Original Investigation / Orijinal Araştırma

DOI: 10.4274/tod.galenos.2020.93899
Turk J Osteoporos 2020;26:98-103

Frequency of Anaemia in Patients with Musculoskeletal Pain

Kas-iskelet Sistemi Ağrısı Olan Hastalarda Anemi Görülme Sıklığı

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Abstract

Objective: This study aimed to determine the frequency of anaemia in patients with musculoskeletal pain who were admitted to our clinic.
Materials and Methods: Three hundred and thirty-eight patients with muscloskeletal pain were divided into 2 groups as follows: Group 1, with diffuse pain, and group 2, with local pain. Serum iron, ferritin, total iron-binding capacity, vitamin B12 and plasma haemoglobin levels were analysed retrospectively.
Results: Patients with iron deficiency and iron-deficiency anaemia were evaluated retrospectively. There was iron deficiency in 35.7% of all patients with musculoskeletal pain and iron-deficiency anaemia in 11.2% of all patients. Iron deficiency was identified in both groups when the patients were evaluated separately according to the painful area. The rates of iron deficiency in the groups were 28.3% in the diffuse pain group and 37.1% in the local pain group.
Conclusion: We suggest that serum iron and ferritin levels should be measured, and if necessary, supplemented for better treatment success in patients with musculoskeletal pain.
Keywords: Anaemia, frequency, musculoskeletal diseases

Öz

Amaç: Bu çalışmada kliniğimize kas-iskelet sistemi ağrısı şikayeti ile başvuran hastalarda görülen anemi sıklığının belirlenmesi amaçlandı.
Gereç ve Yöntem: İskelet-kas sistemi ağrısı olan 338 hasta grup 1 (yaygın ağrı) ve grup 2 (lokal ağrı) olmak üzere 2 gruba ayrıldı. Hastaların serum demir, ferritin, total demir bağlama kapasitesi, vitamin B12 ve plazma hemoglobin düzeyleri geriye dönük olarak analiz edildi.
Bulgular: Demir eksikliği ve demir eksikliği anemisi olan hastalar geriye dönük olarak değerlendirildi. Kas-iskelet sistemi ağrısı olan tüm hastaların %35,7'sinde demir eksikliği, %11,2'sinde demir eksikliği anemisi vardı. Hastalar ağrı bölgesine göre ayrı ayrı değerlendirildiğinde her iki grupta da demir eksikliği olduğu görüldü. Demir eksikliği oranları yaygın ağrı grubunda %28,3 ve lokal ağrı grubunda %37,1 olarak saptandı.
Sonuç: Kas-iskelet sistemi ağrısı olan hastalarda serum demir ve ferritin düzeylerinin ölçülmesini ve tedavi başarısının artırılması için gerekirse tedavi edilmesini öneriyoruz.
Anahtar kelimeler: Anemi, kas-iskelet sistemi hastalıkları, sıklık

Introduction

Musculoskeletal disorders are painful conditions and lead to disability. Musculoskeletal system diseases are a group of diseases that may have different causes in terms of pathophysiology, but common characteristics are pain and impaired physical function. The prevalence of musculoskeletal system diseases is high worldwide. World Health Organization (WHO) reports that 1/3 to 1/5 people (including children) have musculoskeletal diseases in a period of their lives (1).

Iron is an important element for almost all life. Nearly two-thirds of the iron involves to the structure of heme and as it is well known the oxygen transport function of hemoglobin in erythrocytes is essential. Additionally, some other proteins containing heme such as myoglobin, cytochrome P450, and the cytochromes a, b, and c have key roles on mitochondrial respiration and adenosine triphosphate synthesis (2).

Iron-deficiency and iron-deficiency anemia are both common though preventable nutritional problems not only in Turkey but also all over the world (3). Determining iron deficiency, particularly before iron-deficiency anemia develops, is very important for the success of treatment. For this purpose, ferritin is used as a reliable marker of iron storage. It has been shown that ferritin is the most valuable test for the detection and follow-up of iron deficiency. Measurement of serum ferritin

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Received/Geliş Tarihi: 30.12.2019 **Accepted/Kabul Tarihi:** 13.03.2020
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levels is useful for the treatment of iron-deficiency before the development of anemia (4).

