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The Comparison of the Biological Rhythms of Patients with Fibromyalgia Syndrome with Biological Rhythms of Healthy Controls

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Background: Fibromyalgia syndrome (FMS) is a rheumatic disease characterized by diffuse body pain and decreased muscle function. The aim of the present study was to compare the biological rhythms of patients with fibromyalgia syndrome with the biological rhythms of healthy controls.

Material/Methods: This was a cross-sectional, single blind, and single center case-control study. The patients with fibromyalgia were evaluated using a Fibromyalgia Impact Questionnaire (FIQ), Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) Scale, Visual Analog Scale (VAS), Pittsburg Sleep Quality Index (PSQI) and Beck Depression Inventory (BDI).

Results: The study included 77 female patients with FMS, and 32 healthy female individuals as the control group. We found that the patients in the FMS group achieved higher scores in VAS, BDI, PSQI, and the BRIAN scale than the patients in the control group ($P<0.001$). An evaluation of the relationship between FMS evaluation parameters and biological rhythm scores in patients with FMS revealed a significant positive correlation between total BRAIN and VAS, FIQ, BDI, and PSQI scores. When the relationship between FMS evaluation parameters and biological rhythm scores was evaluated in patients with FMS, a significant positive correlation was found between total BRAIN and VAS, FIQ, BDI, and PSQI scores (r=0.555, $P<0.001$; r=0.461, $P<0.001$; r=0.630, $P<0.001$; and r=0.551, $P<0.001$ respectively).

Conclusions: We consider that an evaluation of the biological rhythm of female patients with FMS, and appropriate treatment when required, would contribute significantly to the treatment and follow-up process of the patients.

MeSH Keywords: **Fibromyalgia • Myalgia • Questionnaires**

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2386 2 — 30

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Background

Fibromyalgia syndrome (FMS) is a chronic rheumatic disorder with an unclear etiology that is characterized by sleep disorders, widespread pain, cognitive impairment, tenderness on certain anatomical locations, fatigue, and common psychological problems [1]. It is common among middle-aged females, but it can also occur in childhood and in older ages [1,2].

Although the etiology of FMS has not been elucidated, neuroendocrine dysfunctions as well as central pain mechanisms have been implicated, while genetic factors, mental stress, trauma, inflammation, and infections can also trigger and modulate neuroendocrine abnormalities [3]. However, FMS includes dysfunction of the nervous systems, neurotransmitters, hormones, stress factors, biological rhythm dysregulation, and psychiatric conditions [3]. Daily biological rhythms are evident in the effects of body temperature, sleep cycles, and hormone levels on mood, attention and cognition. The deterioration of these daily rhythms is associated with mood disorders [4].

Compromises in the biological rhythm of patients with affective disorders have been reported, particularly among those suffering from depression [4], and this is considered to be associated with neurochemical, neurophysiological, and pharmacological changes [5]. Anti-depressant medications that are utilized in the fibromyalgia treatment have been shown to increase melatonin levels by increasing norepinephrine and serotonin levels [6], and in addition, the use of melatonin, which has a significant role in the regulation of biological rhythm, has been reported to increase the duration and quality of sleep in patients with FMS [7]. Previous studies have found lower levels of serotonin, melatonin, and cortisol in FMS, the levels of which are regulated by the circadian rhythm [8]. In this regard, disturbances in melatonin secretions that are implicated in the etiopathogenesis of FMS are thought to affect biological rhythm in patients with FMS, although no study exists in literature evaluating the relationship between FMS and biological rhythm.

The purpose of this study was to compare the biological rhythms of patients with fibromyalgia syndrome with the biological rhythms of healthy controls.

Material and Methods

The present study was designed as a cross-sectional analysis, comprising both patients with fibromyalgia and healthy controls. The biological rhythms of the participants were evaluated in a single blind fashion. The ethical approval was obtained from the local ethics committee of Gaziantep University.

Participants

The study analyzed female patients aged between 18 and 60 years who were admitted to the outpatient clinics of the Department of Internal Medicine between July 2014 and September 2015, and who were subsequently diagnosed with FMS according to the classification criteria of the American College of Rheumatology (ACR) [1]. Age-matched healthy volunteer women were recruited as the control group. All patients and healthy controls were informed about the study, and all provided written consent.

A detailed medical history was obtained from all participants. Those with a history of neurological disorders, diabetes mellitus, myopathy, goiters, kidney or liver disease, inflammatory rheumatic disorders, complex regional pain syndrome, osteomalacia, osteoporosis, depression or a history of psychiatric disorder, and patients who had received any medical therapy for neuropathic or nociceptive pain in the last 1 month, were excluded from the study.

