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Relationship Between Pica and Laboratory Values in Patients with Iron Deficiency

Demir Eksikliği Hastalarında Pika ve Laboratuvar Değerleri Arasındaki İlişki

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Abstract

Introduction: Pica is one of the symptoms of iron deficiency and a pathology that exacerbates the condition. In this study, we sought to identify the biomarkers associated with pica in iron-deficient patients.

Materials and Methods: The study included female iron deficient clinic applicants from April 2021 to August 2022. The main iron deficit inclusion criterion was ferritin <30 ug/L. Patients' demographics, hemograms, iron parameters, c-reactive protein levels, and presence and types of pica were recorded. Independent sample tests and logistic regression tests were used to analyze the data.

Results: There were a total of 381 patients who met the study's eligibility requirements (mean age 38.67+10.10). Fifty-three (13.9%) patients described pica. One hundred four of 381 patients (27.3%) showed non-anemic iron deficiency, while 277 (72.7%) had anemia. Pica was found in 9 (8.7%) non-anemic iron deficient individuals and 44 (15.9%) iron deficiency anemia patients. Pica subtypes geophagia (39.6%) and pagophagia (28.2%) were most common. Among the laboratory values, unsaturated iron binding capacity (UIBC), total iron binding capacity (TIBC) and transferrin saturation differed significantly between groups with and without pica. UIBC and TIBC were significant again with univariate logistic regression.

Conclusion: Elevated UIBC and TIBC values and decreased transferrin saturation appear to be associated with pica in iron-deficient patients.

Keywords: Iron deficiencies; anemia; pica; biomarkers; iron binding capacity; transferrin saturation.

Özet

Giriş: Pika, demir eksikliğinin semptomlarından biridir ve durumu daha da kötüleştiren bir patolojidir. Bu çalışmada, demir eksikliği olan hastalarda pika ile ilişkili biyobelirteçleri tanımlamayı amaçladık.

Gereç ve Yöntemler: Çalışmaya Nisan 2021-Ağustos 2022 tarihleri arasında demir eksikliği kliniğine başvuran kadınlar dahil edildi. Temel demir eksikliği dahil etme kriteri ferritin <30 ug/L idi. Hastaların demografileri, hemogramları, demir parametreleri, c-reaktif protein seviyeleri ve pika varlığı ve türleri kaydedildi. Verileri analiz etmek için bağımsız örneklem testi ve lojistik regresyon testleri kullanılmıştır.

Bulgular: Çalışmanın uygunluk şartlarını karşılayan toplam 381 hasta vardı (ortalama yaş 38.67+10.10). Elli üç (%13,9) hastada pika tanımlamıştır. Üç yüz seksen bir hastanın 104'ünde (%27,3) non-anemik demir eksikliği, 277'sinde (%72,7) anemi vardı. Non-anemik demir eksikliği olan bireylerin 9'unda (%8,7) ve demir eksikliği anemisi olan hastaların 44'ünde (%15,9) pika saptandı. Pika alt tipleri arasında en sık geofaji (%39,6) ve pagofaji (%28,2) görülmüştür. Laboratuvar değerlerinden demir bağlama kapasitesi (UIBC), toplam demir bağlama kapasitesi (TIBC) ve transferrin satürasyonu pika olan ve olmayan gruplar arasında anlamlı farklılıklar gösterdi. Tek değişkenli lojistik regresyonda ise yalnızca UIBC ile TIBC anlamlı bulunmuştur.

Sonuç: Yüksek UIBC ve TIBC değerleri ile transferrin satürasyonu düşüklüğü demir eksikliği olan hastalarda pika ile ilişkili görünmektedir.

Anahtar Kelimeler: Demir eksikliği; anemi; pika; biyobelirteçler; demir bağlama kapasitesi; transferrin saturasyonu.

