

## Is Iron Deficiency Anemia Associated with Cognitive Functions in Reproductive-Age Women?

### Demir Eksikliği Anemisi Üreme Çağındaki Kadınlarda Bilişsel Fonksiyonlarla İlişkili midir?

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#### Abstract

**Objectives:** The aim of the study was to determine whether iron deficiency anemia (IDA) affects cognitive functioning, physical functioning, psychiatric morbidity, fatigue and quality of life in reproductive-age women.

**Materials and Methods:** Thirty-three women aged between 18-50 years with IDA and 32 non-anemic healthy women were included in the study. Laboratory analyses, neuropsychological tests, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), VAS fatigue, Health Assessment Questionnaire (HAQ-DI) and Short Form-36 (SF-36) were assessed.

**Results:** There was no significant difference in demographic characteristics of the patients between groups. Digit Forward/Backward, Digit Span Total, HAQ-DI, BAI, BDI, SF-36, fatigue scores in IDA group were significantly lower than the controls. Correlation analysis revealed that education, serum iron, ferritin, and hemoglobin levels were associated with cognitive test scores and fatigue. Serum iron, ferritin, and hemoglobin levels were found to be associated with HAQ-DI, BAI, BDI, and SF-36 scores.

**Conclusion:** IDA negatively affects cognition, physical functioning, quality of life, fatigue, symptoms of anxiety and depression in reproductive-age women.

**Key words:** Iron deficiency anemia, reproductive-age women, cognition

#### Öz

**Amaç:** Bu çalışmanın amacı, üreme çağındaki kadınlarda demir eksikliği anemisinin bilişsel fonksiyonlar, fiziksel fonksiyonellik, psikiyatrik morbidite, yorgunluk ve yaşam kalitesi üzerindeki etkilerini incelemektir.

**Materyal ve Metot:** Yaşları 18-50 arasında değişen ve demir eksikliği anemisi olan 33 kadın ve anemisi olmayan 32 sağlıklı kadın çalışmaya dahil edildi. Laboratuvar analizi, nöropsikolojik testler, Beck Depresyon Ölçeği, Beck Anksiyete Ölçeği, VAS yorgunluk, Sağlık Değerlendirme Anketi ve Kısa Form-36 değerlendirildi.

**Bulgular:** Gruplar arasında demografik özellikler açısından anlamlı fark saptanmadı. Demir eksikliği Anemisi olan grupta Digit Forward/Backward, Digit Span Total, Sağlık Değerlendirme Anketi, Beck Depresyon Ölçeği, Beck Anksiyete Ölçeği, Kısa Form-36 ve yorgunluk skorları kontrol grubuna göre anlamlı olarak daha düşüktü. Korelasyon analizinde eğitim, serum demir, ferritin ve hemoglobin düzeyleri ile bilişsel test skorları ve yorgunluk arasında anlamlı ilişkili bulundu. Serum demir, ferritin ve hemoglobin düzeyleri ile Sağlık Değerlendirme Anketi, Beck Depresyon Ölçeği, Beck Anksiyete Ölçeği ve Kısa Form-36 skorları arasında anlamlı ilişki bulundu.

**Sonuç:** Demir eksikliği anemisi üreme çağındaki kadınlarda bilişsel fonksiyonları, fiziksel fonksiyonelliği, yaşam kalitesini, yorgunluğu, anksiyete ve depresyon semptomlarını negative yönde etkilemektedir.

**Anahtar kelimeler:** Demir eksikliği anemisi, üreme çağındaki kadınlar, bilişsel fonksiyonlar

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## Introduction

Iron deficiency (ID) is the most prevalent cause of anemia in both developing and developed countries affecting more than 50% of women of reproductive age.<sup>1</sup> Iron deficiency manifests not only as anemia but also have negative effects on mental development, motor performance, cognitive and behavioural functions.<sup>2-4</sup>

Multiple studies showed that ID and IDA are directly related with various pathologies in the central nervous system including cognitive deficits. These effects are marked at infancy and early childhood. The most affected functions involved in cognition are learning and memory. There are many different pathways which ID can affect cognition.<sup>3,4</sup> Iron is essential for neurotransmitter synthesis and myelin formation in the cortex.<sup>4</sup> Synthesis of neurotransmitters such as dopamine and norepinephrine in the hippocampus, striatum and cortex is a iron dependent pathway. Alterations of these neurotransmitters metabolism and decrement of D<sub>2</sub> receptors in the brain are responsible for cognitive deficits. Animal studies have shown that ID is also related to demyelination of neurones. Long-term pathologic process may result in decreased conduction velocity and memory problems.<sup>3</sup>

