ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

Med J SDU / SDÜ Tıp Fak Derg ▶ 2020:27(1):113-118 doi: 10.17343/sdutfd.634438

FREQUENCY OF IRON DEFICIENCY AND IRON DEFICIENCY ANEMIA IN FIBROMYALGIA SYNDROME

FİBROMİYALJİ SENDROMUNDA DEMİR EKSİKLİĞİ VE DEMİR EKSİKLİĞİ ANEMİSİ GÖRÜLME SIKLIĞI

Fatih BAYGUTALP[1], Duygu ALTINTAŞ[1], Ayhan KUL[1]

[1] Department of Physical Therapy and Rehabilitation, School of Medicine, Ataturk University, Erzurum, Turkey

Cite this article as: Baygutalp F, Altıntaş D, Kul A. Frequency of Iron Deficiency and Iron Deficiency Anemia in Fibromyalgia Syndrome. Med J SDU 2020; 27(1): 113-118.

Öz

Amaç

Etiyolojisi tam olarak bilinmeyen kronik bir ağrı durumu olan fibromiyalji sendromu (FMS) temel olarak yaygın ağrı, uyku bozuklukları, hafıza sorunları ve yaşam kalitesini ciddi şekilde bozan yorgunluk ile karakterizedir. Kandaki azalmış demir seviyelerinin bir sonucu olarak biyojenik amin nörotransmiterlerinin üretimindeki azalma FMS'nin patofizyolojisinde rol oynayabilir. Bu çalışmada FMS'li hastalarda demir eksikliği ve demir eksikliği anemisinin prevalansının araştırılması ve FMS'li hastalarda demir eksikliği prevalansına dikkat çekilmesi amaçlanmıştır.

Gereç ve Yöntem

Hastanemiz fiziksel tip ve rehabilitasyon polikliniği'ne son beş yıl içinde müracaat eden hastalardan FMS tanısı alan ve serum ferritin, total demir bağlama kapasitesi (TDBK),vitamin B12 konstantrasyonları ile plazma hemoglobin konstantrasyonları belirlenmiş olan hastalar retrospektif olarak değerlendirilmiştir. Veriler SPSS 23 paket programı kullanılarak analiz edilmiştir.

Bulgular

FMS'li kadın ve erkek hastalar arasındaki bağımsız grup karşılaştırmalarında, plazma hemoglobin ve serum demir düzeylerinin kadın hastalarda erkek hastalara göre anlamlı derecede düşük olduğu görülmüştür (sırasıyla, p = 0.009 ve p = 0.002). FMS'li erkek ve kadın hastalar arasında serum B12 düzeyleri ile serum ferritin düzeyleri arasında istatistiksel olarak anlamlı bir fark görülmemiştir (sırasıyla p = 0.344, p = 0,093). Ayrıca, tüm FMS hastalarının % 28'inde demir eksikliği ve% 12'sinde demir eksikliği anemisi olduğu belirlenmiştir.

Sonuç

FMS tedavisinde başarının artırılması için FMS hastalarında serum ferritin seviyelerinin ölçülmesi ve gerektiğinde demir eksikliğinin tedavi edilmesi önerilmektedir.

Anahtar Kelimeler: Demir eksikliği, ferritin, fibromiyalji sendromu, sıklık

Abstract

Objective

Fibromyalgia syndrome (FMS), which is a chronic pain condition of unknown etiology, is mainly characterized by widespread pain, sleep disturbances, memory problems, and fatigue, which seriously impair quality of life. Decreased production of biogenic amine neurotransmitters as a result of decreased iron levels in the blood may play a role in the pathophysiology of FMS. This study aimed to investigate the prevalence of iron-deficiency and iron-deficiency anemia in patients with FMS and to draw attention to the prevalence of iron-deficiency in patients with FMS.

İletişim kurulacak yazar/Corresponding author: drbaygutalp@gmail.com
Müracaat tarihi/Application Date: 11.11.2019 • Kabul tarihi/Accepted Date: 13.02.2020
Available online at http://dergipark.gov.tr/sdutfd
Makaleye http://dergipark.gov.tr/sdutfd web sayfasından ulaşılabilir.

Material and Methods
The patients who applied to the physical medicine and rehabilitation outpatient clinic of our hospital in the last five years, who were diagnosed as FMS and whose serum ferritin, total iron-binding capacity (TIBC), vitamin B12 concentrations and plasma hemoglobin concentrations were determined were analyzed retrospectively. Data were analyzed by using SPSS 23 package program.

