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Ferric carboxymaltose therapy reduces pain and improves the quality of life in female patients with fibromyalgia

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Abstract. – OBJECTIVE: The efficacy of treatments for fibromyalgia is limited and many factors have been identified to trigger the current complaints. Iron deficiency anemia is one of these factors. We aimed to re-evaluate the quality of life of fibromyalgia patients with the Fibromyalgia Impact Questionnaire after ferric carboxymaltose treatment.

PATIENTS AND METHODS: This study was conducted on 90 female patients older than 18 years of age with ferritin <60 mcg/dL who presented to the Internal Medicine outpatient clinic in a large tertiary care hospital in Eskişehir, Turkey, with FM symptoms. Patients were selected from women who had previously received oral iron therapy for at least 3 months and whose ferritin could not be increased to >60 mcg/dL. Patients who met the 2010 criteria of the American College of Rheumatology for fibromyalgia were included in the study. Patient characteristics and laboratory parameters were recorded. The Fibromyalgia Impact Questionnaire (FIQ1, FIQ2) was applied and compared before and after IV iron treatment.

RESULTS: The mean age of the patients was 40±12 years (18-83). There was a significant change in the total score (FIQ1 mean: 54, FIQ2 mean: 21) and all parameters of the FIQ questionnaire after ferric carboxymaltose treatment (p=0.000).

CONCLUSIONS: Ferric carboxymaltose treatment reduces pain levels and improves the quality of life in women with fibromyalgia.

Key Words:
Fibromyalgia, Ferric carboxymaltose, FIQ.

Introduction

Iron is necessary for the continuation of many biosynthesis mechanisms. Low iron level in the body leads to decreased synthesis of biological amines, which is indicated as a pathological mechanism in fibromyalgia (FM) patients[1]. According to the guidelines for staging iron deficiency[2], a serum ferritin level below 60 mcg/dL is considered as deficiency with mild anemia, whereas a serum ferritin level below 40 mcg/dL is classified as deficiency with severe anemia. It is estimated that approximately 50% of anaemia in women is iron deficiency[3]. Iron deficiency anaemia (IDA) is primarily treated with iron supplementation, which can be oral or parenteral. Oral preparations are inadequate in moderate to severe anaemia where a more rapid improvement in haemoglobin (Hb) levels and replenishment of iron stores are desired. Therefore, parenteral iron preparations are the mainstay of treatment in moderate to severe anaemia. An intravenous (IV) iron preparation, ferric carboxymaltose (FCM), has been developed with a favorable side-effect profile compared to traditional parenteral iron products[4]. Its properties allow the administration of high doses (maximum 1,000 mg/infusion) in a single session (15-minute infusion) without the need for a test dose[5-7].

Fibromyalgia (FM) includes chronic widespread musculoskeletal pain, fatigue, and psychiatric symptoms[8]. Decreased ferritin, a storage iron in the body, can cause fibromyalgia-like symptoms and an increase in existing symptoms[9]. Although nonanemic FM patients have relatively similar serum iron levels compared to healthy individuals, patients with IDA are at higher risk of developing FM compared to patients without IDA[10]. The pain experienced in FM patients is thought[1] to be due to nervous system dysfunction caused by decreased levels of biogenic amine metabolites, and this phenomenon can be explained by FM pathophysiology. Since iron is a cofactor for several enzymes involved in the synthesis of neurotransmitters such as tryptophan hydroxylase (for serotonin)

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and tyrosine hydroxylase (for norepinephrine and dopamine), decreased production of these biogenic amines in patients with FM may reflect iron deficiency[11]. However, the relationship between IDA and FM has not yet been adequately explored, and whether the administration of IDA affects the risk of developing FM in patients requires further evaluation.

This study aimed to analyze the effect of iron treatment on quality of life by applying the FQI questionnaire before and after IV FCM treatment in FM patients with low ferritin levels.