Evaluation of participants

All of the study participants were evaluated between 08: 00 and 10: 00 AM in the morning. Gender, age, weight (kg), height (cm), body mass index (BMI, kg/m^2) and educational status were recorded. The participants were examined for posture, gait, range of joint motion, and motor, sensorial, and deep tendon reflexes. The patients with FMS were asked about the number of tender points, paresthesia, fatigue, sleep disorders, presence of dysmenorrhea in premenopausal women, headache, irritable bowel syndrome, morning stiffness, bloating, restless leg syndrome, Raynaud's phenomenon and pain brought on by stress.

Parameters used in the study

The patients with fibromyalgia were evaluated using the Fibromyalgia Impact Questionnaire (FIQ), Visual Analog Scale (VAS), Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) scale, Pittsburg Sleep Quality Index (PSQI), and Beck Depression Inventory (BDI).

Fibromyalgia Impact Questionnaire (FIQ)

This is a scale used in the evaluation of the status of a patient with FMS and the consequences of the disease, and contains 10 subscales that include feel good, physical function, do job, missed work, fatigue, stiffness, rested, pain, depression, and anxiety. The maximum possible score for each item was 10 points, meaning a maximum total score of 100 points. Higher scores indicated the symptom severity of FMS. The credibility and validity of the scale for use in Turkey was evaluated by Sarmer et al. [9].

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Visual Analog Scale (VAS)

This scale is utilized to evaluate subjective pain intensity on a scale rated from 0–10 points (VAS 0=no pain, 10=the most severe pain). The patient is asked to indicate the number that correspond best to their pain level [10].

Biological Rhythms Interview of Assessment in Neuropsychiatry (BRAIN) scale

The BRAIN is a self-rated, Likert-type scale consisting of 21 items. The scale addresses 5 main areas, including sleep, activities, social rhythms, eating patterns, and predominant rhythm (chronotype). Each item was rated using a 4-point scale from 1–4 points, and the total score was calculated by adding the scored of each area. Total scores can range from 21–84 points. No cutoff value has been calculated for this scale; its use is not recommended in comparative studies. This scale was recommended for use in evaluating disturbances in the biological rhythms of patients [11], and the Turkish language version of the scale has been evaluated for validity and reliability [12].

Beck Depression Inventory (BDI)

The BDI scale measures emotional, bodily, cognitive, and motivational symptoms of depression. It was adapted to Turkish patients. This scale consists of 21 items, each comprising 4 sentences that were ranked between steady state (0 points) and the most severe condition (3 points). The maximum score in this scale was 63 points [13].

Pittsburgh Sleep Quality Index (PSQI)

The PSQI scale assesses sleep quality during the previous month. It has been adapted to the Turkish population. The scale consists of 7 items, including sleep latency (quality, efficiency, duration, disturbances), use of sleeping drugs, sleep efficiency, and daytime dysfunction. Each item was scored on a scale of 0–3, with a 0 score given if the item had not occurred in the past month: 1 point was given if it occurred less than once in a week: 2 points if it occurred once or more a week, and 3 points if it occurred more frequently. In the assessment of sleep quality, 0 points indicated very good sleep, 1 point indicated quite good sleep, 2 points indicated quite bad sleep, and 3 points indicated very bad sleep. The global score has a range of 0–21, with a score of 5 and higher indicating significantly poor sleep quality [14].

Statistical analysis

The data was analyzed using the SPSS (Statistical Package for Social Sciences) software package, version 18.0 (SPSS Inc., Chicago, IL, USA). The distribution of the groups was analyzed with a Kolmogorov-Smirnov test, and the Student's *t*-test was used to compare the data of the patients and the controls. Pearson tests were used for correlation between parameters. All parametric results were expressed as mean±standard deviation for each group and the significance level was set at $P<0.05$.

Results

A total of 150 female patients with FMS and 60 healthy female controls were measured for inclusion in the study, among which 77 patients with FMS and 32 healthy controls were found to be eligible.

There wasn't any significant difference between the FMS patient group and control group in terms of age and BMI: mean age 39.4±2.4 and 37.8±3.80 years, respectively, ($P=0.108$), while the mean BMI was 26.4±3.2 and 25.2±2.8 kg/m^2 ($P=0.320$). In the FMS group, the scores related to VAS, BDI, PSQI, and total biological rhythm were significantly higher than the control group: VAS was 7.0±1.9 and 1.7±1.2 respectively ($P<0.001$). BDI was 13.4±3.4 and 3.2±1.9 respectively ($P<0.001$). PSQI was 9.4±2.3 and 4.9±1.6 respectively ($P<0.001$). Total BRAIN score was 51.0±8.1 and 41.8±6.7 respectively ($P<0.001$) (Table 1).