Introduction

Iron is the most prevalent metal in the earth's crust and the most prevalent in soil (1,2). The soil's high concentration of iron is a crucial element for the beginning of the food chain. Iron is the most essential micronutrient for the continuation of the existence of plants, animals, and humans due to their respective needs to obtain it. Iron deficiency (ID) and iron deficiency anemia (IDA), which are caused by a lack of this metal in humans, remain the most prevalent micronutrient deficiency and anemia worldwide (3). ID/IDA manifests with several symptoms, the majority of which are nonspecific. Pica is the most unusual and intriguing of this spectrum o

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nonspecific symptoms, the most prominent of which is fatigue (4). Pica is also studied under the main category of eating disorders and is defined as the repeated ingestion of non-nutritious substances with no nutritional value for at least one month (5). Only a minuscule proportion of pica patients have ID/IDA (6). Earth, ice, and starch are frequently ingested by ID/IDA patients with pica. Other typical examples of pica include clay, paper, chalk, ash, charcoal, and ground coffee. In addition, there are specific terms for the consumption of these substances. Geophagy is used to consume soil, pagophagy to consume ice, and amylophagy to consume carbohydrate. With iron replacement therapy, pica can improve markedly in these patient populations (7). On the other hand, consuming certain inorganic substances, such as soil, can be a symptom of iron deficiency; however, this compulsive behavior can exacerbate the iron deficiency. It is interesting that humans subconsciously attempt to compensate for their iron deficiency with something containing the most common iron content on earth, "soil and the like," which has potentials associated with its own creation or existence story. It is unclear why not all ID/IDA patients exhibit pica. Despite the fact that the precise pathophysiology is unknown, it can be interpreted as the effect of ID on the central nervous system (8). In particular, the biochemical relationship between pica and iron deficiency has not been investigated beyond hemoglobin and/or hematocrit in published studies (9). In this investigation, we aimed to determine which biomarkers are most strongly associated with pica in ID/IDA patients.

Materials and Methods

The sample and patient selection: All patients who applied to the Ordu University Training and Research Hospital Iron Deficiency Outpatient Clinic between April 2021 and August 2022 will comprise the sample for the study, which is designed as a retrospective-cross-sectional investigation. The two basic inclusion criteria for cases from this population were women over the age of 18 and the presence of ID/IDA-associated biochemical parameters.

Data type and the final data set: Microsoft Excel was used for collecting demographic data, medical history, hemogram, biochemical results of c-reactive protein (CRP), ferritin (FER), iron, and iron binding capacity from physical and digital patient files. Transferrin saturation (TSAT) was derived from the iron parameters and included as a new variable to the dataset. The primary inclusion criterion for iron deficiency was a ferritin level below 30 ug/L. Normal hemoglobin levels were not regarded exclusion criteria for non-anemic iron deficiency (NAID) in patients. Ferritin values exceeding 30 ug/L and TSAT values exceeding 30% were eliminated from the data set. Those with elevated CRP but low ferritin levels were maintained in the data set. Again, observations with widespread parameter deficits were omitted from the data set (Figure-1).

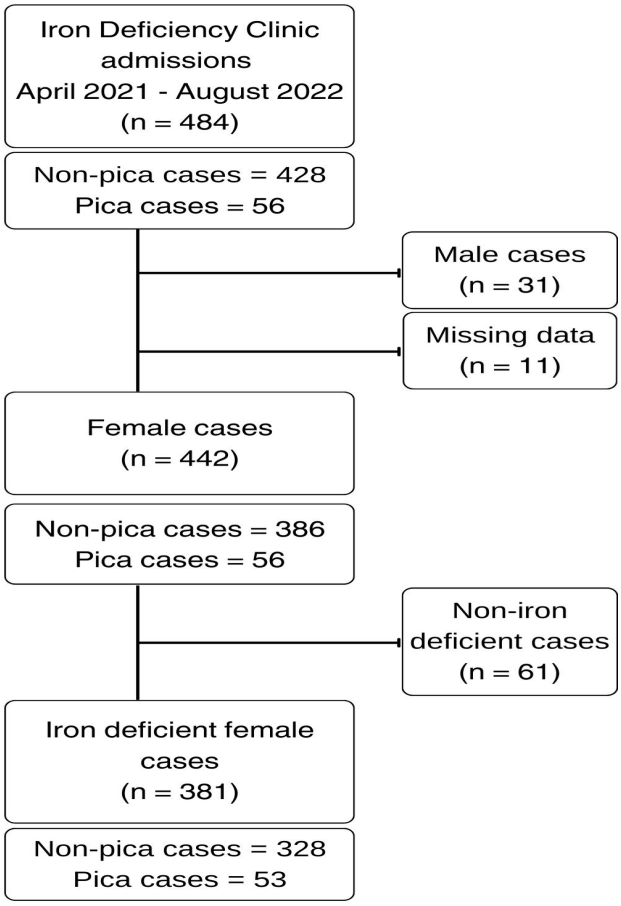

Figure 1. Flowchart of the study's patient selection process.