Results
In the independent group comparisons between female and male patients with FMS, both plasma hemoglobin and serum iron levels were significantly lower in female patients than in male patients (p =0.009 and p = 0.002, respectively). There were no statistically significant differences between serum vitamin B12 levels and serum ferritin levels between male and female patients with FMS (p= 0.344, p=0,093 respectively). Besides, iron-deficiency and iron-deficiency anemia were observed in 28% and 12% of all FMS patients, respectively.

Conclusion
Measuring serum ferritin levels in FMS patients and treating iron-deficiency when necessary is recommended to increase the success of FMS treatment.
Keywords: ferritin, fibromyalgia syndrome, frequency, iron-deficiency

Introduction

Fibromyalgia syndrome (FMS), which is a chronic pain condition of unknown etiology, is mainly characterized by widespread pain, sleep disturbances, memory problems, and fatigue, which seriously impairs quality of life (1-3). The definition, diagnosis, pathogenesis, and treatment of FMS continue to be points of contention (4). Besides, the causes of FMS remain unclear, and unfortunately, quantitative research cannot explain the patient's individual narratives and perceptions. However, FMS is generally accepted as a syndrome with pathogenesis centered in the nervous system and abnormalities occurring in pain regulating mechanisms at various levels of peripheral and central nervous systems (5). In FMS, sometimes factors like surgery, infection, physical trauma or significant psychological stress trigger symptoms. In other cases, symptoms develop gradually over time without a single triggering event (6). FMS is present in 2-4% of the population and a costly condition due to delay in diagnosis (1,5,7). Health care costs are more than $4000/year for patients with FMS (5). FMS may be considered a multi-systemic disease and thus, a multidisciplinary approach in the treatment of FMS is required. With a multimodal approach to the treatment of FMS, non-pharmacological strategies (exercise and psychoeducational approaches etc.) should be added to the treatment and avoid the simple prescription of a drug (5, 8, 9). Drug therapy only plays a supporting role in the management of symptoms (pain, sleep disorders, and psychological disorders). The drugs (duloxetine, and pregabalin, etc.) should be started at low doses and increased carefully (4).

Recently, it has been reported that there is a strong relationship between FMS and obesity due to the role of obesity in inflammation and chronic pain. This relationship will contribute to the understanding of the epidemiology and pathogenesis of FMS. Besides, obesity has negative effects on the course of FMS. Obese patients with FMS have more pain, reduced mobility and function and they are more depressive and use more medication. Furthermore, the applicability and effectiveness of treatment interventions are difficult, especially in terms of physical activity, which is severely reduced in obese patients and it is well known that physical activitiy. is the mainstream of FMS treatment (10,11).

Other studies showed that the use of occupational therapy programs, such as a floristry course or the exercises such as Tai Chi have significantly greater effects on patients with FMS than in standard care; therefore, it is stated that therapy courses or exercises can be used as an alternative treatment to improve the quality of life patients with FMS (3,7). Kösehasanoğulları et al. (12) investigated whether FMS has a neuropathic pain component. The authors have concluded that FMS is a neuropathic pain syndrome and sensorial symptoms (paraesthesia, hyperalgesia, and allodynia) were more widespread and the scores of neuropathic pain scales in FMS patients were significantly higher than in the control group. In another study, perceived social support was displayed to be strongly related to anxiety, burnout, depression, and severity of pain in FMS patients (13).

Ferritin has a significant role in the storage of intracellular iron. Serum ferritin measurement, which was discovered in the 1930s and developed in the 1970s as a clinical test, is commonly used in diagnosing and monitoring many diseases associated with iron-deficiency or iron overload. Thus, determining serum ferritin levels is a clinically useful tool (14). In a study investigating the relationship between FMS and se-

rum ferritin levels in patients with primary FMS, it was found that the mean serum ferritin level of patients with FMS was lower than that in the control group (healthy females). It was expressed that there was a possible relationship between FMS and low serum ferritin levels (15).

In another study, the efficacy and safety of ferric carboxymaltose in iron-deficient patients with FMS after application of ferric carboxymaltose was evaluated against the placebo (the patients treated with normal saline). It was found that the application of ferric carboxmaltoose improved measurement of fibromyalgia severity and ferric carboxmaltoose was well tolerated. Thus, it has been stated that ferric carboxmaltoose may be beneficial in the treatment of iron-deficient patients with FMS (16).

