RESEARCH ARTICLE

Sukran Berkman[1]
Ozlem Suvak[2]

[1] Çankaya Kerkük Family Practice Center, Ankara, Türkiye
[2] Dışkapı Yıldırım Beyazıt Research and Training Hospital, Department of Family Medicine Ankara, Türkiye

Corresponding Author:
Özlem Suvak
mail: ozlemgucsuvak@yahoo.com

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konuralptipdergi@duzce.edu.tr
konuralptipdergisi@gmail.com
www.konuralptipdergi.duzce.edu.tr

The Effect of Iron Replacement on Cognitive Functions in Reproductive Women with Iron Deficiency

ABSTRACT

Objective: Iron plays key role in brain development including neurogenesis, myelination, synaptic development, energy and neurotransmitter metabolism as well as normal brain functioning. The aim of this study is to examine the effect of iron replacement on cognitive functions in women with iron deficiency.

Methods: An intervention study was conducted in 165 women aged 15-49 years with low iron levels (ID;hemoglobin >12 gr/dl, ferritin <15 ng/mL) or iron deficiency anemia (IDA; hemoglobin <12 gr/dl, ferritin <15 ng/mL). 165 participants were subjected to 1st Montreal Cognitive Assessment (MoCA) scale in order to determine their preliminary cognitive function status. The women were given ferrous glycine sulfate at 100 mg/day (for those with ID) and 200 mg/day (for those with IDA), respectively, for eight weeks. Eight weeks later, the 2nd MoCA scale and control hemogram and ferritin tests were administered to 81 patients who came for follow-up and used iron treatment appropriately. Wilcoxon Signed Ranks Test was preferred when two dependent groups were compared, and Mann-Whitney U test was used when two independent groups were compared, and Kruskal Wallis test was used when three or more independent groups were compared. The analyze between age and cognitive function scores was evaluated with the Spearman correlation test.

Results: There was not a significant difference between the 1st MoCA scores of patients with ID or IDA in 165 women at the onset of the study. There was a significant increase in hemogram and ferritin levels of 81 patients who received a 200 mg/day iron replacement as expected (p<0.001). Cognitive functions were found to be significantly lower in single women with a high education level and a low body mass index (p<0.001). Average pretreatment MoCA score was 21 (min: 18- max:21), whereas post treatment average score was 26 (min:23- max:27) (p<0.001). For all cognitive functions, subgroup scores significantly increased after treatment. This improvement in cognitive functions was determined independently of demographic data. A low negative correlation also was found between age and total cognitive function score (r:-0.335, p <0.001).

Conclusions: In this study, we observed that after replacement therapy there was a significant increase in total and subgroup scores corresponding to cognitive functions of women diagnosed as iron deficiency or anemia. Considering the effect of iron replacement therapy on cognitive functions in women in the reproductive period, it should not be neglected.

Keywords: Iron Deficiency, Iron Replacement, Cognitive Functions, Female.

Demir Eksikliği Olan Üreme Dönemindeki Kadınlarda Demir Replasmanının Bilişsel İşlevlere Etkisi

ÖZET

Amaç: Demir normal beyin fonksiyonunda olduğu gibi, nörogenez, miyelinasyon, sinaptik gelişim, enerji ve nörotransmitter metabolizması dahil olmak üzere beyin gelişim süreçlerinde kilit rollere sahiptir. Bu araştırmanın amacı, demir eksikliği olan kadınlarda demir replasmanın zihinsel fonksiyonlar üzerine etkisini incelemektir.

Gereç ve Yöntem: Demir düzeyi düşük (hemoglobin >12 g/dl, ferritin <15 ng/mL) veya demir eksikliği anemisi (hemoglobin <12 g/dl, ferritin <15 ng/mL) olan 15-49 yaş arası 165 kadında müdahale çalışması yapılmıştır. 165 katılımcıya ön bilişsel işlev durumlarını belirlemek amacıyla 1. Montreal Bilişsel Değerlendirme (MoCA) ölçeği uygulandı. Kadınlara, sekiz hafta süreyle sırasıyla 100 mg/gün (DE olanlara) ve 200 mg/gün (DEA olanlara) demir glisin sülfat verildi. Sekiz hafta sonra kontrole gelen ve demir tedavisini uygun şekilde kullanan 81 hastaya 2. MoCA skalası ile kontrol hemogram ve ferritin testleri uygulandı. Bağımlı iki grubun karşılaştırılmasında Wilcoxon İşaretli Sıralar Testi, bağımsız iki grubun karşılaştırılmasında Mann-Whitney U testi, üç ve daha fazla bağımsız grubun karşılaştırılmasında ise Kruskal Wallis testi tercih edildi. Yaş ve bilişsel fonksiyon puanları arasındaki ilişki Spearman korelasyon testi ile değerlendirildi.