In order to prevent a decrease in pica cases, cases with missing data were not removed from the dataset after this phase.

Ethical approval: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Ordu University (Approval Date: 09.01.2023, No:2023/05).

Statistical analyses: The data was analyzed using the Jamovi (version 2.3.28) program (10). The descriptive statistics were derived from the

collected variables, and the categories of patients with pica were identified. The rates of NAID and anemia among cases were evaluated as well. The sample was then divided into two categories based on the presence of pica, and the variables were compared between the two groups. On the basis of analyses for data normality and variance homogeneity, two appropriate independent groups were compared. Kolmogorov-Smirnov test was used for normality and Levene's test was used for homogeneity of variance. The differences in HGB, HCT, MCV, MCH, serum iron, UIBC, TBIC, TSAT, and ferritin between these two groups were investigated. In statistical analyses, p values less than 0.05 were considered to be significant. Lastly, analyses of univariate logistic regression were conducted.

Results

The sample had a mean age of 38.67±10.11 and a median age of 39 (19-80). In Table-1, descriptive statistics for this state of the data set are presented.

Table 1: Descriptive statistics of variables of continuous data.

Variables	n	Mean ± SD
Age (years)	381	38.67 ± 10.113
HGB (g/dL)	381	10.59 ± 1.859
HCT (%)	381	34.26 ± 4.933
MCV (fL)	381	77.39 ± 9.591
MCH (pg)	381	23.95 ± 3.833
Iron (mcg/dL)	366	37.66 ± 22.979
UIBC(mcg/dL)	364	379.06 ± 67.520
TBIC	364	416.84 ± 57.702
TSAT (%)	364	9.45 ± 6.241
FERR (mcg/L)	371	8.95 ± 6.271

Abbreviations: HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; UIBC, unsaturated iron binding capacity; TIBC, total iron binding capacity; TSAT, transferrin saturation; FERR, ferritin; SD, standard deviation.

While the initial sample consisted of 484 patients, 56 (11.5%) were determined to have pica. After removing the missing data, the total number of patients decreased to 381 and the ultimate number of picas reduced to 53 (13.9%). A patient was pregnant. In another case, ice and pica for coffee were both present. This case's pica subtype was considered to be coffee. The subtypes of all 53 patients with pica are detailed in Table 2.

Table 2: The number and ratio of subtypes of pica identified in patients.

Pica Type	n	%
Earth (geophagia)	21	39.6
Ice (pagophagia)	15	28.3
Coffee grounds, coffee beans	5	9.4
Sheet, newspaper (xylophagia)	2	3.7
Lime	2	3.7
Dry mint	2	3.7
Dust	1	1.8
Coal	1	1.8
Chocolate	1	1.8
Parsley	1	1.8
Lemon	1	1.8
Sugary foods	1	1.8
Total	53	100

104 (27.3%) of 381 patients had NAID, while 277 (72.7%) had iron deficiency anemia. 9 patients (8.7%) with NAID and 44 patients (15.9%) with iron deficiency anemia had pica. Only age, RBC, MCV, MCH, UIBC, and TIBC were normally distributed when comparing the laboratory values of patients with pica (n=53) and patients without pica (n=328), which was the main purpose of the study. Among the variables, only age, RBC, MCV, MCH, UIBC and TIBC were normally distributed. On the other hand, variances of all variables were homogeneously distributed (p>0.05). The variables with normal distribution were compared between groups by Student's t-test and the others by Mann-Whitney U test. Then, hemogram parameters and iron levels at baseline were compared between groups with and without pica (Table-3). Consequently, only UIBC, TBIC and TSAT demonstrated a significant difference between the two groups (p = 0.029, p = 0.045, p=0.030, respectively). Parallel to the t-test, in univariate logistic regression, only UIBC (OR = 0.995, p = 0.030) and TIBC (OR = 0.995, p = 0.047) resulted in statistically significant findings (Table-4).

Table 3: Descriptives of variables and independent t-test result according to pica presence. The significant p-values has shown in bold.

