Ankara Med J, 2018;(3):410-8
DOI: 10.17098/amj.448386

The Association of IGF-1 with Clinical Symptoms in Female Patients with Fibromyalgia Syndrome

Fibromiyalji Sendromlu Kadın Hastalarda IGF-1'in Klinik Semptomlarla İlişkisi

Sevgi Gümüş Atalay[1]

[1]University of Health Sciences, Umraniye Teaching And Research Hospital, Department of Physical Medicine and Rehabilitation, İstanbul

Abstract

Introduction: Fibromyalgia syndrome (FMS) is a disease of unknown etiology, which is characterised by chronic pain. Disturbed growth hormone response, low serum insulin-like growth factor-1 (IGF-1) may play a role in etiopathogenesis of fibromyalgia and may be related to the severity of some symptom. The aim of this study is to investigate serum IGF-1 levels and relationship of clinical symptoms in female patients with fibromyalgia syndrome.

Materials and Methods: Thirty-seven patients with FMS and thirty healthy subjects were included in this study. All individuals were assessed for clinical findings, widespread pain (Visual Analogue Scale), functional disability and health state (health assesment questionnarie and fibromyalgia impact questionnarie), anxiety (anxiety State and Trait Anxiety Inventory) and depression (Beck depression inventory). Likert scale was used for evaluate morning stiffness, level of fatigue, pain, muscle spasm and tenderness.

Results: In this study, serum IGF-1 levels of patients with fibromyalgia were significantly lower compared to the control group (p=0.004). The IGF-1 levels were significantly correlated with age (r=-0.496; p<0.01), muscle spasm (r=-0.333; p<0.05), tender points (r=-456; p<0.01) and morning stiffness (r=-0.463; p<0.01).

Conclusion: Low levels of serum IGF-1 in female patients with fibromyalgia syndrome were associated with number of tender points, muscle spasm and stiffness. We have concluded that low levels of serum IGF-1 might play role in the pathogenesis of fibromyalgia and might be related to severity of symptoms.

Key words: Fibromyalgia syndrome (FMS), insulin-like growth factor-1 (IGF-1), growth hormone

Öz

Amaç: Fibromiyalji sendromu (FMS), kronik ağrı ile karakterize, etiyolojisi bilinmeyen bir hastalıktır. Bozulmuş büyüme hormonu yanıtı, düşük serum insülin benzeri büyüme faktörü-1 (IGF-1) FMS etyopatogenezinde rol oynayabilir ve bazı semptomların şiddeti ile bağlantılı olabilir. Bu çalışmanın amacı fibromiyalji sendromlu kadın hastalarda serum IGF-1 düzeylerini ve klinik semptomlarla ilişkisini araştırmaktır.

Materyal ve Metot: Çalışmaya FMS'lu 37 kadın hasta ve 30 sağlıklı kadın dahil edildi. Tüm bireyler klinik bulgular, ağrı şiddeti (görsel ağrı skalası), fonksiyonel disabilite ve sağlık durumu (sağlık değerlendirme skalası ve fibromiyalji etki skalası), anksiyete (anlık ve sürekli anksiyete ölçeği) ve depresyon (Beck depresyon ölçeği) açısından değerlendirildi. Sabah sertliği, yorgunluk şiddeti, uykusuzluk şiddeti, ağrı şiddeti, kas spazmı şiddeti ve hassasiyet şiddetini değerlendirmek için Likert skalası kulanıldı.

Bulgular: Çalışmamızda FMS hastalar kontrol grubuyla kıyaslandığında serum IGF-1 düzeyleri belirgin olarak daha düşüktü (p=0,004). IGF-1 düzeyi ile yaş (r=-0,496; p<0,01), kas spazmı (r=-0,333; p<0,05), hassas nokta sayısı (r=-456; p<0,01) ve sabah tutukluğu (r=- 0.463; p<0.01) arasında belirgin korelasyon mevcuttu.

Sonuç: Fibromiyalji sendromlu kadın hastalarda serum IGF-1 düzeyi düşüklüğü, hassas nokta sayısı, kas spazmı ve tutukluk ile ilişkiliydi. Çalışmamızda serum IGF-1 düzeyindeki düşüklüğünün, fibromiyaljinin etyopatogenezinde rol alabileceğini ve semptomların şiddeti ile ilişkili olabileceği sonucuna vardık.