Normal iron function and hemostasis have crucial importance for the normal function of the central nervous system due to the role of iron having a cofactor role in the function of many enzymes involved in neurotransmitter synthesis such as serotonin, norepinephrine, and dopamine (5). Decreased synthesis of these neurotransmitters may take part in pain generation, particularly in neuropathic pain generation (6).

There are very few studies investigating the possible relationship between iron-deficiency and pain. One experimental animal study has demonstrated that iron-deficiency increases acute and chronic pain responses in mice (7). One clinical study with a small sample size has shown that serum ferritin levels are significantly lower in patients with chronic neck pain compared to healthy controls (8).

The lack of a comprehensive descriptive study in the literature investigating the possible association between anemia in a wide range of muscoloskletal pain conditions prompted us to perform this study.

This study aimed to determine anemia frequency of patients who have musculoskeletal system pain, retrospectively.

Materials and Methods

Five hundred and fifty patients suffering from musculoskeletal pain admitted to Physical Medicine and Rehabilitation outpatient clinic of our hospital within the last five years (between January 1, 2014 and December 1, 2018) were analyzed retrospectively using hospital automation system and patient file archives.

The inclusion criteria were as follows:

1. Patients with musculoskeletal pain
2. Patients who have test results of serum ferritin, iron, vitamin B12 concentrations, total iron-binding capacity (TIBC) 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. Pregnancy and breastfeeding

After the inclusion and exclusion criteria were applied, the study was completed with the data of the remaining 338 patients divided into 2 groups as follows:

Group 1: Diffuse pain

Group 2: Local pain (artralgia, upper extremity pain, lower extremity pain, neuropathic pain, spinal pain)

Demographic data and serum ferritin, iron, TIBC, vitamin B12 levels and plasma hemoglobin levels 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 (9). 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 insufficiency (10). 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). A 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.

Ethical Issues

The study met the approval of Turkish Statistical Institute (with authorization number 23.08.2019/19496) and the approval of Atatürk University Faculty of Medicine Local Clinical Research Ethics Committee (approval date: 26.09.2019, decision no: 423).

Statistical Analysis

The results were evaluated in SPSS 23 package program. Descriptive statistics (mean, standard deviation, frequency) were made. Independent samples t-test was performed to determine the difference of age and biochemical parameters between independent groups (comparison of group 1-group 2 and comparison of male-female in all patients, in group 1 and in group 2). P<0.05 values were accepted as statistically significant in a 95% confidence interval.

Results

The ages and biochemical parameters of all musculoskeletal pain patients and of the patients divided into 2 groups were demonstrated in Table 1, Table 2 and Figure 1.

The mean age of all patients was 44.7±14.4 years, and there was no statistically significant difference between the ages of male and female patients (p<0.05).

Table 1. Demographic characteristics and biochemical parameters of patients

	Diffuse pain (n=53)	Local pain (n=285)	p (Diffuse pain- local pain)
Age (year)	43.8±14.4	44.9±14.4	0.619
Hemoglobin (g/dL)	13.5±1.5	14±7.6	0.681
Iron (ug/dL)	73.9±32.5	71.4±31.9	0.602
Ferritin (ng/mL)	44.2±41.5	37.8±39.4	0.287
TIBC (pg/dL)	287.8±89	288.8±91.8	0.941
Vitamin B12 (pg/mL)	363.5±154.3	361±187	0.925

TIBC: Total iron-binding capacity, results were given as mean ± standard deviation, p: Independent samples t-test statistics p value