There is a strong evidence that IDA during infancy and childhood negatively impacts neurodevelopment, learning capacity, attention, concentration and memory.<sup>4,5</sup> However, only a few studies have evaluated relationship between IDA and cognitive performance in young adults.<sup>1,2,6,7</sup> Women of reproductive age have a higher risk for IDA due to inadequate dietary intake, high menstrual loss and pregnancy.<sup>8</sup> Because of these, it is important to reveal the effects of IDA on cognition in reproductive-age women.

Beside of cognitive dysfunction, IDA may be an important determinant of impaired physical functioning, decreased quality of life, anxiety, depression and fatigue.<sup>9,10</sup> Some previous studies indicated that development of depression, anxiety and fatigue may be related to the existence of IDA. As a consequence, health related quality of life in subjects with IDA may be affected negatively. On the other hand, the literature on fatigue, mental health and physical health is limited and results are controversial.<sup>11</sup>

The aim of the study was to determine whether IDA in reproductive-age women affects cognitive functioning, physical functioning, anxiety, depression, fatigue and quality of life.

## Materials and Methods

Thirty-three women between the ages of 18-50 years with IDA were included in the study. All patients admitted to a physical medicine and rehabilitation outpatient clinic for arthralgia and/or myalgia. The criteria for inclusion of women in the study were age between 18-50 years with IDA, non-pregnant, no medical disease that may affect cognitive and physical function like endocrinological disease, neurological disease and vitamin B<sub>12</sub>/folate deficiency, no drug usage that may cause sedation during last 6 months, no iron treatment during last 6 months. Iron deficiency anemia was defined as Hb concentration less than 12 g/L for women, a mean corpuscular volume less than 80 fL, and a serum ferritin level less than 20 ng/ml.<sup>11</sup> Thirty-two non-anemic healthy women matched for age and education were included as a control group. This study

was performed with the approval of the local ethics committee. All patients provided written informed consent to participate.

Laboratory analyses for complete blood count, serum iron and ferritin levels, total iron binding capacity, thyroid function tests, vitamin B<sub>12</sub> and folate levels, liver and kidney function tests were performed in all participants. Neuropsychological tests, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), VAS fatigue, Health Assessment Questionnaire (HAQ-DI) and Short Form-36 (SF-36) were assessed in all participants.

Neuropsychological evaluation was carried out by an experienced psychiatrist using Digit Span (including Digit forward and Digit backward) and Digit Symbol tests. These tests are subunits of Weschler Intelligence Scale-III. Forward and backward Digit Span tests are used for short-term working memory. Digit Span is measured for forward and backward recall of digit sequences. Digit sequences continue by increasing the series of numbers. Testing ceases when the subject fails to accurately report either trial at one sequence length or when the maximal list length is reached (9 digits forward, 8 backward). The number of lists reported correctly in each test is recorded. The scores of Digit-forward and Digit-backward are combined to form Digit Span Total score.<sup>7</sup> Digit Symbol test is mainly used to assess processing speed. It consists of 9-digit symbols matched with their corresponding numerical digit. It requires the patient to copy the symbols that are matched to each number as fast as possible within the allowed time (90 seconds).<sup>12</sup> Turkish validity and reliability of Weschler Intelligence Scale-III were made by Savasir et al.<sup>13</sup>

Health Assessment Questionnaire Disability Index (HAQ-DI) is widely used to measure physical function of both upper and lower extremities. It is a 20-item questionnaire with eight domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities. Each item is scored between 0 and 3. Higher score shows more disability. The validity and reliability of the Turkish version has been previously performed by Kucukdeveci et al.<sup>14</sup>

The quality of life of study subjects was measured using the Short Form-36 (SF-36). It is a 36-item questionnaire with 8 domains measuring physical and mental health status (SF-36 PCS and SF-36 MCS, respectively). Each item is scored and summed according to a standardized scoring protocol and each domain is scored between 0 and 100. Higher scores indicate better health status. The validity and reliability of the Turkish version of the SF-36 has been done by Pinar.<sup>15</sup>

Depressive symptoms and anxiety of the subjects were assessed by Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI), respectively. Both inventories are 21-item self-administered questionnaires. These provide a quantitative measure of depressive symptoms and anxiety symptoms. Each item was scored between 0 and 3 points. Higher scores indicate greater levels of anxiety and depression. The Turkish validity and reliability of the BDI has been performed by Hisli.<sup>16</sup> The Turkish validity and reliability of the BAI has been done by Ulusoy et al.<sup>17</sup>

0-100 mm VAS was used to assess the fatigue of study subjects. Subjects were asked to mark the point corresponding to the fatigue during the past week.