Variables	Descriptives			T-Test Results		
	Pica	n	Mean ± SD	Statistic	df	p
Age (years)	+	53	37.51 ± 9.027			
	-	328	38.86 ± 10.278	-0.900	379	0.369*
	Total	381	38.67 ± 10.113			
HGB (g/dL)	+	53	10.25 ± 1.880			
	-	328	10.65 ± 1.852	7610	-	0.146**
	Total	381	10.59 ± 1.859			
HCT (%)	+	53	33.54 ± 4.454			
	-	328	34.37 ± 5.003	7573	-	0.133**
	Total	381	34.26 ± 4.933			
MCV (fL)	+	53	76.09 ± 8.513			
	-	328	77.60 ± 9.750	-1.064	379	0.288*
	Total	381	77.39 ± 9.591			
MCH (pg)	+	53	23.23 ± 3.883			
	-	328	24.06 ± 3.818	-1.467	379	0.143*
	Total	381	23.95 ± 3.833			
Iron (mcg/dL)	+	49	33.09 ± 23.076			
	-	317	38.36 ± 22.920	6456	-	0.057**
	Total	366	37.66 ± 22.979			
UIBC (mcg/dL)	+	48	398.87 ± 69.438			
	-	316	376.06 ± 66.824	2.193	362	**0.029***
	Total	364	379.06 ± 67.520			
TBIC	+	48	432.36 ± 57.539			
	-	316	414.48 ± 57.451	2.009	362	**0.045***
	Total	364	416.84 ± 57.702			
TSAT (%)	+	48	8.14 ± 6.304			
	-	316	9.64 ± 6.218	6110	-	**0.030****
	Total	364	9.45 ± 6.241			
FERR (mcg/L)	+	50	8.81 ± 7.062			
	-	321	8.97 ± 6.151	7364	-	0.349**
	Total	371	8.95 ± 6.271			

Abbreviations: HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; UIBC, unsaturated iron binding capacity; TIBC, total iron binding capacity; TSAT, transferrin saturation; FERR, ferritin; SD, standard deviation.
*Student's t-test.
**Mann-Whitney U test.

Discussion

If we begin with the results of this study, the frequency of pica appears to be lower than that of a recent meta-analysis. In this meta-analysis of 70 studies published in 2016, and in this study of patients up to the 12th month of pregnancy and/or postpartum, the incidence of pica was estimated to be 27.8% (11). In our study, this rate was found to be lower (13.9%), and among patients with pica, there was a single case of pregnancy. This circumstance can be attributed to ID/IDA, which is more prevalent during pregnancy (12). During pregnancy, pica-like symptoms, such as cravings, are also common. In addition to micronutrient deficiency during pregnancy and the postpartum period, it was believed that the potential for a higher incidence of neuropsychological factors associated with pica may have had an impact on this prevalence (13).

In the literature, it is noteworthy that investigations of pica due to iron deficiency in adult patients are predominantly conducted on pregnant women.

Tablo 4: Univariate logistic regression analysis on the association of laboratory values with the presence of pica. The significant p-values has shown in bold.

	Estimate	Odds Ratio	95% CI	p value
Age (years)	0.0134	1.01	0.98, 1.04	0.368
HGB (g/dL)	0.113	1.12	0.96, 1.31	0.148
HCT (%)	0.0318	1.03	0.97, 1.09	0.257
MCV (fL)	0.0150	1.02	0.98, 1.04	0.289
MCH (pg)	0.0557	1.06	0.98, 1.14	0.144
Iron (mcg/dL)	0.0113	1.01	0.99, 1.03	0.137
UIBC (mcg/dL)	-0.00502	0.995	0.99, 1.0	0.030
TBIC	-0.00528	0.995	0.99, 1.0	0.047
TSAT (%)	0.0438	1.04	0.98, 1.1	0.123
FERR (mcg/L)	0.00406	1.00	0.95, 1.05	0.869

Abbreviations: HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; UIBC, unsaturated iron binding capacity; TIBC, total iron binding capacity; TSAT, transferrin saturation; FERR, ferritin.