Bulgular: Çalışma başlangıcında DE veya DEA olan 165 kadının ilk MoCA skorları arasında anlamlı fark saptanmadı. 200 mg/gün demir replasmanı alan 81 hastanın hemogram ve ferritin düzeylerinde beklendiği gibi anlamlı artış oldu (p<0.001). Bekar, yüksek eğitim düzeyi ve düşük beden kitle indeksi olan kadınlarda bilişsel fonksiyonlar anlamlı düşük saptandı (p<0.001). Tedavi öncesi MoCA skor ortalaması 21(min:18-max:23) iken tedavi sonrası 26 (min:23-max:27) olarak saptandı (p<0,001) ve tüm fonksiyon alt grup skorlarında da tedavi sonrasında anlamlı yükselme görüldü. Bilişsel fonksiyonlardaki bu iyileşme demografik verilerden bağımsız olarak saptandı. Yaş ile toplam bilişselfonksiyon skoru arasında negatif yönde düşük düzeyde bir ilişki saptandı r:-0,335,p <0,001).

Sonuç: Bu çalışmada demir eksikliği veya anemi tanısı alan kadınlarda replasman tedavisi sonrası bilişsel işlevlere karşılık gelen toplam ve alt grup puanlarında anlamlı artış olduğunu gözlemledik. Reproduktif dönemdeki kadınlarda demir replasman tedavisi bilişsel fonksiyonlara etkisi göz önünde bulundurularak, ihmal edilmemelidir.

Anahtar Kelimeler: Demir Eksikliği, Demir Replasmanı, Bilişsel Fonksiyon, Kadın.

INTRODUCTION

Anemia affects roughly one third of World population, where half of the cases are caused by iron deficiency (ID)(1). World Health Organization (WHO) determined that, prevalence of anemia is 38.2% for pregnant women and 29.4 % for reproductive women and severe anemia is strongly associated with mortality and has cognitive and functional consequences(2). ID hinders cognitive and motor development, and causes fatigue and loss of productivity (2,3).

As far as its effects on brain are considered, iron (Fe) plays key roles in brain development processes including neurogenesis, myelination, synaptic development, mitochondrial energy and neurotransmitter metabolism. Neurodegenerative disorders are strongly associated with impaired homeostasis of iron (4).

Between the ages of 15-50, when women are most active and productive, they also encounter with nutritional deficiencies such as IDA(5,6). It is controversial whether ID has detrimental effects on cognition, mental health, and fatigue in women of childbearing age and iron replacement contributes positively to cognitive functions in these women(5). The aims of this paper was to find three answers regarding effects of IDA on cognitive functions in women of childbearing age;

1. Is the change in iron status related to cognitive functions?

3. Is there any difference in terms of cognitive between women of childbearing age with ID or IDA?

4. Is there any correlation between hemoglobin level and mental functioning in women of childbearing age with ID or IDA?

MATERIAL AND METHODS

Between the April 1,2018 and October 1,2018 a total of 165 women aged 15-49 and had either ID or IDA were enrolled and underwent to scale in Family medicine outpatient clinics. It was planned to direct patients who had hemoglobin (Hb) levels lower than 10 gr/dl and whose hemoglobin levels did not increase after treatment to hematology clinic. Together with hemoglobin and ferritin values of patients, data such as age, marital status, education level, occupation, current chronic conditions and body weight were recorded. Each participant provided informed written consent.

Sample Population – Participants: Participants are summarized in Figure 1.