Anahtar kelimeler: Fibromiyalji sendromu (FMS), insülin-benzeri büyüme faktörü (IGF-1), büyüme hormonu

Correspondence / Yazışma Adresi:
Dr. Sevgi Gümüş Atalay
University of Health Sciences, Umraniye Teaching And Research Hospital, Department of Physical Medicine and Rehabilitation, İstanbul
e-mail: sevgigumusatalay@hotmail.com
Date of submission: 22.07.2018
Date of admission: 04.09.2018

Introduction

Fibromyalgia syndrome (FMS) is a disease of unknown etiology, which is characterised by chronic widespread musculoskeletal pain, fatigue, poor sleep, gastrointestinal complaints and psychological problems.[1,2] One of the main complaints in FMS is reduced pain tolerance and particularly the presence of multiple tender points.[3] FMS is affected by factors such as weather, physical activity, stress and sleep quality. Patients generally complain about headache, irritable bowel syndrome (IBS), asthenia and menstrual disturbances. Prevalence of FMS is 0.5-10% and increases as education and socioeconomical level decreases.[4] Its requency increases with age, and it is most commonly seen between fourth and sixth decades. It is 4-9 times more frequent in females.[5-7]

Etiology of FMS is not known exactly. Current concept is that FMS is associated with complicated interactions between peripheral nociceptive events and changes in central nervous system which may be neuro-physchiatric or neurochemical. Sleep disorders, changes in muscle oxygenation, pyschological, biochemical, hormonal and immunological factors are suggested in etiopathogenesis of FMS.[8,9]

Growth hormone (GH) is an anabolic peptide which stimulates synthesis of deoxyribonucleic asic, ribonucleic asid and proteins. GH plays an important role in muscle homeostasis and repair. IGF-1 has anabolic effects and is the major mediator of GH, which is essential in normal muscle homeostasis. Since half life of GH is very short, serum IGF-1 levels are measured in studies. Serum basal IGF-1 secretion is affected by age, gender, body mass index, food intake, blood glucose levels, serum fatty acids, body position and quality of sleep. IGF-1 levels should be assessed by taking into account age and gender.[10]

It has been reported that 80% of GH is secreted during the fourth phase of sleep.[6] Due to the disturbances in the fourth phase of sleep, GH secretion is disrupted, which, in turn causes reduction in serum basal IGF-1 level.[11] This is suggested to have a role in physiopathology of FMS and myalgia. FMS patients commonly suffer from GH deficiency, with impaired GH responses, leading to reduced insulin-like growth hormone [12] As these hormones are involved in muscle microtrauma repair, the healing of this tissue could be affected by sleep disturbances.[11] Previous studies have shown that GH replacement in low IGF-1 patients can significantly improve some symptoms and quality of life in FMS.[13] The purpose of the study is to investigate the differences of serum IGF-1 levels and its relationship of clinical symptoms in female patients with fibromyalgia syndrome.

Materials and Methods

A total of 37 female out-patient individuals between 18-55 years of age and diagnosed to have FMS in the polyclinic of Physical Medicine and Rehabilitation were included

into the study. These patients had the criteria issued by American College of Rheuomatology in 1990 for fibromyalgia.[14] Control group, however, consisted of 32 healthy subjects between 18-55 years of age, who resembled the patient group in terms of age and gender and who had no previous systemic disease. The study was conducted in accordance with the declaration of Helsinki, and the Ethical Committee approval and informed consents were obtained.

These criteria to include were:

1) Widespread pain for at least 3 months, on both sides of the body and above and below the waist, and pain at 11 of 18 tender points on digital palpation (cervical spine or anterior chest or thoracic spine or low back pain)
2) The presence of at least 11 tender point sites[14]
3) The patients with normal hemogram, biochemical blood analysis, thyroid function tests

These criteria to exclude were:

1) Those patients with diagnosed to have a known sistemic, metabolic and endochrine, as well as tumoural, neurologic or infectious disease
2) Male patients
3) FMS patients and normal controls who had were a recent or past history of psychiatric disorders, such as major depressive disorder, schizophrenic or paranoid disorder, personality disorders and somatoform disorders

Demographical and clinical properties and test results of the patients were recorded on the evaluation form. Regarding the clinical state, sleep state, morning stiffness, headache and any other complaints were questioned in both patient and control groups. In order to assess the disease activity, pain duration, pain severity, fatigue, morning stiffness duration and sleep disorder were taken as parameters. Presence of any other symptoms accompanying FMS were also questioned and recorded.