It is known that the concentrations of certain biogenic amine metabolites including dopamine, norepinephrine, and serotonin are reduced in the cerebrospinal fluid of patients with FMS (15). Decreased production of biogenic amine neurotransmitters as a result of decreased iron levels in the blood may play a role in the pathophysiology of FMS.

Study aimed to investigate the prevalence of iron-deficiency and iron-deficiency anemia in patients with FMS and to draw attention to the prevalence of iron-deficiency in patients with FMS.

Material and Methods

One hundred and twenty patients suffering from FMS admitted to Physical Medicine and Rehabilitation outpatient clinic of Buhara Hospital within the last five years (between January 1, 2014 and December 31, 2018) were analyzed retrospectively using hospital automation system and patient file archives.

The inclusion criteria were as follows:

1. Patients with FMS
2. Patients who have test results of serum ferritin, iron, vitamin B12 concentrations, total iron-binding capacity, and plasma hemoglobin levels.

The exclusion criteria were as follows:

1. Acute and chronic infections (since ferritin is an acute phase reactant)
2. Inflammatory diseases
3. Rheumatic diseases
4. Malignancies
5. Depression
6. Pathological fracture
7. Osteoporosis
8. Pregnancy and breastfeeding

All exclusion criteria were applied according to the patient history information using hospital automation system and patient file archives. Additionally, patients with erythrocyte sedimentation rate (ESR) level higher than 20mm/h and CRP level higher than 5 mg/dl were assumed with inflammatation and excluded from the study. After the inclusion and exclusion criteria were applied, the study was completed with the data of the remaining 75 patients with FMS.

Demographic data and serum ferritin, iron, TIBC, vitamin B12 levels, and plasma hemoglobin levels of these patients were recorded.

Serum ferritin levels of less than 15 ng/dl were evaluated as iron-deficiency. In addition to iron-deficiency, patients with hemoglobin values below 12 g/dl in premenopausal women and 13 g/dl in postmenopausal women and men were evaluated as iron-deficiency anemia (17). B12 deficiency was evaluated serum total vitamin B12 concentrations of less than 300 pg/ml values were evaluated as vitamin B12 deficiency and less than 200 pg/ml values were evaluated as vitamin B12 deficiency (18). In our laboratory, the reference range of serum iron level is 37-145 ug/dl and the reference range of serum TIBC level is 127-450 (pg/dl). Classification was made by applying these criteria and patients were identified as follows: patients with iron-deficiency, patients with iron-deficiency anemia, patients with vitamin B12 deficiency, patients with vitamin B12 insufficiency, iron level under the reference range and TIBC level outside the reference range.

The results were evaluated in SPSS 23 package program. Descriptive statistics (mean, standard deviation, frequency) were made. To determine the difference of age and biochemical parameters according to gender, the t-test was performed in independent groups and $p < 0.05$ values were accepted as statistically significant in a 95% confidence interval.

The study was approved by the local Ethics Committee of Ataturk University School of Medicine (Approval number: 26.09.2019/424).

Results

The demographic characteristics and results of biochemical parameters of patients with FMS were demonstrated in Table 1.

The mean age of all patients was 41,43±15,52 years, and there was no statistically significant difference between the ages of male and female patients with FMS (p =0,048).

In the independent group comparisons between female and male patients with FMS, both plasma hemoglobin and serum iron levels were significantly lower in female patients than in male patients (p =0.009 and p = 0.002, respectively).

There were no statistically significant differences between serum vitamin B12 levels and serum ferritin levels between male and female patients with FMS (p= 0.344, p=0,093 respectively).

Percentages of patients with iron-deficiency, iron-deficiency anemia, vitamin B12 deficiency, vitamin B12 deficiency, the iron level below the reference range and TIBC level outside the reference range were determined patients with FMS (Table 2).

Discussion

In this study, we determined the plasma hemoglobin level and also vitamin B12, ferritin and iron levels in serum of female and male patients with FMS. It was found that the plasma hemoglobin and serum iron levels of female patients with FMS were found to be statistically lower compared to those of male patients with FMS. When evaluated in terms of vitamin B12 and ferritin levels in serum, their levels were lower in female patients with FMS, however, there was no significant difference between male and female patients with FMS. Besides, iron-deficiency and iron-deficiency anemia were observed in 28% and 12% of all FMS patients, respectively.