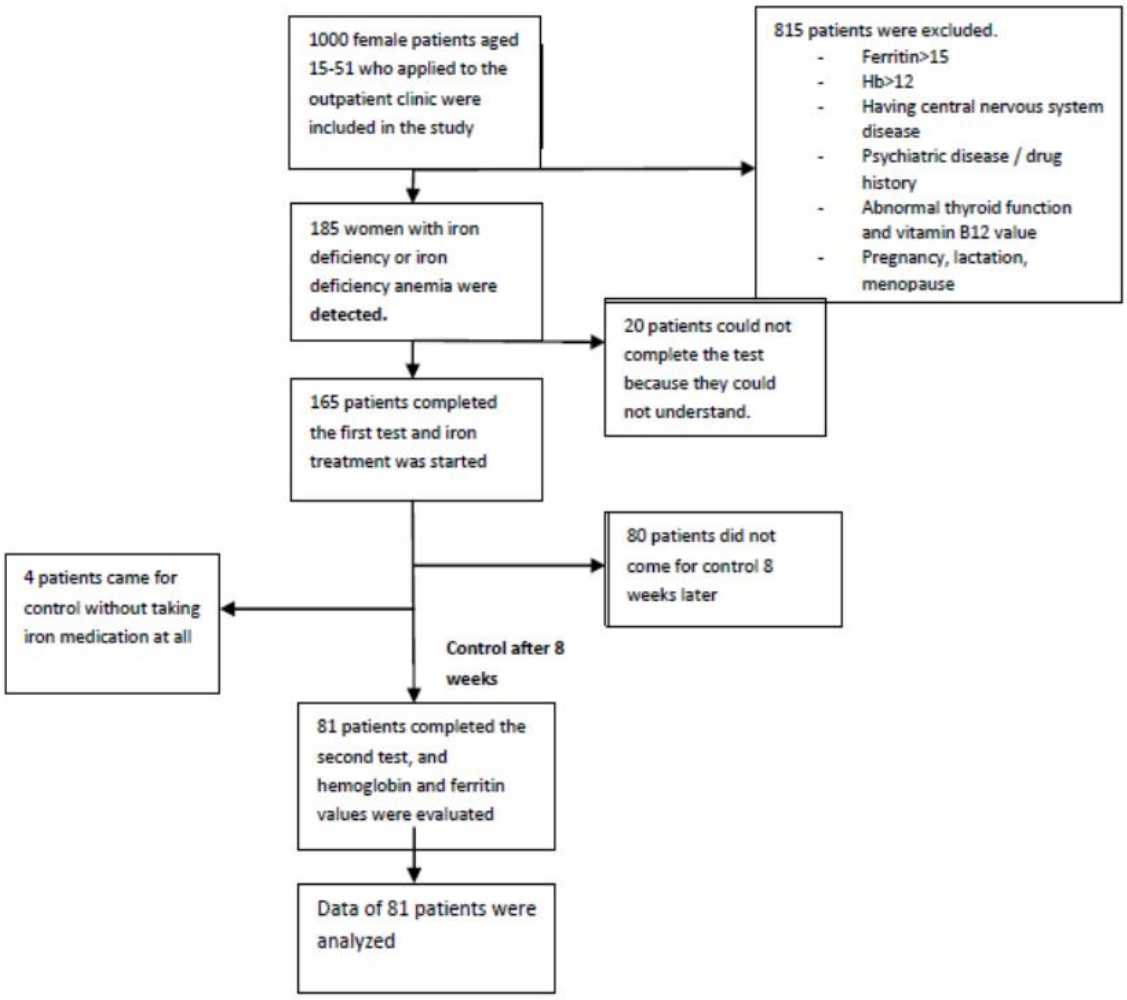

Figure 1. The scheme of choice for women with iron deficiency or iron deficiency anemia.

Study Design: 165 women had ID or IDA were subjected to a MoCA scale in order to assess cognitive function levels initially. The eight-week iron supplementation was provided to the participants in ID and group. The ferrous glycine sulfate doses were planned for ID as 100 mg/day and IDA as 200 mg/day. Participants were invited for a follow up after 8 week. Only 85 of the participants came back to the outpatient clinic for control. 4 women were excluded from the second phase of the study because they did not use the treatment as described. 81 participants completed assessments of MoCA scale and the analysis of hemogram and ferritin tests.