Table 2. Distribution of parameters by gender				
All patients	**All patients (n=338)**	**Female patients (n=311)**	**Male patients (n=27)**	**p (Male-female)**
Age (year)	44.7±14.4	45±14.2	40.9±16.4	0.151
Hemoglobin (g/dL)	13.9±7	13.8±7.3	15.2±1.8	0.325
Iron (ug/dL)	71.8±32	70.2±30.6	90.3±41.6	0.002
Ferritin (ng/mL)	38.8±39.7	35.9±36.7	72.9±55.4	<0.001
TIBC (pg/dL)	288.6±91.2	292.1±92.1	248.5±70.3	0.017
Vitamin B12 (pg/mL)	361.4±182.1	358±160.6	400.2±347.3	0.249
Group 1 (Diffuse pain)	**All patients (n=53)**	**Female patients (n=47)**	**Male patients (n=6)**	**p (Male-female)**
Age (year)	43.8±14.4	44.8±14.2	35.8±15.1	0.151
Hemoglobin (g/dL)	13.5±1.5	13.3±1.4	15.3±0.9	0.002
Iron (ug/dL)	73.9±32.5	68.7±28.7	114.3±34.5	0.001
Ferritin (ng/mL)	44.2±41.5	40.5±40.2	72.6±44.2	0.075
TIBC (pg/dL)	287.8±89	295.3±91	228.7±37.2	0.084
Vitamin B12 (pg/mL)	363.5±154.3	362.7±160.7	370.1±100.9	0.913
Group 2 (Local pain)	**All patients (n=285)**	**Female patients (n=264)**	**Male patients (n=21)**	**p (Male-female)**
Age (year)	44.9±14.4	45.1±14.2	42.3±16.9	0.403
Hemoglobin (g/dL)	14±7.6	13.9±7.9	15.2±2	0.460
Iron (ug/dL)	71.4±31.9	70.4±31	83.4±41.5	0.073
Ferritin (ng/mL)	37.8±39.4	35±36	73±59.2	<0.001
TIBC (pg/dL)	288.8±91.8	291.5±92.5	254.2±77	0.073
Vitamin B12 (pg/mL)	361±187	357.2±160.9	408.8±392.3	0.224

TIBC: Total iron-binding capacity, Results were given as mean ± standard deviation, p: Independent samples t-test statistics p value

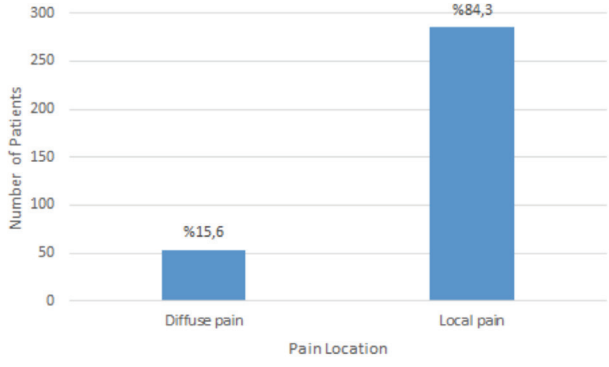

Figure 1. Number and frequency distribution of patients with musculoskeletal pain by pain location

In the independent group comparisons between female and male patients, both serum ferritin and serum iron levels were significantly lower in female patients than in male patients (p<0.001 and p<0.05, respectively).

Serum TIBC levels were significantly higher in female patients than in male patients (p=p<0.05).

There was no statistically significant difference between serum vitamin B12 levels and plasma hemoglobin levels between male and female patients (p>0.05 for both parameters).

The differences of parameters between pain groups (diffuse pain group and local pain group) were also evalulated with independent samples t-test. There were no significant differences in all parameters (age, hemoglobin, iron, ferritin, TIBC, vitamin B12) between all group comparisons (all group 1 patients-all group 2 patients, female group 1 patients-female group 2 patients, male group 1 patients-male group 2 patients) (p>0.05 for all parameters in all comparisons) (Table 3).

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 in all patients and in the patients divided into 2 groups (Table 4, Figures 2, 3).

