

The Study of Blood Biomarkers in the Pathogenesis of Fibromyalgia: A Case-Control Study

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Abstract- Fibromyalgia (FM) is a chronic musculoskeletal syndrome characterized by pain and fatigue; however, its etiology remains unknown, and various hypotheses and biomarkers have been proposed. This study it is aimed to investigate blood biomarkers in the pathogenesis of FM. The current case-control study has been conducted on 45 females with the documented diagnosis of FM and 45 healthy controls referring to the outpatient clinic of rheumatology in 2018-19. The serum levels of dehydroepiandrosterone (DHEAS), erythrocytic sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC), and thyroid-stimulating hormone (TSH) was measured and compared between the groups. DHEAS serum levels in cases and controls were 27.55 ± 18.80 and 33.55 ± 21.80 , ($P=0.16$), ESR was 29.17 ± 9.75 and 17.37 ± 2.82 ($P<0.001$), CRP was 4.17 ± 1.53 and 3.53 ± 1.15 ($P=0.02$), TSH was 3.307 ± 0.27 and 3.41 ± 0.22 ($P=0.09$), respectively. The two groups were similar in CBC indices, including hemoglobin, hematocrit, white blood cell, lymphocyte, neutrophil, and platelet count ($P>0.05$). DHEAS was slightly, but insignificantly, lower among the females with FM than healthy cases. On the other hand, the serum ESR and CRP levels were remarkably higher among the females with FM; however, in the normal range, a fact representing the possible traces of inflammation in the pathogenesis of FM.

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Introduction

Fibromyalgia (FM) is a musculoskeletal syndrome accompanied by widespread pain and fatigue for the least period of three months along with other clinical manifestations, including sleep disorders, memory impairment, psychological distress, morning stiffness, malaise, gastrointestinal complaints, paresthesia, urinary urgency, dizziness and orthostatic hypotension (1).

FM's pathogenesis is unknown; however, varieties of hypotheses, including central abnormalities in pain modulation and disturbances in the neuroendocrine system, have been raised (2,3). These hypotheses have been reinforced by the measurements showing the decreased activity of the pituitary-hypothalamus axis among cases representing patterns of symptoms similar to FM (4).

Dehydroepiandrosterone (DHEA) and its sulfate ester

(DHEAS) are secreted from the cortex of adrenal glands and controlled by adrenocorticotrophic hormone (5). The serum concentration of DHEAS increases gradually and reaches its most within the third-to-fourth decades of life; after that, the trend of decrease initiates, whereas it reaches 20% of optimal levels by the 70s (6). Although DHEAS is the most abundant steroid in plasma, this hormone's substantial role is not well-understood. Nevertheless, it has been demonstrated that DHEA has some physiological activities through transformation into the other body steroid components such as androgens or estrogens (7).

Besides, DHEAS is a neuroactive agent interacting with receptors of other transmitters such as N-methyl-D-aspartate (NMDA) and gamma-aminobutyric acid (GABA), which play a role in pain sensation modulation (8). Sigma receptors are the place of DHEAS binding responsible for the excitability and plasticity of neural

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regulation (9). The real correlation of FM with DHEAS is not well-understood, and studies have presented controversial outcomes. Besides, the trials about the alterations in the DHEAS levels following FM treatment have not revealed valuable knowledge in this regard (10,11). Therefore, the current study aims to assess and compare DHEAS concentration in FM patients and compare it with the general population.

Materials and Methods

This is a case-control study conducted on 45 cases with the diagnosis of fibromyalgia and 45 healthy controls referred to the rheumatology outpatient clinic of Khorshid Hospital affiliated with Isfahan University of Medical Sciences from April 2018 to August 2019.

The Ethics Committee of Isfahan University of Medical Sciences approved the study protocol. Then, it was explained for both of the study groups entirely, and written consent was obtained.

The 18-60-year-old females diagnosed with fibromyalgia based on the revised diagnostic criteria of the American College of Rheumatology in 2016 (12) were included. Co-occurrence of the other rheumatologic or endocrine disorders, drug abuse or addiction, hormonal replacement therapy, and reluctance to participate in the study were considered the exclusion criteria.