The frequency of pica was computed to be 17.5% among 320 patients with iron deficiency anemia who presented to the hematology clinic in a separate study conducted in Morocco, where pregnant women were not mentioned and a 6-year period was examined (14). In a study of 119 patients with iron deficiency anemia conducted in Turkey, among whom 5 were male and 6 were pregnant, the frequency of pica was found to be 34.4% (15). This frequency, which differed considerably from ours, suggested that factors such as the prospective nature of the relevant study, the higher number of expectant women, and the anemic status of all patients may have contributed to the increase. On the other hand, various prevalence rates for pica types have been reported in the literature. 16% of IDA (HGB 12 g/dL, ferritin 12 ng/mL) patients had pagophagia, according to a Japanese study of 81 IDA (HGB 12 g/dL, ferritin 12 ng/mL) patients (16). In our study, where the ferritin cutoff was set at 30 ng/mL, the prevalence of pagophagia was determined to be 28.3%. In the above-mentioned research from Morocco, it was found that 75% of the population practiced geophagy. In contrast to the existing literature, our investigation observed variations in iron binding capacity and transferrin saturation among the groups, rather than erythrocyte indices. Specifically, there were significant differences observed in iron binding capabilities (UIBC and TIBC) between patients with and without pica. Additionally, these capacities were found to be strongly associated with pica in the univariate logistic regression analysis. When examining the literature regarding the relationship between pica and biochemical parameters, which is the primary focus of our investigation, a variety of reports are found. In a cohort study involving 11.418 blood donors conducted in 2021, the relationship between pica and biochemical and demographic factors was examined (17). In the related study in which pica was identified in 256 (2.2% of) patients, ferritin and RDW levels were statistically significant as predictors independent of pica. In the same study, ferritin levels were assessed using three ordinal variables: 12, 12–50, and >50 ng/ml. Despite the fact that pica symptoms were over 2.5 times more prevalent in iron-deficient donors with ferritin 12 ng/ml than in donors with ferritin >50 ng/ml, cases of pica with ferritin >50 ng/ml appear to be relatively high at 24%. In our study, the overall mean ferritin concentration was 8.95 mcg/L. The mean ferritin levels of individuals with and without pica were very similar (8.81±7.06, 8.97±6.15, p=0.349). In a separate study that included 1693 cases with a history of nine or more blood donations, only hematocrit values from 16 distinct variables were identified as an independent risk factor for the presence of pica. Notably, only cases with ferritin levels 50 ng/mL were found to have pica in the same study. With this study, the researchers reiterated the importance of maintaining iron replacement programs in order to reduce the prevalence of pica among donors (18). Pica was found to be present in 42% of patients who received 400 dialysis treatments, whose iron parameters were not examined, and whose HGB average (10.3±2.3 g/dL) was comparable to our study; however, multivariate analysis provided a significant prediction only for CRP among biochemical parameters (19). In the same study, it was

discovered that hyponatremia was a significant predictor of pica in the subgroup defined as having severe pica. Given that the prevalence of pica in our study was 13.9%, this high prevalence among patients on dialysis is quite intriguing. In a separate study, a cohort of 35 female patients of reproductive age were evaluated, and no biochemical parameter was identified as a significant predictor for pica behavior, either positively or negatively (20). The analysis revealed a noteworthy association between pica and the age of menarche, as indicated solely by the results of the univariate analysis. The study reported the mean values of HGB and ferritin as (9.99±0.97 g/dL, 4.23±1.96 ng/mL, respectively), and indicated that the prevalence of pica was 32.4%.
In an additional study involving a cohort of 109 expectant mothers, the application of a logistic regression model revealed that solely the erythrocyte zinc level exhibited statistical significance in relation to pica among the various biochemical indicators (21). A study comprising of 262 patients with a pica rate of 45% identified MCV, RDW, and platelet as significant biochemical parameters with predictive value for pica among patients with iron deficiency (22). In the same study, there was a significant difference in TIBC between patients with and without pica.
Study limitations: Our investigation was limited by the fact that it was retrospective, there were partial data losses for some variables, and only female patients were evaluated. Consequently, it restricted the ability to compare the findings of our study to those in the literature.

Conclusion

In iron-deficient patients, the present study revealed a correlation between pica and iron binding capacity and transferrin saturation. Notable was that this association was with iron parameters rather than erythrocyte indices.

Ethics approval statement: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Ordu University (Approval Date: 09.01.2023, No:2023/05).
Conflict of interest: We have no conflicting financial interests to report.
Financial Support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author contributions: Study design, analyze and writing (M.Ö.), Data collection and processing (S.Y., E.D.)
Availability of data and materials: The authors confirm that the data supporting the findings of this study are available within the article.

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