## Statistical Analysis

Independent samples t-test and chi-square test were performed to compare the demographic and clinical characteristics between the two groups. Results are expressed as means  $\pm$  SD. Pearson's correlation analysis was performed to assess the contributions of education and laboratory parameters on cognitive functions, SF-36, HAQ-DI, BDI, BAI and fatigue. Pearson's correlation coefficients ( $r$ ) were accepted as follows: 0.81–1.0 as excellent, 0.61–0.80 very good, 0.41–0.60 good, 0.21–0.40 fair, and 0–0.20 poor.<sup>18</sup> SPSS version 17 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.  $p$ -values less than 0.05 were considered to represent a significant difference.

## Results

There was no significant difference in demographic characteristics of the patients between groups ( $p > 0.05$ ). The demographic characteristics and laboratory data of the groups have been shown in Table 1.

Scores of Digit Forward, Digit Backward and Digit Span Total in IDA group were significantly lower than the controls ( $p < 0.001$ ). Digit Symbol scores were lower in IDA group, but the difference did not reach the level of significance ( $p > 0.05$ ). HAQ-DI, BAI, BDI, SF-36 PCS and MCS, VAS fatigue scores were significantly impaired in IDA group ( $p < 0.05$ ) (Table 1).

In correlation analysis, education, hemoglobin, serum iron and serum ferritin levels have moderate to good positive correlations with scores of Digit Forward, Digit Backward and Digit Span ( $p < 0.05$ ). While education and serum iron level were correlated positively with Digit Symbol score ( $p < 0.05$ ), there were no significant correlations between Digit Symbol score and levels of hemoglobin and serum ferritin ( $p > 0.05$ ) (Table 2).

Moderate negative correlations were detected between HAQ-DI scores and levels of serum iron, ferritin, and hemoglobin ( $p < 0.05$ ). No significant correlation was detected between HAQ-DI score and levels of education ( $p > 0.05$ ). Hemoglobin, serum iron and serum ferritin levels were moderately negatively correlated with scores of BAI and BDI scores ( $p < 0.05$ ). There was no significant correlation between education and scores of BAI and BDI ( $p > 0.05$ ). Hemoglobin, serum iron and serum ferritin levels have moderate to good positive correlations with SF-36 PCS and MCS ( $p < 0.05$ ). Education was not found to correlate significantly with SF-36 PCS and MCS ( $p > 0.05$ ). There were moderate to good negative correlations between levels of hemoglobin, serum iron and serum ferritin and fatigue VAS score ( $p < 0.05$ ) (Table-3).

## Discussion

Iron deficiency with and without anemia is one of the most important health problems among women of reproductive age. Iron is an important element for brain growth, myelination, neurotransmitter synthesis.<sup>19</sup> As a consequence, IDA seems to be linked to motor and cognitive dysfunction and socio-emotional problems.<sup>4</sup> Many studies on cognitive functioning and physical functioning have focused on infants and early childhood.<sup>4,5</sup> Less research had focused on the effects of IDA in women of reproductive age.<sup>1,6</sup> This study revealed that decreased serum iron, ferritin, and hemoglobin levels are associated with poorer cognitive and motor performance, increased anxiety and

depressive symptoms, impaired quality of life and increased fatigue in women of reproductive age.