In patients with fibromyalgia, such clinical parameters as common body pain, fatigue, Fibromyalgia Impact Questionnaire (FIQ), Tender Point Number (TPN), Beck Depression Scale (Beck DS), morning stiffness, headache and sleep disorder were evaluated. Pressure was performed on tender points so much that thumbnail of the examiner became white (nearly 4 kg/cm2).

Beck Depression Inventory (BDI) was used to evaluate psychological state of the patients and controls. BDI score ≥9 was defined as depression.[15] Fibromyalgia Impact Questionnaire (FIQ) which was developed by Burkhardt et al. and was found to be valid and reliable for Turkish population, was used to evaluate the quality of life. Turkish version of FIQ was used which was developed for FMS and evaluates physical functioning, work record, depression, anxiety, working difficulty, sleep, pain, stiffness, fatigue and overall well-being.[16,17] State Trait Anxiety Inventory (STAI) was used to evaluate anxiety. For STAI, participants were questioned about feeling, thought or behaviour as “not at all”, “somewhat”, “moderately so”, “very much so”.[18] Health Assessment Questionnarie (HAQ) was used to evaluate functional disability and health state. Likert scale (range 0-4, 0=none, 1=mild, 2=moderate, 3=severe, 4=very severe) was used to evaluate morning stiffness, fatigue, severity of insomnia, pain, muscle

spasm and tenderness. Visual Analogue Scale (VAS) was used to measure the severity of widespread musculoskeletal pain in both patient and control groups. Pain was evaluated with a 100mm VAS with maximum pain on the right end, being pain-free on the left end.

There is no specific laboratory finding to diagnose Fibromyalgia syndrome. Any disorder cannot be detected through routine blood and urine tests. Rather, rheumatic, neurologic, psychiatric, infectious, endochrine reasons and malignities that lead to chronic widespread pain should be taken into consideration for its diagnosis. For the determination of the accompanying diseases, which should be taken into account for differential diagnosis, total blood count, biochemical blood analysis, erythrocyte sedimentation rate, thyroid function tests, liver function tests, urinary analysis and electrolyte values of all the patients and controls were checked.

Depression, anxiety, post-traumatic stress disorder, panic disorder, emotional disorders like somatization, acutely severe or continuous mental stress, inability to cope with difficulties are factors that aggravate symptoms in fibromyalgia. At the same time, accompanying different psychiatric disorders exacerbate different symptoms. Therefore, those with major depression and definite psychiatric anamnesis were excluded from the study. Individuals with abnormal laboratory findings due to any other medical problems, with diabetes mellitus, obesity or liver dysfunction were also excluded.

Electrochemiluminescence Immunassay (ECLIA) (1010/1020 Elecsys Systems Immunoassay; Roche Diagnostics, Mannheim, Germany) was used to measure serum IGF-1 levels. Blood was drawn by venous puncture, clotted at room temperature, serum removed by centrifugation. Although IGF-1 levels do not fluctuate greatly throughout the day for an individual person, the blood samples were collected between 08:00 AM and 10:00 AM.[10]

Statistical evaluation

Statistical analyses were performed using SPSS 11.5 package programme. Student's t test was used for the comparison of differences between the groups. Pearson correlation analysis was performed to assess the association between the variables in the patient group. Differences were considered statistically significant if $p \leq 0.05$.

Results

All 37 of fibromyalgia patients and 32 controls included in the study were females, mean age was 39.08 ± 9.78 for the patient group and 39.06 ± 11.48 for the control group. Mean Body mass index (BMI) was 27.76 ± 4.96 kg/m² in the patient group and 26.09 ± 3.09 kg/m² in the control group. Statistically significant difference was not found between the two groups regarding age and BMI ($p>0.05$). In the patient group, disease duration was 9-120 months, mean duration was 22.97 ±19.29 months.

Symptoms of patients with FMS and of healthy control subjects were given in Table 1. There was not any difference between both groups in terms of age, occupation, Raynaud phenomenon and pain during urination. However, there was a statistically significant difference between the patient and control groups for widespread pain, headache, fatigue, mouth dryness, paresthesia, swelling, raynaud, difficulty in falling

asleep, morning tiredness, pollakiuria, constipation, morning stiffness, cold sensitivity, humidity, overworking, noise, dysmenorrhea and stress (Table 1).