The cases were recruited through convenience sampling until achieving the desired number of people. For the selection of the control group, age- and menstrual status-matched healthy females without any past medical history of musculoskeletal, rheumatologic, or inflammatory disease were invited to the study from the family member or friends of the cases to be examined thoroughly, and a laboratory test for the measurement of DHEAS, erythrocytic sedimentation rate (ESR), C-reactive protein (CRP), thyroid-stimulating hormone (TSH), and complete blood count (CBC) was sent for free. The participants' menstruation phase was

determined based on an ultrasonography evaluation and sexual hormones measurements, follicular stimulating hormone (FSH), and luteinizing hormone (LH).

Participants in both groups underwent blood sampling from the antecubital venous at 8:00 to 9:00 in the morning. The samples were centrifuged, and following the separation of the serum, it was stored at -70° centigrade. The Serum levels of DHEA-S were measured using Microparticle Enzyme Immunoassay (Abbott Laboratories, Abbott Park, IL, USA).

The obtained data were eventually entered into the Statistical Package for Social Sciences (SPSS) version 23. The descriptive data were presented in mean and standard deviation. For analytics, the Mann-Whitney test and independent-sample *t*-test were used. *P* less than 0.05 was considered as a significant level.

Results

In the current study, ninety females consisting of 45 ones diagnosed with FM and 45 healthy ones were assessed. Both of the cases and controls consisted of 25 postmenopausal and 20 premenopausal females. The mean age of cases was 50.44 ± 5.56 years (range: 37-60 years), and controls were 48.13 ± 7.72 (range: 35-58 years). The comparison of the patients regarding their age revealed an insignificant difference ($P=0.18$).

The drugs used by the patients with FM included gabapentin, pregabalin, duloxetine, DMARDs, and danazol by 28 (62.22%), 2 (4.44%), 32 (71.11%), 21 (46.66%), and 11 (24.44%) of patients, respectively.

Table 1 represents the comparison of the DHEAS, ESR, CRP, and CBC indices between the studied groups. Based on this table, the mean of DHEAS was not remarkably different between cases and controls ($P=0.16$), while the ESR ($P<0.001$) and CRP ($P=0.02$) levels were statistically higher among those with FM. The comparison of CBC indices between the two groups revealed an insignificant difference ($P>0.05$).

Table 1. The comparison of blood biomarkers between the case and control groups

| Variables | Fibromyalgia females | Healthy females | <i>P</i> |
|---------------------------------|-------------------------|-----------------|----------|
| | mean±standard deviation | | |
| Dehydroepiandrosterone sulfate | 27.55±18.80 | 33.55±21.80 | 0.16* |
| Erythrocytic sedimentation rate | 29.17±9.75 | 17.37±2.82 | <0.001** |
| Hemoglobin | 11.34±2.09 | 11.73±2.05 | 0.36* |
| Hematocrit | 36.98±5.10 | 35.47±4.78 | 0.15* |
| White blood cells | 10.39±1.65 | 9.46±2.69 | 0.055* |
| Neutrophil | 6.94±2.41 | 6.73±2.40 | 0.68* |
| Lymphocyte | 1.96±0.67 | 2.04±0.62 | 0.52* |
| Platelet | 227.03±78.46 | 230.17±5.59 | 0.84* |
| Thyroid-stimulating hormone | 3.307±0.27 | 3.41±0.22 | 0.09* |
| C-reactive protein | 4.17±1.53 | 3.53±1.15 | 0.02* |

* Independent sample T-test

** Mann-Whitney

Discussion

In the current study, we tried to respond to a question about the role of DHEAS in the pathogenesis of fibromyalgia and the other inflammatory marker, ESR. In this regard, to eliminate the potential role of age, gender, and menstruation status, the cases and controls were selected from age- and menstruation status-matched females. Therefore, the obtained results about the etiologic role of DHEAS and ESR in FM's pathogenesis are merely contributed to these factors, but the demographic ones.