Laboratory Analysis: Blood samples were taken by experienced nurses. Purple-top EDTA coated tubes were used for hemogram and yellow-top heparin tubes were used for ferritin analysis. Blood samples were analyzed in Hospital Biochemistry Laboratory. The method for hemogram analysis was electrical impedance, volumetric technique with a Beckman Coulter LH780 (Houston, USA 2014) analyzer, and chemiluminescence technique was applied with a Beckman Coulter DXI 800 (California, USA 2014) analyzer. In the preparation of the study, support of Scientific Researches and Projects Commission (SRPC) was received for hemogram and ferritin tests after 8 weeks iron treatment of patients(On 04/01/2018. Decision number: 67).

Instruments: The socio-demographic questionnaire involved questions about the participants' age, education, occupation, body mass index and presence of chronic disease.

A Turkish version of MoCA scale translated by Selekler et al (7) who repeated reliability and validity analyses was employed for determining cognitive function levels. MoCA is an easy to apply scanning test for detecting minor cognitive disorders and is utilized for assessing a set of cognitive functions. Among these functions are short-term memory, visuospatial skills, executive functions, attention, language and orientation. MoCA scale can be administered in approximately 10 minutes.

Statistical Methods: Data were presented in the form of descriptive statistics, such as frequency, percentages, mean, and standard deviation were performed with SPSS® IBM 20.0 software((IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to verify the normality of distribution. The Mann–Whitney U test was performed to compare data with non-normal distributions. The Wilcoxon signed-rank test was used for abnormally distributed quantitative variables to compare the measurements taken at the baseline and after three months (Hemoglobin, ferritin and MoCA scores). If there was a significant difference in the comparison of three or more groups, the group that caused the difference was determined by making multiple comparisons between the two groups with Mann-Whitney U test. The correlation of total cognitive function scores with age was analyzed by Spearman correlation test. The results were considered significant at $p < 0.05$.

Ethical Consideration: The ethics committee of the University of Health Sciences, Dışkapı Yıldırım Beyazıt Health Training and Research Hospital approved the study protocol (IRB number 47/11 and date of March 19,2018).The Scientific Research Support Board supported for hemogram and ferritin kit(Decision no: 67 and date of Jan 4, 2018). The directives and content of study were explained to all participants and provided to written informed consent.

RESULTS

Initially, 1000 female patients aged 15-51 years who applied to the outpatient clinic were included in the study. ID or IDA were occurred in 185 women. 20 participants could not complete the scale due to not comprehend. 81 of 165 females included in the study were between the ages of 15-49 (Median=34,13) (Figure 1). 14,8% (n=12) of the participants had a chronic disease and 18.5% (n=15) were also working. According to body mass index (BMI) 3.6% of the patients were underweight, 50.9% was in normal range, 30.3% was overweight, 12.7% was obese class I, 1.2% was obese class II and 1.2% was obese class III. 38.3%(n=50) of them had ID and 61,7%(n=31) of those had IDA. Participants' data is summarized in Table 1.

According to the results of the independent sample t-test to see if the treatment was effective, both hemoglobin and Ferritin measurements increased significantly ($p<0.001$)(Table 2). MoCA scores of the groups were also analyzed separately to determine whether demographic parameters were related to mental status. Group comparisons are summarized in Table 1. It was observed that MoCA scores of married patients were higher as compared to single patients and the difference was statistically significant.

Table 1. Comparison of MoCA Scores of Demographic Groups

	Demographic data	TotalMoCA Score	*p*	MoCA Score difference	*p*
Marital Status	**n , %**		**<0.001***		0.299
Married	58 (71.5)	20 (17-23)		3 (2-5)	
Single	23 (28.5)	23 (21-26)		3 (1.5-4.5)	
Employment State	**n , %**		0.136		0.956
Employed	15 (18.5)	21 (18-24)		4 (2.5-4)	
Unemployed	66 (81.5)	21 (18-24)		3 (2-5)	
Chronic Condition	**n , %**		0.063		0.478
Yes	12 (14.8)	21 (16-22)		4 (3-5)	
No	69 (85.2)	22 (19-24)		3 (2-5)	
Education Level	**n , %**		**<0.001****		0.872
Primary Education	19 (23.5)	17 (15-20)		3 (2,5-4.5)	
Secondary Education	15 (18.5)	19 (18-21)		4 (2-5)	
Higher Education	26 (32.1)	22 (20-24)		3 (2-4)	
University	21 (25.9)	24 (22-26)		3 (2-4)	
BMI	**n , %**		**<0.001***		0.556
Normal Range	43 (53.1)	22 (20-25)		3 (2-4.5)	
Overweight	27 (33.3)	21 (18-23)		4 (3-5)	
Obese	11 (13.6)	18 (15-20)		4 (3-4)	
Anemia Condition	**n , %**		0,718		**0.019***
Iron deficiency	50 (61.7)	21(14-28)		3(0-8)	
Iron deficiency anemia	31 (38.3)	22(11-29)		4 (1-8)	