Patients and methods

Study Design and Participants

This study was conducted on 90 female patients older than 18 years of age with ferritin <60 mcg/dL who presented to the Internal Medicine outpatient clinic in a large tertiary care hospital in Eskişehir, Turkey, with FM symptoms. Patients were selected from women who had previously received oral iron therapy for at least 3 months and whose ferritin could not be increased to >60 mcg/dL. The selected patients had not previously benefited from oral iron therapy or could not tolerate oral therapy. These patients were given IV iron therapy after administration of the FIQ1 questionnaire to assess the impact of FM. FIQ assesses the quality of life and impact in patients with FM. It consists of 10 questions assessing activities of daily living and pain and is divided into three main categories: function, general impact and symptoms. The maximum score is 100. A higher score indicates that the impact of the syndrome on the person is more pronounced[12]. The cumulative dose of FCM for iron supplementation is based on the patient's body weight and Hb level[13].

FCM was administered to the patient as an IV infusion, not exceeding 1,000 mg iron per infusion, as part of standard care. Haemogram and ferritin values were re-studied 4-6 weeks after treatment. FIQ2 questionnaire was re-administered. Patients with systemic, metabolic, endocrine, tumoral, infectious or neurological diseases were excluded from the study. Data including patient characteristics (age, smoking and antidepressant use) were recorded. The diagnosis of FM was based on the 2010 criteria of the American College of Rheumatology consisting of the widespread pain index (WPI) and symptom severity (SS) scale, the presence of similar symptoms for at least three months, and the absence of any other disorder to explain the pain. Patients were compared with laboratory parameters and FIQ questionnaires before and after iron treatment.

Statistical Analysis

Statistical analysis was performed by using Statistical Package for the Social Sciences (SPSS) version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented as mean ± standard deviation (SD) for normally distributed variables and median (min-max) for non-normally distributed variables. Categorical data were expressed as numbers and percentages. If the numerical data were normally distributed, Student's *t*-test was used; for non-normally distributed variables, the Mann-Whitney U test was used to compare the two groups. The Chi-square test was used to examine the relationships between categorical variables. $p < 0.05$ was considered statistically significant.

Results

The mean age of the 90 women who participated in the study was 40±12 years (p=0.056). The mean haemoglobin was 11.1 g/dL, and the mean serum ferritin was 4.4 µg/L. Antidepression medication was used by 6.7% of the patients, and 28.9% were smokers. Patient characteristics and laboratory parameters are shown in Table I.

The mean FIQ1 score of all patients was 54.065 (min-max: 5.02-87). The mean FIQ score was 60.99 in patients using antidepressant drugs and 60.81 in smoking patients. The mean FIQ2 score after ferric carboxymaltose treatment was 21.051 (min-max: 0-73.6). There was a significant difference between the mean FIQ scores before and after iron treatment (p=0.000). FIQ score evaluations are shown in Table II.

After FCM treatment, 17.8% (n=16) of the patients (mean; min-max: 43.16; 8.6-69.2) had a total score of 0 on FIQ2. 53.3% (n=48) of the patients (mean: 49.18) had a mean FIQ2 score of 6.60 after treatment. This showed an 84.4% improvement in 53.3% of the patients. The least improvement was found in 4.4% of the patients (FIQ1 mean: 81.14; FIQ2 mean: 69.93).

When the FIQ questionnaire questions were evaluated before and after iron treatment, a significant decrease was observed in the scores in all parameters (p=0.000). Detailed analyses of the questionnaire questions are shown in Table III.

Table I. Patient characteristics.