**Table 1.** Demographic and clinical characteristics of the subjects

|                         | IDA group (n=33)<br>(mean±SD or %) | Control group (n=32)<br>(mean±SD or %) | P       |
|-------------------------|------------------------------------|----------------------------------------|---------|
| Age (years)             | 32.8±8.4                           | 29.4±8.0                               | 0.091   |
| Education level (years) | 6.8±3.3                            | 7.1±3.5                                | 0.261   |
| Marital status (%)      |                                    |                                        |         |
| Married                 | 75.75                              | 71.82                                  | 0.720   |
| Single                  | 24.25                              | 28.18                                  |         |
| Occupation (%)          |                                    |                                        |         |
| Housewife               | 56.91                              | 53.11                                  | 0.692   |
| Worker                  | 38.09                              | 40.68                                  |         |
| Retired                 | 5                                  | 6.21                                   |         |
| Hemoglobin (g/dl)       | 10.6±1.1                           | 13.2±0.7                               | <0.001* |
| Hematocrit (%)          | 33.9±3.4                           | 39.3±1.5                               | <0.001* |
| MCV (fL)                | 75.2±7.0                           | 88.2±4.1                               | <0.001* |
| RDW (%)                 | 16±2.4                             | 13.3±1.1                               | <0.001* |
| Serum iron (mcg/dl)     | 33.8±15.4                          | 92.6±11.3                              | <0.001* |
| TIBC (mcg/dl)           | 454.7±75.5                         | 291.4±48.9                             | <0.001* |
| Serum ferritin (ng/ml)  | 8.2±7.4                            | 35.3±13.6                              | <0.001* |
| Digit Span              |                                    |                                        |         |
| Total                   | 7.1±2.5                            | 9.9±2.4                                | <0.001* |
| Digit forward           | 4.1±1.6                            | 5.8±1.7                                | <0.001* |
| Digit backward          | 3.0±1.1                            | 4.1±1.1                                | <0.001* |
| Digit Symbol            | 31.8±15.8                          | 35.9±15.7                              | 0.293   |
| HAQ-DI                  | 0.8±0.4                            | 0.1±0.3                                | 0.004*  |
| BAI                     | 26.3±13.2                          | 16.4±12.5                              | 0.003*  |
| BDI                     | 17.6±11.3                          | 10.5±8.2                               | 0.005*  |
| SF-36 PCS               | 42.7±21.8                          | 73.3±24.2                              | <0.001* |
| SF-36 MCS               | 49.6±22.5                          | 69.4±22.4                              | 0.001*  |
| Fatigue(VASmm)          | 71.3±25.1                          | 32.5±27.5                              | <0.001* |

IDA: iron deficiency group, MCV: mean corpuscular volume, RDW: red blood cell volume distribution width,

TIBC: total iron binding capacity, HAQ-DI: Health Assessment Questionnaire Disability Index,

BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory,

SF-36 PCS: Short Form-36 Physical Component Summary,

SF-36 MCS: Short Form-36 Mental Component Summary,

\*: statistically significant difference

Infants and young children are at higher risk for IDA during their first 2 years of life.<sup>11</sup>

In this age group, IDA has been shown to cause disturbances in psychomotor development and cognitive functions.<sup>4,5</sup> Women of reproductive age also have high rates of IDA because of pregnancy, menstruation and inadequate intake of iron.<sup>11</sup>

However, there are only a few studies to investigate the effects of IDA on cognitive functioning in women of reproductive age in the literature.<sup>1,2,20</sup> Khedr et al. showed

that subjects aged 16-28 years with IDA performed poorer on Digit forward, Digit backward and Digit Symbol tests than control subjects.<sup>2</sup>

**Table 2.** Pearson’s correlation coefficients for the association between education, serum hemoglobin, iron, and ferritin levels and cognitive tests scores (n=65)

|                | <b>Digit Forward</b> | <b>Digit Backward</b> | <b>Digit SpanTotal</b> | <b>Digit Symbol</b> |
|----------------|----------------------|-----------------------|------------------------|---------------------|
| Education      | 0.58*                | 0.59*                 | 0.55*                  | 0.55*               |
| Hemoglobin     | 0.43*                | 0.44*                 | 0.45*                  | 0.19                |
| Serum iron     | 0.61*                | 0.56*                 | 0.60*                  | 0.35*               |
| Serum ferritin | 0.27*                | 0.28*                 | 0.24*                  | 0.21                |

\*: statistically significant difference (p<0.05)

Murray-Kolb et al. showed that iron-sufficient women performed better on cognitive tests than IDA women who aged 18-35 years.<sup>1</sup> Similar to these studies, we detected that women of reproductive age with IDA had lower scores of Digit Forward, Digit Backward and Digit Symbol tests than the women without IDA. The difference in Digit Symbol test scores was also found lower than that of the control group, but the difference did not reach level of significance. Similarly, Ukkirapandian et al. found no significant difference in Digit Symbol test scores between anemic young women and healthy young women.<sup>20</sup> The different results in Digit Symbol test scores were attributed to the different sample size and education level of the study subjects. Education level of subjects has not been assessed in the previous studies. According to our results, IDA seems to cause different cognitive impairments not only in early stages of development, but also in adult life.