MoCA: Montreal Cognitive Assessment ; BMI. body mass index
*Mann Whitney U Test, ** Kruskal Wallis test, p < 0.05 was were considered significant

Occupational status, having whether a chronic condition or not had no significant effect, also. For education levels, a statistically significant direct relationship with several subgroup scores was observed except Total Scores and subgroup of orientation. A low negative correlation was found between age and total cognitive function score (r:-0.335, p <0.001).When MoCA scores of ID and IDA patients were compared, there were no statistically significant differences between ID and IDA groups for all subgroups of MoCA tests (p>0,05).

*Independent-samples t-test

Table 2. Comparision of Test Results Before and After Iron Replacement Therapy *

	Before Replacement(n=81)	After Replacement(n=81)	p	Z
Measurements	Median (min-max)	Median (min-max)		
Hemoglobin(g/dL)	12.4(10.5-13.6)	13.3 (12.4-14.1)	**0.000**	-6.656
Ferritin(µg/L)	5.7(3.5-7.9)	11.4(7.7-16.5)	**0.000**	-7.803
MoCA score	21(19-24)	26 (23-27)	**0.000**	-7.238

*Independent-samples t-test

Average pretreatment MoCA score was 21 (min: 18- max:21), whereas post treatment average score was 26 (min: 23- max:27) (p<0.001). A statistically significant increase for both total MoCA scores and subgroup scores were observed (p<0.001). For all cognitive functions, subgroup scores significantly increased after treatment. 1st and 2nd MoCA scores of 81 patients were summarized in Figure 2.

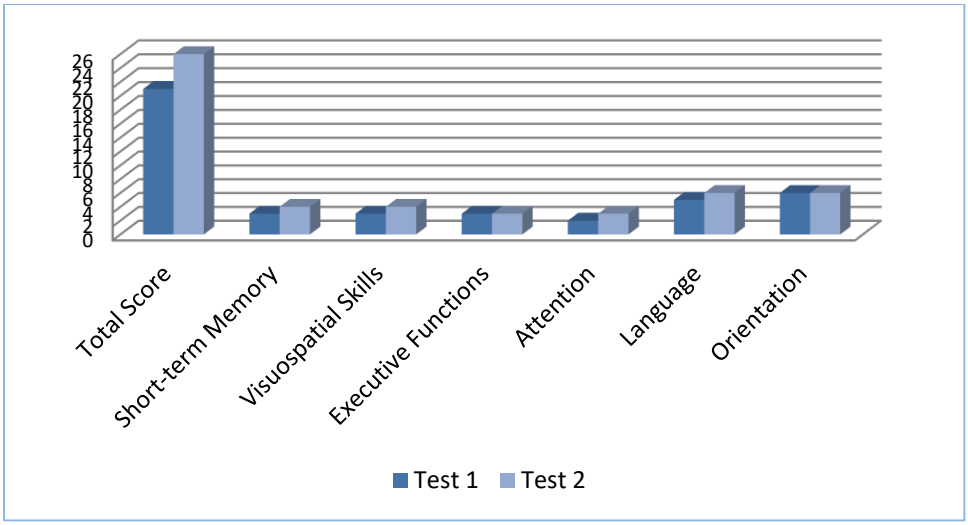

Figure 2. A comparison of Total and Subgroup MoCA Scores Before and After Treatment

Hemoglobin and ferritin measurements and MoCA scores of 81 women increased significantly after iron replacement, as expected ($p<0.000$) (Table 2). Additionally, the scatterplot referring the relationship between MoCA scores and Hemoglobin is given in Figure 3.