When the relationship between FMS evaluation parameters and biological rhythm scores was evaluated in patients with FMS, a significant positive correlation was found between total BRAIN and VAS, FIQ, BDI, and PSQI scores (r=0.555, $P<0.001$; r=0.461, $P<0.001$; r=0.630, $P<0.001$; and r=0.551, $P<0.001$, respectively (Table 2).

Discussion

As the first study to analyze biological rhythm in female patients with FMS, this present study reported significantly higher scores in the total biological rhythm scale in patients with FMS when compared to the control group, and found a significant positive correlation between the total BRAIN score and the VAS, FIQ, BDI, and PSQI scores.

Different peripheral and central factors have been suggested as contributing to pain and other symptoms in patients with FMS [15]. Recent studies have tended to focus on abnormalities of the central nervous system due to the fact that studies of patients with FMS have reported controversial results regarding muscle pathologies, with no concrete evidence emerging for any particular condition [16]. Neuroendocrine dysfunction, sleep disturbances, and psychiatric disorders are the main central factors implicated in the etiology of FMS [17]. Yunus et al. highlighted that central factors play a more significant role in the emergence of FMS, while neuroendocrine dysfunction and

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Table 1. Comparison of demographic and clinical characteristics of participants.

	FMS (n=77) [Mean±SD]	Control (n=32) [Mean±SD]	*P*
Age (years)	39.4±2.4	37.8±3.80	0.108
Duration of disease (months)	78.5 ±4.8	–	
Education±SD (years)	7.5±2.1	7.9±1.6	0.330
BMI (kg/m^2)	26.3±4.2	25.8±2.8	0.250
BDI score	13.4±3.4	3.2±1.9	**<0.001****
VAS score	7.0±1.9	1.7±1.2	**<0.001****
FIQ score	59.9±8.2	–	
PSQI score	9.4±2.3	4.9±1.6	**<0.001****
BRAIN-sleep score	14.4±2.9	12.0±2.4	**<0.001****
BRAIN-activity score	14.8±3.3	9.0±2.9	**<0.001****
BRAIN-social score	7.9±2.9	6.7±2.0	**0.014***
BRAIN-eating patterns score	8.4±2.8	8.1±2.5	>0.05
BRAIN- chronotype score	5.2±1.6	3.3±0.5	**<0.001****
BRAIN-total score	51.0±8.1	37.2±6.4	**<0.001****

* *P*<0.05; ** *P*<0.001. SD – standard deviation; BMI – body mass index; BDI – Beck Depression Inventory; VAS – Visual Analog Scale; FIQ – Fibromyalgia Impact Questionnaire; PSQI – Pittsburg Sleep Quality Index; BRAIN – Biological Rhythms Interview of Assessment in Neuropsychiatry.

Table 2. Correlation analysis between fibromyalgia clinical rating scores and biological rhythm scores.

	BRAIN-sleep score	BRAIN-activity score	BRAIN-social score	BRAIN-eating patterns score	BRAIN-chronotype score	BRAIN-total score
Age	–0.003 *P*>0.05	**0.417**** *P*>0.001	0.094 *P*>0.05	–0.090 *P*>0.05	–0.121 *P*>0.05	0.172 *P*>0.05
Duration of Disease	0.050 *P*>0.05	0.036 *P*>0.05	0.047 *P*>0.05	–0.107 *P*>0.05	–0.052 *P*>0.05	–0.003 *P*>0.05
VAS score	**0.250**** *P*>0.001	**0.646**** *P*>0.001	**0.233*** *P*>0.05	0.085 *P*>0.05	**0.293**** *P*>0.001	**0.555**** *P*>0.001
FIQ score	0.180 *P*>0.05	**0.586**** *P*>0.001	**0.309**** *P*>0.001	**0.279*** *P*>0.05	**–0.278*** *P*>0.05	**0.461**** *P*>0.001
BDI score	**0.340**** *P*>0.001	**0.533**** *P*>0.001	**0.496**** *P*>0.001	**0.367**** *P*>0.001	0.121 *P*>0.05	**0.630**** *P*>0.001
PSQI score	**0.253**** *P*>0.001	**0.613**** *P*>0.001	**0.311**** *P*>0.001	0.188 *P*>0.05	0.166 *P*>0.05	**0.551**** *P*>0.001

* *P*>0.05; ** *P*>0.001. SD – standard deviation; BMI – body mass index; BDI – Beck Depression Inventory; VAS – Visual Analog Scale; FIQ – Fibromyalgia Impact Questionnaire; PSQI – Pittsburg Sleep Quality Index; BRAIN – Biological Rhythms Interview of Assessment in Neuropsychiatry.

biochemical changes, and many symptoms related to FMS, have been linked to neuroendocrine and metabolic disturbances [15]. In this regard, studies have addressed disturbances in the hypothalamo-pituitary-adrenal (HPA) axis, and changes in cortisol, serotonin, substance P, glutamate, and somatomedin C levels in the pathophysiology of FMS [16].