FMS is not a deforming, progressive and life-threatening syndrome. However, depression and anxiety are seen commonly in patients with FMS. Although its etiology remains unclear, the regulation in neuroendocrine and autonomic systems is understood based

Table 1 The demographic characteristics and results of biochemical parameters of patients with FMS

	All patients (n=75)	Female patients (n=62)	Male patients (n=13)
Age (year)	41,43±15,52	43,41±14,14	31,85±18,77
Hemoglobin (g/dl)	13,54±1,41	13,35±1,37	14,45±1,26
Iron (ug/dl)	75,46±33,46	69,96±30,87	102,10±33,85
Ferritin (ng/ml)	30,13±21,81	28,23±22,25	39,39±17,36
TIBC (ug/dl)	346,44 ± 74.70	347,36±76,83	339,70±70,00
Vitamin B12 (pg/ml)	383,21±162,52	375,02±161,49	422,31±168,27

TIBC: Total iron binding capacity, results are presented as mean±standard deviation.

Table 2 The frequency of clinical conditions in patients with FMS

Clinical condition	All patients (%)	Female patients (%)	Male patients (%)
Iron-deficiency	28,00	32,25	7,69
Iron-deficiency anemia	12,00	13,84	0,00
Vitamin B12 deficiency	36,00	35,48	38,46
Vitamin B12 insuffuciency	8,00	9,67	0,00
Iron level under the reference range	10,66	12,90	0,00
TIBC level outside the reference range	1,33	1,61	0,00

TIBC: Total iron binding capacity

on FMS. For the diagnosis of FMS, various laboratory tests (complete blood count, the determination of creatinine phosphokinase, vitamin D and erythrocyte sedimentation rate and rheumatoid factor, etc.) are performed. These tests are important to rule out other possible disorders (19). Besides, in some studies, proinflammatory cytokines, oxidized low-density lipoprotein (Ox-LDL) and ferritin levels have been investigated in patients with FMS to better understand FM syndrome (15). Pamuk et al. (20) evaluated the prevalence of FMS in patients with iron-deficiency anemia and also prevalence of iron-deficiency anemia in outpatients with FMS. They studied on 205 patients iron-deficiency anemia and 100 healthy controls and found that the prevalences of FMS in patients with iron-deficiency anemia were 17.6% and higher than that (6%) in healthy controls. Compared to iron-deficiency anemia patients without FMS, the majority of iron-deficiency anemia patients with FMS were female, married and with a history of pica. On the other hand, there were no significant differences between the iron parameters and serum hemoglobin levels of iron-deficiency anemia patients with and without FMS. Besides, iron-deficiency anemia was detected in 24.5% of FMS patients.

Ortancil et al. (15) investigated the relationship between FMS and serum ferritin levels in patients with FMS and determined the mean serum ferritin levels of the patients with FMS and control group (healthy females) as 27.3 ± 20.9 and 43.8 ± 30.8 ng/mL, respectively. The researchers stated that there is a possible relationship between FMS and low serum ferritin levels, even if within normal limits, and iron, which is a cofactor in the production of serotonin and dopamine, may play a role in the etiology of FMS. Furthermore, Boomershine et al. (16) reported that intravenous administration of ferric carboxymaltose (15 mg/kg) to FMS patients with low ferritin and low transferrin saturation, which indicates depletion of total body iron stores, was useful to improve the fibromyalgia symptoms and that the use of ferric carboxymaltose was safe and well-tolerated in these patients. Soppi (21) stated that muscle and joint pain associated with iron deficiency are considered FMS, thus, it is more useful to listen to the descriptions of patients for their symptoms than to use the full blood count to eliminate iron deficiency. If the symptoms indicate iron-deficiency and the patients have <75 µg/L of serum ferritin concentration, there is iron deficiency in the patients. The symptoms associated with iron deficiency may be caused by the metabolic systems in which many iron-containing proteins. Therefore, iron deficiency should always be treated.

Conclusion

Consequently, the investigation of iron-deficiency, the measurement of serum ferritin levels in patients with FMS, and treating iron-deficiency, if necessary, will be beneficial to improve the success of FMS treatment.

Previous presentation

This study was presented as an oral presentation at 5th International Eurasian Congress on Natural Nutrition, Healthy Life & Sport which was held on 2th-6th October 2019, in Ankara, Turkey.

Acknowledgment

The authors thank to Dr. Hulki Aşır, Head of Buhara Hospital, for his kind help on data sharing.