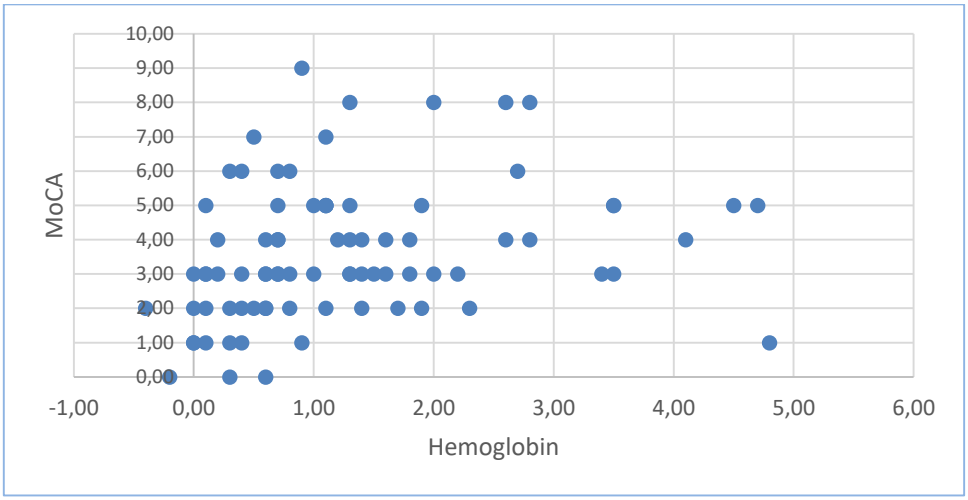

Figure 3. Scatterplot of Hemoglobin vs. MoCA scores after intervention

DISCUSSION

The young and middle-aged women are at risk of ID and IDA because of the increased iron requirement due to menstruation and pregnancy (2). The most of studies investigating the relationship between nutrient, element deficiency and cognitive functions are concentrated in childhood, antenatal period or adolescents (8-13). However, in the reproductive period of women, the most active and productive age of life, women's cognitive performances attracted the attention of few researchers (3,5,6,14) In women in this age group, researchers were generally interested in the relationship of iron in pregnancy with children's intelligence tests after birth (9,15). In 1970, Elwood et al. conducted a study in which anemic women aged 20 or older were randomized as a daily iron supplement group and a placebo group for 8 weeks and were applied cognitive test; they found that there was a reduction in the number of mistakes made when completing a maze in women taking iron, but there were no differences for cognitive tests (16). In 1996, Bruner et al. found that 81 adolescents with IDA performed better than girls in the control group in special learning and memory tests after 650 mg of iron supplementation against placebo. He did not find any difference attributable to iron in the Symbol Digit Modalities Test, Visual Search and Attention Test, or Short Attention Test (10). In 2007, Murray-Kolb and Beard found that 42 women with ID between the ages of 18-35 completed cognitive functions in a shorter time (5-7 times) with Detterman's Cognitive Ability Test (11). In 2014, Leonard et al. administered 60 and 80 mg of ferrous sulphate and compared with placebo, with 24 women aged 18 to 35 years with iron deficiency and taking no iron replacement. IntegNeuro Cognitive Scale was applied initially; women treated with iron (at both doses) had a significant reduction in impulsivity, but researchers could not find any difference in memory, response speed, attention, information processing, executive function or emotion identification. The increase in hemoglobin was associated with the time to complete the test (12). Gençay-Can et al., conducted a study in 33 anemic women 18-50 years of age is nearly accepted as fertility period in Turkey and 32 non-anemic control group with neuropsychological tests and life quality tests to determine the cognitive functions of women (6). They found a correlation with education, serum Fe, ferritin, and hemoglobin levels were associated with cognitive test scores and fatigue. But they didn't execute and observe the test scores after treatment of IDA. In our study, a total of 81 female patients diagnosed with ID or IDA were compared before and after the iron replacement with MoCA scale total score and MoCA scale sub scores, which are close memory, visual-spatial skills, executive functions, attention, language and orientation scores. There was a significant increase in total score and all subgroup scores. The increase in hemoglobin and ferritin after replacement therapy was also significant. Considering the correlation of this significant increase in hemoglobin and ferritin with the increase in MoCA scores, there was a significant correlation between the increase in hemoglobin and the MoCA scores, but no correlation between ferritin and MoCa scores. It was found that a strong positive correlation between hemoglobin increase and increases in MoCa score differences. These results correspond to the majority of previous studies (11, 12).