Discussion

Our retrospective analysis results have shown that there was iron-deficiency in 35.7% of all patients with musculoskeletal system pain and iron-deficiency anemia in 11.2% of all patients. Iron-deficiency was determined in both groups when the patients were evaluated separately according to the pain area. Iron-deficiency rates were determined as follows: in diffuse pain: 28.3% and in spine pain: 37.1%.

In addition to iron deficiency, iron-deficiency anemia was determined in both groups with the rates 11.7% in upper

Table 3. Distribution of parameters between diffuse pain and local pain patients			
Female and male patients	**Group 1 (Diffuse pain)**	**Group 2 (Local pain)**	**p (group 1-group 2)**
Age (year)	43.8±14.4	44.9±14.4	0.619
Hemoglobin (g/dL)	13.5±1.5	14±7.6	0.681
Iron (ug/dL)	73.9±32.5	71.4±31.9	0.602
Ferritin (ng/mL)	44.2±41.5	37.8±39.4	0.287
TIBC (pg/dL)	287.8±89	288.8±91.8	0.941
Vitamin B12 (pg/mL)	363.5±154.3	361±187	0.925
Female patients	**Group 1 (Diffuse pain)**	**Group 2 (Local pain)**	**p (group 1-group 2)**
Age (year)	44.8±14.2	45.1±14.2	0.910
Hemoglobin (g/dL)	13.3±1.4	13.9±7.9	0.629
Iron (ug/dL)	68.7±28.7	70.4±31	0.727
Ferritin (ng/mL)	40.5±40.2	35±36	0.345
TIBC (pg/dL)	295.3±91	291.5±92.5	0.796
Vitamin B12 (pg/mL)	362.7±160.7	357.2±160.9	0.829
Male patients	**Group 1 (Diffuse pain)**	**Group 2 (Local pain)**	**p (group 1-group 2)**
Age (year)	35.8±15.1	42.3±16.9	0.402
Hemoglobin (g/dL)	15.3±0.9	15.2±2	0.903
Iron (ug/dL)	114.3±34.5	83.4±41.5	0.110
Ferritin (ng/mL)	72.6±44.2	73±59.2	0.989
TIBC (pg/dL)	228.7±37.2	254.2±77	0.444
Vitamin B12 (pg/mL)	370.1±100.9	408.8±392.3	0.815
TIBC: Total iron-binding capacity, results were given as mean ± standard deviation, p: Independent samples t-test statistics p value			

extremity pain, 11.3% in diffuse pain and 11.2% in lcoal pain.

Determining iron-deficiency accurately is an important issue for clinicians. For this purpose, measurement of serum ferritin levels is used as a reliable and non-invasive method to indirectly show iron stores of the body and decreased serum ferritin level is considered as a sign of iron depletion (11).

Although there is a wide consensus on the determinative role of ferritin in iron deficiency, different expert organizations recommend various cut-off limits for the diagnosis of iron deficiency. In our study, we used the highly accepted cut-off limit recommended by WHO, which defines iron-deficiency with the ferritin levels less than 15 ng/dL (9).

However, the concentration of ferrite required to maintain the normal function of muscle tissue and other organs has not been fully established. It has been recommended that, when ferritin levels are below 50 ng/mL, the targeted ferritin concentration in the treatment of iron-deficiency 50 ng/mL (12).

Iron, a cofactor of the cytochrome oxidase enzyme system, has a vital role in the energy production of muscle. Thus, iron-deficiency causes a deterioration in muscle energy production and contributes to the development of muscle fatigue, poor endurance and myofascial pain (13).

An experimental mouse model study has demonstrated that iron-deficiency triggers a reducement in pain threshold and an increment in pain feeling (7,14).

Another perspective for the relationship of iron deficiency and anemia is focused on the role of iron as an essential cofactor of several enzymes which are key elements of neurotransmitter synthesis, particularly tryptophan hydroxylase (in serotonin synthesis) and tyrosine hydroxylase (in norepinephrine and dopamine synthesis) (5,6).