Studies that have evaluated the hypothalamo-pituitary-adrenal (HPA) axis in patients with FMS have found a flattened diurnal pattern and high cortisol levels that could not be suppressed by dexamethasone administration; studies have also found lower cortisol levels in the 24-hour urine samples of patients with FMS when compared to healthy controls, and higher urinary cortisol levels at nights in patients with FMS [16,18].

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In addition, patients with FMS have been shown to have reduced cortisol response to stimulation with a corticotrophin-releasing hormone (CRH) when compared to a control group. Furthermore, the differences in baseline and nocturnal plasma free cortisol levels have been linked to impairments in the HPA axis, while reduced cortisol response to CRH has been linked to decreased adrenal responsiveness [16,18–20].

Cytokines are considered as playing a role in the pathogenesis of FM. Currently, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and IL-1 are reported to be important cytokines in the sympathetic nervous system and hypothalamo-pituitary-adrenal (HPA) axis [21,22]. Patients with FMS have been reported as having an insufficient adrenocorticotropic hormone (ACTH) response to interleukin-6 (IL-6) administration [21,22].

It has been reported that non-restorative sleep associated with disturbances in melatonin secretion is an important component of FMS [7,8,23]. Melatonin, which has the main function of protecting the biological clock and arranging the rhythm of the body, is involved in many biological and physiological processes, with other important functions including the renewal of cells, strengthening the immune system and the regulation of sleep rhythm and body temperature [7]. Low melatonin levels have been reported as playing a role in the pathogenesis of many psychiatric disorders, such as panic disorder, depression, bipolar disorder, anxiety, and obsessive-compulsive disorder [7,23]. In addition, changes in the circadian rhythm have been observed in affective disorders, particularly in depression, indicating a disturbance of the biological rhythm [7,23]. The use of supplementary melatonin, which influences the regulation of biological rhythm, has been revealed to get better sleep duration and sleep quality in patients with the disorders of rapid eye movement (REM) sleep, restless leg syndrome, delayed sleep phase syndrome, manic patients with sleep problems, and patients with fibromyalgia [7]. In addition, there are studies suggesting that common sleep problems in patients with fibromyalgia are rarely related with the symptoms of FMS, and that FMS is not the main symptom [3]. It was Moldofsky et al. that first showed the presence of abnormal patterns in the electroencephalographies (EEG) of the patients with fibromyalgia [24]. In their study, an increase in the amplitude of bioelectrical activity was reported during the transition to sleep, and they reported many alpha waves that had not been previously observed. In normal individuals, an alpha EEG anomaly accounts for 25% of non-REM sleep, while this rate is more than 60% in patients with FM [25,26]. Low levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) secreted in the fourth phase of non-REM sleep have been suggested as playing a role in the pathogenesis of FMS, and are particularly associated with fatigue, muscle dysfunction, deconditioning, and cold intolerance [25,26]. The aforementioned factors are likely to result in lower scores in terms of sleep quality in the FMS group when compared to the control group. Furthermore, it is an important finding that the present study found a significant relationship between sleep quality and biological rhythm in the FMS group.

Low serotonin levels in patients with FMS are contemplated to be related to depression, anxiety, sleep disorders, and disruption in muscle functions [27]. There are numerous studies in literature showing higher depression scores in FMS patients when compared to healthy controls; although the casual relationship between pain and depression has not been fully elucidated [28]. Depression scores were also higher in the FMS group when compared to the control group in the present study, and a further significant positive correlation was identified between the depression scores and biological rhythm scores.

Anti-depressant medications, melatonin, vitamin B12, chronotherapy, and bright light therapy have been reported as having beneficial effects on biological rhythm [29,30]. Fibromyalgia patients take a lot of medication. These drugs may be predisposing to depression by causing disruption of biological rhythms. After sufficiently enlightening the relationship between fibromyalgia and biological rhythm, the convenient treatment options for the regulation of biological rhythm can be evaluated for their contribution to the treatment of patients with FMS.

The cross-sectional design of the study, the inclusion of female patients with primary FMS aged between 18 and 60 years, the evaluation of cases only in the summer season, not questioning the drugs they use, and the lack of classification of the participants according to habits of physical exercise were the main limitations of the study.

Conclusions

In conclusion, we consider that an evaluation of female patients with FMS in terms of their biological rhythm, and the appropriate treatment modalities of patients when required, would contribute significantly to the treatment and follow-up process of the patients. That said, further studies that analyze a larger number of patients are required.

Conflict of interest

None.

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