In the past few years, most of the studies investigating the relationship between iron and cognitive status have used iron-rich foods. In 2017, Murray-Colb et al. reported that 150 women aged

18-27 showed a 17% greater improvement in spatial attention speed, a 68% greater improvement in productivity, and > 2 times greater improvement in memory intake specifity and speed after consuming iron-biologically treated beans (86.1 ppm iron) or control beans (50.1 ppm iron) daily for 18 weeks (3). According to the present study, a statistically significant increase in hemoglobin and ferritin levels was achieved before and after iron replacement in 81 female patients. Unlike others, 8-week replacement treatment was provided with Ferrous sulfate preparation, which has high dose (200 mg/day) and high bioavailability instead of foods with high iron content. This method may have been effective in providing clear data and clinical recovery quickly.

Higher iron levels in women are associated with better attention and planning. However, it is not related to all cognitive sub-features (17). In the first phase of the study, there was no difference in cognitive functions between women with ID and IDA. In this respect, the results were consistent with literature on this subject (10).

There is only one cross-sectional study about the association of IDA with cognitive functions in a similar sample group in Turkey. They found middle positive correlation between education, serum iron, ferritin, and hemoglobin levels were associated with cognitive test scores and fatigue (6). We think that we carry the contributions of this study forward in terms of revealing the results of the post-intervention tests, as well as overlapping with the results of the first part of our study.

Despite the fact that the occupations and development of brain capacity is affected by many unmeasured confounders from a large number of demographic, dietary, environmental, and lifestyle factors (18,19). However, in our study, we showed the positive contribution of iron, regardless of demographic characteristics. In the first stage of our study, it was observed a statistically significant difference between the groups in terms of educational status, marital status and BMI in women with ID and IDA. It has been found that single individuals have higher MoCA scale scores than married ones, and there was a positive correlation with education level. According the study by Liu et al., divorced and widowed older adults are particularly vulnerable to cognitive impairment (19). The reason of this contradiction might be higher education and younger age of single participants. Another finding is positive correlation between MoCA scores and education level which was unsurprising. In certain studies, obesity is negatively related to cognitive performance in humans and that deterioration may increase over time and cause dementia (20). Verdejo-García et al. demonstrated that the performances of inhibition and mental flexibility in executive areas were significantly lower in obese compared to healthy ones in adolescents (21). However, significant differences were not found in the executive functions such as working memory, planning, and reasoning between these two groups. These results were interpreted as indication of selective alterations of executive functions in overweight adolescents. Similar to this study, it was concluded that as BMI increased, cognitive functions decreased. It was precipitated that normal weight individuals scored significantly higher than overweight and obese individuals, and overweight individuals were scored significantly higher than obese individuals. According to a meta-analysis, replacement in all age groups regardless of iron status enhances cognitive performance (22). This results have given countenance to previous substantial researches. In contrary to the 1st MoCA scores iron was found to contribute positively to the cognitive function levels of the participants, regardless of individual characteristics including age, marital status, occupation, chronic disease, education level, and BMI, after replacement.

The strengths of the present study are the improvement in cognitive functions 8 weeks after being treated with high dose ferrous sulfate, and there are no studies comparing the cognitive functions of women with ID and IDA. The limitations of the study that are small number of samples, only half of patients at the start completed phases of the study and the absence of a control group. In addition, control levels could not be observed 6 months after the initiation of the treatment.

CONCLUSION

We have corroborated others' previous findings and contributed to them by demonstrating improvement in cognitive functions, as independence of demographic characteristics even if iron replacement was given for a short-time. In this study, we would like to emphasize that cognitive capacity is affected by the lack of iron mineral, which is one of the components of the diet, and also iron replacement has a positive contribution to mental functions in women with or without anemia. We think that our study might have reflect the importance of iron supplementation in terms of cognitive clinical reflection and be a step for prospective cohort studies in women reproductive age.

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