Table 1. Symptoms of patients with FMS and of healthy control subjects

	Fibromyalgia n (%)	**Control (n)**	**p**
Widespread pain	37 (100)	0	<0.001
Headache	32 (86.48)	3	<0.001
Fatigue	34 (91.89)	1	<0.001
Sleeping disorder	25 (67.56)	1	<0.001
Mouth dryness	24 (64.86)	1	<0.001
Paresthesia	33 (89.18)	1	<0.001
Swelling	30 (81.08)	0	<0.001
Raynaud	14 (37.83)	9	0.393
Difficulty in falling asleep	26 (70.27)	0	<0.001
Morning tiredness	33 (89.18)	5	<0.001
Pollakiuria	13 (35.13)	2	0.004
Constipation	15 (40.54)	3	0.003
Morning stiffness	26 (70.27)	0	<0.001
Painful urination	8 (21.62)	2	0.700
Cold sensitivity	29 (78.37)	2	<0.001
Humidity	26 (70.27)	0	<0.001
Overworking	35 (94.59)	5	<0.001
Noise	22 (59.45)	0	<0.001
Dysmenorrhea	20 (54.05)	0	<0.001
Stress	34 (91.89)	6	<0.001

Demographical and clinical findings of patients with FMS and of healthy control subjects were given in Table 2. Statistically significant difference was found between patients and control in terms of IGF-1 levels (p=0.004), tender point count (p<0.001), STAI (state anxiety inventory) (p<0.001), Beck depression inventory (BDI) (p<0.001), FIQ (fibromyalgia impact questionnarie) (p<0.001), HAQ (health assessment questionnarie) (p<0.002), stiffness (p<0.001), fatigue (p<0.001) and muscle spasm (p<0.001). BMI, duration of pain, trait anxiety, Beck depression inventory, FIQ score, HAQ score, tender point count, stiffness, fatigue, insomnia, VAS, degree of muscle spasm, tenderness and IGF-1 levels of patient and control groups were compared (Table 2).

When we evaluated the correlation between serum IGF-1 levels and clinical symptoms and findings in patients with FMS, significant correlation was found between serum IGF-1 levels and age (r=-0.496; p<0.01), muscle spasm (r=-0.333; p<0.05), tender point count (r=-456; p<0.01), and morning stiffness (r=-0.463; p<0.01), respectively. No

significant correlation was found between serum IGF-1 levels and BDI, STAI, FIQ and HAQ, respectively, for the FMS group.

Table 2. Demographical and clinical findings of patients with FMS and of healthy control subjects

	Fibromyalgia (n=37)	**Control (n=32)**	**P values**
Age (yr)	39.89±9.78	39.06±11.48	0.747
Body mass index (kg/m^2)	27.76±4.96	26.09±3.09	0.105
FIQ	4.72±1.36	0.57±0.11	<0.001
HAQ	0.72±0.72	0.27±0.31	0.002
Tender point count	16.48±1.70	4.87±1.77	<0.001
Stiffness	1.91±0.82	0	<0.001
Fatigue	2.70±0.70	0.03±17	<0.001
Insomnia	2.00±0.88	0	<0.001
VAS	3.56±0.92	0	<0.001
BDI	17.81±9.26	8.50±7.73	<0.001
Degree of muscle spasm	2.18±0.56	0	<0.001
Tenderness	2.37±0.86	0.06±0.24	<0.001
IGF-1	100.97±38.62	135.02±54.45	0.004
STAI	48.13±10.21	40.03±6.69	<0.001

VAS; Visual Analogue Scale, IGF-1; Insulin-like growth hormone, FIQ; Fibromyalgia impact questionnarie, STAI: State-trait anxiety inventory, HAQ; Health assessment scale, BDI: Beck depression Inventory

Discussion

In this study, we aimed to investigate the differences between female fibromyalgia patients and controls in terms of serum IGF-1 levels, clinical symptoms and findings.

The main symptom of FMS is chronic, widespread pain. The most common symptoms in fibromyalgia; sleep disorders 89.1%, fatigue 88.6%, widespread pain 85.2%, paresthesias 67.6%, cognitive problems 66.3%, headache 64.7%, depression 47.5%, irritable colon syndrome 46.3%, constipation 41.9%.[14,19] In our study, all of the patients had complaints about widespread pain, headache in 86,48%, fatigue in 91.89%, paresthesia in 89.18%, swelling in %81.08, difficulty in falling a sleep in 70.27%, and constipation in 40.54%.