	Mean	Minimum	Maximum	Standard Deviation
Age	40	18	84	12
Hb 1 (g/dL)	11.1	5.8	14.7	1.6
Haematocrit 1 (%)	35.1	22.3	44.4	3.9
RBC 1 (mn/mm^3)	4.6	3.8	5.9	0.5
MCV 1(fL)	75.3	53.7	93.8	7.8
MCH 1 (pg)	23.7	14.0	33.3	3.6
Ferritin 1 (µg/L)	4.4	1.4	10.5	2.2
Hb 2 (g/dL)	13.4	10.2	16.2	1.1
Haematocrit 2 (%)	40.5	32.5	49.2	3.2
RBC 2 (mn/mm^3)	4.9	3.9	5.9	0.4
MCV 2 (fL)	82.3	58.3	94.7	5.7
MCH 2 (pg)	27.4	18.3	31.3	2.4
Ferritin 2 (µg/L)	157.6	10.0	440.5	100.0
25 OH Vitamin D (µg/L)	14.8	4.6	39.8	7.4
Vitamin B12 (µg/L)	227	53	892	118

%, percentage; µg/L, micrograms per litre; fL, femtolitre; g/dL, grams per decilitre; Hb, haemoglobin; MCH, mean corpuscular haemoglobin; MCV, mean red blood cell volume; mn/mm^3, million divided by cubic millimetres; pg, pictograms; RBC, red blood cell.

Table II. FIQ score evaluations.

	Non-Anti-depressant Medication N %	Anti-depressant Medication N %	Smokers N %	Non Smokers N %	*p*
FIQ1 (mean)	93.3% , (53.48)	6.7%, (6099)	71.1%, (60.81)	28.9%, (51.32)	
p	*p*=0.909		*p*=0.502		
FIQ1 (mean) (min-max)	54.0652 (5-87.06)				*p*=0.000
FIQ2 (mean) (min-max)	21.0512 (0-73.61)				

Discussion

In our study, according to the FIQ questionnaire results, pain sensation was high, and quality of life was low in patients with FIA with low storage iron (FIQ1 mean: 54, FIQ2 mean: 21). Fibromyalgia is a complex syndrome consisting of various symptoms including fatigue, sleep quality disorder, cognitive dysfunction, depression, and intense pain. These symptoms significantly reduce the quality of life of patients[14]. Many studies[15-18] have suggested a link between iron deficiency and FM. In a cohort study[15] conducted in a large population in Taiwan, it was reported that the risk of FM was higher, and symptoms were more severe in patients with IDA. Women diagnosed with FM showed lower levels of iron, calcium, and magnesium in hair samples compared to healthy controls[16]. In a study carried out by Ortancil et al[9], the levels of ferritin in FM patients were found to be significantly lower than those in the control group (p=0.003). The study also employed multiple logistic regression analysis, which demonstrated that having a serum ferritin level below 50 ng/ml resulted in a 6.5-fold increase in the risk of developing FM[9]. In our study, the mean FIQ1 score of patients with low ferritin levels was 54.065 (min-max: 5.02-87), while the mean FIQ2 score decreased to 21.051 (min-max: 0-73.6) after ferric carboxymaltose treatment. A significant difference existed between the mean FIQ scores pre- and post-iron treatment (p=0.000). These findings validate the results of Ortancil et al[9]: a decline in iron levels was correlated with an el-

Table III. Analysis of FIQ survey questions.

	Mean	Minimum	Maximum	p
Can you do the following activities? 1	2.7	0	7.8	p=0.000
Can you do the following activities? 2	0.4	0	3.3	
How many days have you felt good in the last week? 1	4.4	0	10.0	p=0.000
How many days have you felt good in the last week? 2	3.1	0	10.0	
How many days during the past week have you been unable to work due to fibromyalgia? 1	2.3	0	10.0	p=0.000
How many days during the past week have you been unable to work due to fibromyalgia? 2	0.4	0	10.0	
How much did your pain and other complaints prevent you from doing your job, at home and work? 1	3	0	10	p=0.000
How much did your pain and other complaints prevent you from doing your job, at home and work? 2	1	0	7	
What was the level of your pain? 1	6	0	10	p=0.000
What was the level of your pain? 2	2	0	10	
How tired are you? 1	7	0	10	p=0.000
How tired are you? 2	3	0	10	
How do you feel when you get up in the morning? 1	7	0	10	p=0.000
How do you feel when you get up in the morning? 2	3	0	10	
How much is your morning stiffness? 1	5	0	10	p=0.137
How much is your morning stiffness? 2	2	0	10	
How frustrated and tense do you feel? 1	7	0	10	p=0.000
How frustrated and tense do you feel? 2	4	0	10	
How sad, exhausted, unhappy or depressed do you feel? 1	7	0	10	p=0.000
How sad, exhausted, unhappy or depressed do you feel? 2	4	0	10	