At this point, it is necessary to examine the relationship between serotonin and pain. Serotonin, a neurotransmitter derived from tryptophan, is produced by neurons in the brainstem. Serotonin is broadly circulated throughout the cortex, limbic system, and thalamus by the connections of serotonergic neurons and thus it has inhibitory effects on some pain pathways. There is increasing evidence pointing out the important role of serotonin [5-hydroxytryptamine, (5-HT)] in the modulation of nociceptive transmission. Various 5-HT receptor subtypes have been identified in the central nervous system (15), and in the spinal cord. Experimental studies have shown that 5-HT produces antinociception and several 5-HT receptors take part in the mediation of antinociception (16).

Due to the cofactor role of iron tyrosine hydroxylase enzyme (leading norepinephrine and dopamine synthesis), determining

Table 4. The incidence of clinical conditions accompanying patients' pain complaints			
Musculoskeletal pain	**All patients (n=338) %**	**Female patients (n=311) %**	**Male patients (n=27) %**
Iron deficiency	35.7	37.6	14.8
Iron-deficiency anemia	11.2	11.5	7.4
Vitamin B12 deficiency	43.1	42.1	55.5
Vitamin B12 insuffuciency	9.1	9.3	7.4
Iron level under the ref. range	12.4	12.2	14.8
TIBC level outside the ref. range	5.3	5.4	3.7
Group 1: Diffuse pain	**All patients (n= 53) %**	**Female patients (n=47) %**	**Male patients (n=6) %**
Iron deficiency	28.3	29.7	16.6
Iron-deficiency anemia	11.3	12.7	0
Vitamin B12 deficiency	37.7	38.2	33.3
Vitamin B12 insuffuciency	11.3	12.7	0
Iron level under the ref range	16.9	19.1	0
TIBC level outside the ref. range	11.3	8.5	0
Group 2: Local pain	**All patients (n=285) %**	**Female patients (n=264) %**	**Male patients (n=21) %**
Iron deficiency	37.1	39	14.2
Iron-deficiency anemia	11.2	11.3	9.5
Vitamin B12 deficiency	44.2	42.8	61.9
Vitamin B12 insuffuciency	8.7	8.7	9.5
Iron level under the ref. range	11.5	10.9	19
TIBC level outside the reference range	6.6	5.3	4.7
TIBC: Total iron binding capacitiy, ref.: Reference			

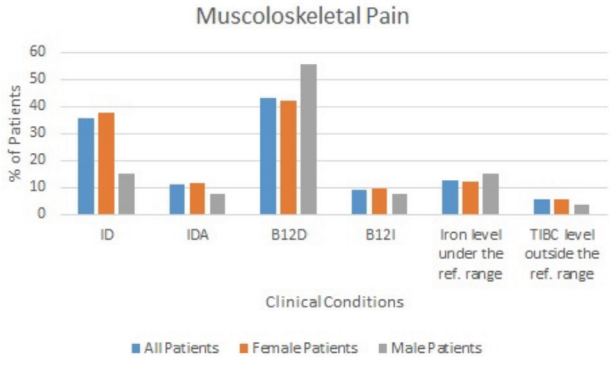

Figure 2. The frequency of clinical conditions associated with pain complaints in patients with musculoskeletal pain
ID; Iron-deficieny, IDA; Iron-deficiency anemia, B12D: Vitamin B12 deficiency, B12I: Vitamin B12 insufficiency, ref.:reference, TIBC: Total iron-binding capacity

the possible role of dopaminergic neurotransmission in chronic pain is an important field of interest for researchers.

Dopaminergic neurotransmission is thought to play a pivotal role in moderating pain sensation and analgesia. Researchers reporting decreased dopamine levels in Fibromyalgia syndrome have concluded that abnormal dopaminergic neurotransmission may be responsible for the painful conditions of fibromyalgia and painful diabetic neuropathy. Another evidence supporting the potent relationship between iron, pain sensation and dopaminergic system is the curative effect achieved by using dopamine agonists in Restless Leg syndrome patients (17).