Besides, its pathogenesis has not been exactly explained; a variety of factors such as sleep disorders, neuroendochrine dysfunction, regional blood flow changes, metabolical and immunological disturbances are suggested to have a role in the pathogenesis.[3,9] There are many studies about serum hormone levels of fibromyalgia patients, but the results are conflicting. GH is an anabolic peptide which stimulates synthesis of DNA, RNA and proteins. GH plays an important role in muscle

homeostasis and repair. IGF-1 has anabolic effects, and it is the major mediator of GH, which is essential in normal muscle homeostasis.

Although, in most of the studies, GH levels of the patients with FMS were found to be lower than healthy controls, in some studies, normal results were also found.[11,20,21] Bennet et al. found also low serum IGF-1 and GH levels in female patients with FMS.[11] Low IGF-1 level is reported as probable reflection of disturbance in GH and hypothalamo-pituitary-adrenal axis response or insufficient adrenal response.[13] Secretion disorder of GH makes the patients prone to muscle microtrauma, distrupting the healing process of muscle. Some investigators observed cessation in GH production in individuals who were intendedly remained sleepless.[7]

Cuatrecasas G et al. found low serum IGF-1 levels in 169 of 493 female patients with primary fibromyalgia.[22] In this study, serum IGF-1 levels were significantly lower in fibromyalgia group compared to healthy controls. In another study, while GH levels were found to be significantly lower in fibromyalgia group compared to controls, no significant difference was detected in IGF-1 levels.[23]

Distrupted secretion of IGF-1 may also be associated with pain and fatigue in fibromyalgia patients with normal physicaly activity.[24] Krsrich et al. have reported that reduction in IGF-1 levels may be associated with increase in post-exercise muscle tissue microtrauma and distruption in repair in fibromyalgia patients.[25,26] In our study, there was also significant correlation between serum IGF-1 levels and skeletal muscle homeostazis especially in tender point count and severity of stiffness.[7]

We found that patients with FMS had significantly poorer quality of life, more anxiety and depression compared to the healthy people but we did not find a significant correlation with IGF-1 levels. Another study found no correlation between serum IGF-1 levels and depression.[27] Cuatrecasas G et al. did not find an association between IGF-1 levels and quality of life.[22]

Many previous studies have demonstrated that serum IGF-1 levels decrease with aging. Mc Call et al. measured serum IGF-1 levels of 24 premenopausal fibromyalgia patients and 27 healthy controls. They found similar results of serum IGF-1 levels in premenopausal fibromyalgia patients and healthy controls; however, they have detected reduction in serum IGF-1 levels with increasing age and obesity.[21] Armağan et al. found that there was negative correlation between age and serum IGF-1 levels.[28] In our study, however, there was a negative correlation between age and serum IGF-1 levels.

In a recent study, 50% reduction in tender point count and VAS of FMS patients were detected with low dose GH therapy. In a similar study, low dose GH implementation was found effective in FMS patients for the reduction of severity of pain and increase in the quality of life.[29]

The major restriction of our study was the limited number of patients. Therefore, more comprehensive studies with larger sample size are needed to confirm our results.

Our study has shown that serum IGF-1 levels of fibromyalgia patients are lower as compared to healthy controls, and low serum IGF-1 levels are significantly correlated with tender point count, stiffness and severity of muscle spasm. We have concluded

that low serum IGF-1 levels may take role in etiopathogenesis of fibromyalgia and may be related to the severity of the symptoms.