We found that although statistically insignificant, the serum levels of DHEAS were less among the cases resenting from FM than the healthy controls. Our findings were in agreement with another case-control study by Abreu Freitas *et al.*, that investigated the levels of DHEAS and cortisol among patients resenting from FM and represented that despite the lower serum levels of the hormones among FM cases, the difference between cases and controls was not statistically significant (11). In another study, Dessiny *et al.*, assessed the serum levels of DHEA and DHEAS among 56 females with FM and represented notifying lower levels of these hormones among the patients compared to the controls (13). A point that may be responsible for an insignificant difference between the cases and controls in our study is the failure to assess the premenopausal and postmenopausal cases separately.

In further investigations, Dessiny presented a remarkable correlation between the pain complaint and levels of DHEA and DHEAS (13), an issue that has been investigated by Abreu Freitas *et al.* as well. Surprisingly, they found that despite the insignificant difference between the DHEAS levels among the cases and controls, there was an inverse correlation between DHEAS serum levels with pressure pain threshold and tolerance (11).

Evidence represents the higher prevalence of FM among females, which increases by age. Also, the major theory about the etiology of FM targets neuroendocrine changes. On the other hand, the primary source of testosterone in females is the adrenal gland by DHEA and DHEAS secretion. Putting the mentioned factors together and the documents insisting on the role of androgen deficiency in pain and fatigue among females reinforces the theory about the role of reduction in serum androgen levels, DHEA and DHEAS prominent contributors of FM and the severity of its symptoms (14-16).

The latter factor that confirms the theory about the role of decreased DHEAS levels in the pathophysiology

of FMS is the complaint of pain, which is usually initiated by generalized pain that proceeds to chronic pain (11). Numerous studies have reported that the hypothalamus-pituitary-adrenal axis hypofunction poses a significant diminishing in the adrenal gland size, leading to a reduction in cortisol levels and, consequently, weak body function toward stressors and an increase in pain sensation (17,18). The other reason of pain complaint among the FM cases is attributed to neuroplasticity and dysfunction in pain generation of the central nervous system, which is correlated with the reduced levels of DHEAS, as this hormone interacts with the receptors of GABA and NMDA and helps the regulation of neural excitability and plasticity as well as its neuroprotection action (9,19).

The latter assessment of the current report showed that the FM females had remarkably higher serum levels of ESR and CRP than healthy matched cases; however, both measurements were normal for both groups. Further investigations in terms of complete blood count were similar in cases versus controls.

The inflammatory process of FM is another debating issue; however, evidence in this regard is limited. Xiao *et al.* conducted a study in order to evaluate the levels of inflammatory factors in FM. They only found marginally higher levels of quantitative C-reactive protein (CRP) compared to healthy cases, while the abnormal CRP levels were found 1.5 fold more in the FM cases than healthy ones. Although the serum levels of the other inflammatory factors, including interleukin 6 (IL-6), interleukin 18 (IL-18), and ESR, did not differ between the healthy cases and the FM ones, these levels were remarkably associated with the measured CRP. Therefore, in conclusion, they defended the theory about the traces of inflammation for FM's pathophysiology (20), an idea that was confirmed in another study by Sturgeon *et al.*, (21).

In accordance with our study, the previous reports have represented normal levels of complete blood count indices among FMS patients, as well (22,23); however, it should be noted that the diagnosis of FMS should be made by rolling the other pathological conditions out.

Although our investigation was the first one in Iran and has been conducted on 45 FM cases that seem an appropriate sample population, it has considerable limitations. One of the notifying limitations of the current study is the failure to assess the premenopausal and postmenopausal cases separately to increase the outcomes' homogeneity. Another issue that should be precisely considered in further investigations is to

ultimately control the confounding variables that could affect the outcomes, such as medications, duration of the disease, presence of concurrent psychological disorders, and sex hormone status. A significant limitation of our study that is recommended to consider in further evaluations is the failure to assess the relation of FMS with mood disturbances as well as failure to assess wide ranges of hormonal and inflammatory factors such as cortisol, CRP, and ILs to present a comprehensive view of this disorder.

In summary, we found that DHEAS was slightly lower among the females with FM than healthy cases, which were consistent with the literature; however, we assume this insignificant difference may have occurred due to the studied population's heterogeneity. On the other hand, the serum ESR levels were remarkably higher among the females with FM, but in the normal range, a fact that represents the possible traces of inflammation in the pathogenesis of FM. Further precise investigations are strongly recommended.

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