Here is an important point is to note that, experimental animal studies have demonstrated that while analgesia is induced by the activation of mesolimbic dopamine neurons by acute stress, chronic stress conditions trigger a reverse effect on pain sensation and lead to hyperalgesia by decreasing mesolimbic dopaminergic output (18).

Although investigating the relationship between pain and Fibromyalgia syndrome is out of the scope of our study, we note that reduced concentration of dopamine, norepinephrine, and serotonin is reported in FMS patients, who have different pain perception from that of the broad population, consequence of degenerated pain processing pathways in the central nervous system (5,19).

An issue must be considered in the planning of a study design investigating ferritin levels is that is the possibility that elevated ferritin levels may be arisen from inflammation conditions because ferritin is an acute-phase reactant. In this study, we excluded patients with inflammatory diseases and rheumatic diseases based on the detailed anamnesis of patients.

The limited studies available in the literature aimed to investigate the possible relationship between iron-deficiency and pain have

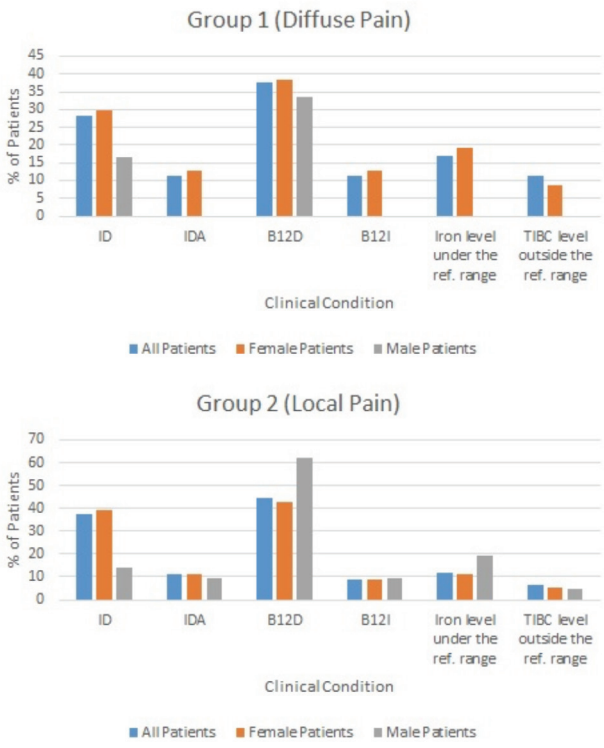

Figure 3. The frequency of clinical conditions accompanying pain complaints in patients with musculoskeletal pain divided into different groups

ID: Iron-deficieny, IDA: Iron-deficiency anemia, B12D: Vitamin B12 deficiency, B12I: Vitamin B12 insufficiency, ref.: reference, TIBC: Total iron-binding capacity

small sample sizes (8). Our study was performed with larger sample size.

Study Limitations

Our study has a limitation with the study design being retrospective.

Conclusion

To the best of our knowledge, this is the first study in English literature, reporting iron-deficiency and iron-deficiency anemia rates in a large number of sample size in various musculoskeletal system pain conditions. Based on our results, we suggest that serum iron and ferritin levels should be measured and, if necessary, treated to improve treatment success in patients with musculoskeletal system pain.

Ethics

Ethics Committee Approval: The study met the approval of Turkish Statistical Institute (with authorization number 23.08.2019/19496) and the approval of Atatürk University Faculty of Medicine Local Clinical Research Ethics Committee (approval date: 26.09.2019, decision no: 423).

Informed Consent: Informed consent is not appliciable.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.B., A.K., Concept: F.B, A.K., Design: F.B., A.K., Data Collection or Processing: F.B, Analysis or Interpretation: F.B., Literature Search: F.B., A.K., Writing: F.B., A.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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