References

1. Clauw DJ. Fibromyalgia: A Clinical Review. JAMA 2014;311(15):1547–55.
2. Bellato E, Marini E, Castoldi F, Barbasetti N, Mattei L, Bonasia DE et al. Fibromyalgia Syndrome: Etiology, Pathogenesis, Diagnosis, and Treatment. Pain Research and Treatment 2012; article ID 426130, doi:10.1155/2012/426130.
3. Yavne Y, Kabaha A, Rosen T, Avisar I, Orbach H, Amital D et al. The Powers of Flowers: Evaluating the Impact of Floral Therapy on Pain and Psychiatric Symptoms in Fibromyalgia. Isr Med Assoc J 2019;21(7):449-53.
4. Häuser W, Fitzcharles MA. Facts and myths pertaining to fibromyalgia. Dialogues Clin Neurosci 2018;20(1):53-62.
5. Fitzcharles MA, Ste-Marie PA, Pereira JX; Canadian Fibromyalgia Guidelines Committee. Fibromyalgia: evolving concepts over the past 2 decades. CMAJ 2013;185(13):E645–E651.
6. Furness PJ, Vogt K, Ashe S, Taylor S, Haywood-Small S, Lawson K. What causes fibromyalgia? An online survey of patient perspectives. Health Psychol Open. 2018;5(2):2055102918802683.
7. Cheng CA, Chiu YW, Wu D, Kuan YC, Chen SN, Tam KW. Effectiveness of Tai Chi on fibromyalgia patients: A meta-analysis of randomized controlled trials, Complementary Therapies in Medicine 2019; 46:1-8.
8. Pastor-Mira MA, López-Roig S, Martínez-Zaragoza F, León E, Abad E, Lledó A, et al. Goal Preferences, Affect, Activity Patterns and Health Outcomes in Women With Fibromyalgia. Front Psychol 2019;10:1912.
9. Pastor-Mira MA, López-Roig S, Peñacoba C, Sanz-Baños Y, Lledó A, Velasco L Predicting walking as exercise in women with fibromyalgia from the perspective of the theory of planned behavior. Women Health 2019:1-14.
10. Aloush V. Fibromyalgia, obesity and all that lies in between. Harefuah 2019;158(9):587-588.
11. Blokh Kerpel A, Tiosano S, Amital D, Comaneshter D, Cohen AD, Amital H. Association of obesity, smoking and socioeconomic strata with the fibromyalgia syndrome, Harefuah 2019;158(9):583-6.
12. Kösehasanoğullari M, Erdinç Gündüz N, Akalin E. Is Fibromyalgia Syndrome a Neuropathic Pain Syndrome? Arch Rheumatol 2018;34(2):196-203.
13. Gunduz N, Uşen A, Aydin Atar E. The Impact of Perceived Social Support on Anxiety, Depression and Severity of Pain and Burnout Among Turkish Females With Fibromyalgia. Arch Rheumatol 2018;34(2):186-95.
14. Wang W, Knovich MA, Coffman LG, Torti FM, Torti SV. Serum ferritin: Past, present and future. Biochim Biophys Acta.

2010;1800(8):760–769.
15. Ortancil O, Sanli A, Eryuksel R, Basaran A, Ankarali H. Association between serum ferritin level and fibromyalgia syndrome. Eur J Clin Nutr 2010;64(3):308-12.
16. Boomershine CS, Koch TA, Morris D. A Blinded, Randomized, Placebo-Controlled Study to Investigate the Efficacy and Safety of Ferric Carboxymaltose in Iron-Deficient Patients with Fibromyalgia. Rheumatol Ther 2018;5(1):271–281.
17. WHO. Serum ferritin concentrations for the assessment of iron status and iron-deficiency in populations. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization 2011; WHO/NMH/NHD/MNM/11.2.
18. Sukumar N, Saravanan P. Investigating vitamin B12 deficiency. BMJ 2019;365:l1865.
19. Jahan F, Nanji K, Qidwai W, Qasim R. Fibromyalgia syndrome: an overview of pathophysiology, diagnosis and management. Oman Med J 2012;27(3):192–195.
20. Pamuk GE, Pamuk ÖN, Set T, Harmandar O, Yesil N. An increased prevalence of fibromyalgia in iron-deficiency anemia and thalassemia minor and associated factors. Clin Rheumatol 2008; 27: 1103.
21. Soppi ET. Iron-deficiency without anemia - a clinical challenge. Clin Case Rep 2018;6(6):1082-6.