1: FIQ1, 2: FIQ2.

evated FM. Additionally, it was observed that appropriately administered iron therapy could effectively reverse this situation.

Several studies[17,18] have mentioned the decrease in biogenic amine levels related to the etiopathogenesis of FM. In addition, serotonin, tryptophan, dopamine, and noradrenaline levels were found to be low in FM patients. As it is known, iron is one of the main components that should be in the synthesis phase of all these metabolites[17,18]. Accordingly, abnormal metabolic disorders and abnormal dopamine and serotonin responses, which are important for pain sensation, are observed in FM patients[19]. In a recent study[20], the number of tender points was found to increase in FM patients, and dopamine and niacin levels decreased[20]. Serotonin and noradrenaline are chemicals produced by the human body and are involved in the regulation of pain, sleep, and mood[21]. Studies[22] report that the frequency of anxiety and depression increases in patients with widespread pain and that smoking also increases. The symptoms have been found[23,24] to be more severe in FM patients who smoked. Concerning this, the FIQ score of patients who smoked (FIQ mean: 60.8) and patients who received antidepressant treatment (FIQ mean: 60.9) was higher than those who did not use it in our study. Iron deficiency in patients with FM can reduce oxygen transport in the muscles and mitochondrial function. This can affect patients' exercise performance and cause frequent fatigue, one of the most prominent clinical symptoms of FM[25]. Tirelli et al[26] examined the efficacy of oxygen-ozone hemotherapy with a cohort of 200 patients diagnosed with fibromyalgia. Ozone therapy, which boosts oxygen levels, was administered, and after a month of follow-up, 76% of patients exhibited full musculoskeletal rehabilitation and a decline in general arthralgia. In our study, a significant improvement was found in all parameters of the FIQ questionnaire consisting of function, general effect, and symptoms after iron treatment (p=0.000). This situation suggested that iron metabolism is an important component in all symptoms occurring in FM. In our study, all of the complaints that were present after the treatment were resolved in 17.8% of the patients (FIQ2=0). After iron treatment, a decrease was found in 84.4% of the complaints in a majority of 53.3% of

the patients. This shows that FM patients should be examined in terms of IDA before being diagnosed.

Conclusions

In conclusion, it reveals that FCM supplementation improves physical function, role limitations due to emotional health issues, social function, and overall health of patients suffering from fibromyalgia. Our study has shown that properly administered IDA treatment reduces pain and improves the quality of life in fibromyalgia patients. However, additional studies are needed to evaluate how differences in IDA severity may affect the risk of developing FM.

Conflict of Interest
The authors declare that they have no conflict of interest.

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Authors' Contributions
H. Hamarat developed the theory, analyzed the data in the conclusion, and wrote the discussion section.
S. Gürcü, BK. Kıvanç, AE. Aydemir evaluated the findings, reviewed, and made necessary adjustments.
H. Hamarat prepared the necessary documents for ethics committee approval.
All authors have seen and approved the final version of the article.

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Informed Consent
Written informed consent was obtained from all patients or a legally authorized representative for the publication of their anonymized information in this article.

Ethics Approval
The study protocol was approved by the Ethics Committee of Eskişehir Osmangazi University Medical Faculty Training and Research Hospital with the number 25403353-050.99-E.86436 and decision number 36.

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