References

1. Gupta A, Silman AJ. Psychological stress and fibromyalgia: a review of the evidence suggesting a neuroendocrine link. Arthritis Res Ther 2004;6:98-106.
2. Goldenberg DL. Fibromyalgia end related sydromes. In Klippel JH Dieppe PA (eds) Rheumatology. London: Mosby;1998.
3. Uveges JM, Parker JC, Smarr KL, et al. Psychological symtomps in primer fibromyalgia syndrome. Relationship to pain, life stres and sleep disturbance: Arthritis Rheum 1990;33(8):1279-83.
4. Forseth KO, Gran JT, Husby GA. Population study of the incidence of fibromyalgia among women aged 26-55 yr. Br J Rheumatol 1997;36:1318-23.
5. Solitar BM. Fibromyalgia: knowns, unknowns, and current treatment. Bull NYU Hosp Jt Dis 2010;68:157-61.
6. Recla JM. New and emerging therapeutic agents for the treatment of fibromyalgia: an update. J Pain Res 2010;3:89-103.
7. Jones GT, Nicholl BI, McBeth J, et al. Role of road traffic accidents and other traumatic events in the onset of chronic widespread pain: Results from a population-based prospective study. Arthritis Care Res (Hoboken), 2011;63:696-701.
8. Spath M. Current experince with 5-HT3 receptor antagonists in fibromyalgia. Rheum Dis Clin North Am 2002;28(2):319-28
9. Güleç H, Sayar K, Güleç Yazıcı M. Fibromiyaljide Tedavi Arayışının Psikolojik Etkenlerle İlişkisi. Türk Psikiyatri Dergisi 2007;18:22-30
10. Engström BE, Karlsson FA, Wide L. Clin Chem 1999;45:1235-9.
11. Bennet RM, Clark CR, Campbell SM, Burckhardt CS. Low levels of somatomedin C in patients with the fibromyalgia syndrome. A possible link between sleep and muscle pain. Arthritis Rheum 1992;35(10):1113-6.
12. Bjersing JL, Dehlin M, Erlandsson M, Bokarewa MI, Mannerkopi K. Changes in pain and IGF-1 in fibromyalgia during exercise: the involvement of cerebrospinal inflammatory factors and neuropeptides. Arthritis Research Teraphy 2012;14(4):R162 [Epub ahead of print].
13. Cuatrecasas G, Alegre C, Casanueva FF. GH/IGF axis disturbances in the fibromyalgia syndrome: is there a rationale for GH treatment? Pituitary 2013, DOI 1007/s 11102-013-0486-0.
14. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990: criteria for the classification of fibromyalgia: Report of the Multi-Center Criteria Committee. Arthritis Rheum 1990;33:160-72.
15. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. Beck Depression Inventory. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561-71.
16. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18:728-33.
17. Sarmer S, Ergin S, Yavuzer G. The validity and reliability of the Turkish version of the Fibromyalgia Impact Questionnaire. Rheumatol Int 2000; 20:9-12.
18. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the State-Trait Anxiety inventory. Palo-Alto: Consulting Psychologists Press; 1970.
19. Wolfe F, Hawley DJ: Evidence of disordered symptom appraisal in fibromyalgia: Increased rates of reported comorbidity and comorbidity severity. Clin Exp Rheumatol 1999;17:297-303.
20. Charles W, Denko C, Malemud J. Serum growth hormone and insulin but not insulin-like growth factor-1 levels are elevated in patients with fibromyalgia syndrome. Rheumatol Int 2005;25:146-51.
21. McCall-Hosenfeld JS, Goldenberg DL, Hurwitz S, Adler GK. Growth hormone and insulin-like growth factor-1 concentrations in women with fibromyalgia. J Rheumatol 2003;30:809-14.
22. Cuatrecasas G, Gonzalez MJ, Alegre C, et al. High prevalence of growth hormone deficiency in severe fibromyalgia syndromes. Clin Endocrinol Metab. 2010;95(9):4331-7. doi: 10.1210/jc.2010-0061. Epub 2010 Jul 14.

23. Bagge E, Bengtsson B, Carlsson E, et al. Low growth hormone secretion in patients with fibromyalgia. A preliminary report on 10 patients and 10 controls. Am J Med 1998;104:227.
24. Russell IJ. Neurochemical pathogenesis of fibromyalgia sydrome. J Muskuloskeletal Pain 1996;4:61-92.
25. Krsrich-Shriwise S. Fibromyalgia syndrome: an overview. Phys Ther 1997;77(1):68-75.
26. Okifuji A, Turk DC. Sex hormones and pain in regularly menstruating women with fibromyalgia syndrome. J Pain 2006;7:851-9.
27. Katetoff D, Lampa J, Westman M, Anderrson M, Kosek E: Evidence of central inflammation in fibromyalgia-increased cerebspinal fluid interleukin-8 levels. J Neuroimmunol 2012;242:33-8.
28. Armağan O, Sırmagül E, Ekim A, Sırmagül B, Taşçıoğlu F, Öner C. Levels of IGF-1 and Their Relationship with Bone Mineral Density in the Premenopausal Women with Fibromyalgia Syndrome. Romatizma 2008;23:118-23.
29. Cuatrecasas G, Alegre C, Fernandez-Solà J, et al. Growth hormone treatment for sustained pain reduction and improvement in quality of life in severe fibromyalgia. Pain 2012; 153(7):1392-9.