are a cause and/or consequence of increased sensitivity to pain in women with FMS.
Conflict of interest

The authors declare there is no conflict of interest.

References