**Table 3:** Pearson’s correlation coefficients for the association between education, serum hemoglobin, iron, and ferritin levels and clinical parameters (n=65)

|                | <b>HAQ-DI</b> | <b>BAI</b> | <b>BDI</b> | <b>SF-36 PCS</b> | <b>SF-36 MCS</b> | <b>Fatigue</b> |
|----------------|---------------|------------|------------|------------------|------------------|----------------|
| Education      | -0.16         | -0.15      | -0.04      | 0.14             | 0.15             | -0.24*         |
| Hemoglobin     | -0.25*        | -0.31*     | -0.29*     | 0.40*            | 0.38*            | -0.42*         |
| Serum iron     | -0.32*        | -0.36*     | -0.30*     | 0.51*            | 0.43*            | -0.56*         |
| Serum ferritin | -0.28*        | -0.28*     | -0.29*     | 0.41*            | 0.35*            | -0.40*         |

HAQ-DI: Health Assessment Questionnaire Disability Index, BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory,

SF-36 PCS: Short Form-36 Physical Component Summary, SF-36 MCS: Short Form-36 Mental Component Summary,

\*: statistically significant difference (p<0.05)

In the present study, we found that cognitive performance had significant correlations with levels of education, hemoglobin, serum ferritin and serum iron in women of reproductive age. There is a substantial amount of variation in the results of previous studies in this field.<sup>1,2,11,21,22</sup> In a similar vein to our study, Murray-Kolb et al. reported the relation of serum ferritin levels and cognitive performance in young adult women.<sup>1</sup> Petranovic et al. reported that hemoglobin levels were significantly correlated with

cognitive function in obese women aged between 25 and 42 years.<sup>22</sup> In contrast, Fordy et al. showed no association between low ferritin levels and poor performance on Digit Span test in young males and females.<sup>21</sup> Khedr et al. found no significant correlation between levels of hemoglobin and serum iron and scores of Digit Forward, Digit Backward, Digit Symbol tests, but found a significant correlation with Mini-Mental State Examination scores and intelligence.<sup>2</sup> It is difficult to make a comparison of results as the different characteristics of study subjects and the different sample sizes. The previous studies did not investigate the relationship between education and cognition.<sup>11</sup> This is the first study to evaluate the relationship between education and cognition and the results need to be confirmed in further studies.

Iron deficiency and IDA may cause some cognitive disfunctions, but it is unclear those disfunctions are the same.<sup>5</sup> Some studies found a correlation between hemoglobin levels and cognitive function, while others found correlation between serum iron levels and cognitive function.<sup>1,5,7,23</sup> In the present study, we found that both iron deficiency and IDA were related to poor cognitive performance. Sareen et al. did not find any correlation between cognitive performance and hemoglobin levels in females aged 18-25 years.<sup>23</sup> Similar to our results, Murray-Kolb et al. reported the relation of ferritin levels and cognitive performance and also a significant relationship between anemia and speed of processing in young adult women. In fact, both ID and IDA cause major changes in dopamine levels in certain brain areas and it is possible to obtain a clear idea that ID and IDA appear to affect cognitive performance.<sup>5</sup>

Nutritional deficiencies especially iron deficiency anemia can affect the psychological state and brain mechanisms that can lead to anxiety disorders and mood disorders such as depression. Reduced muscle strength and fatigue are commonly associated with anemia and may have detrimental effects on quality of life, therefore anemia facilitates the development of anxiety and depressive symptoms. On the other hand, the data are quite limited for anxiety and depression.<sup>9</sup> In the present study, we found that anxiety and depression scores were significantly higher in IDA group than that of the normal subjects. Correlatively to our study, Semiz et al. reported that anxiety and depression scores were significantly higher in young adult patients with IDA than the controls.<sup>24</sup> We also found that the levels of serum iron, ferritin, and hemoglobin had moderate negative correlation with scores of depression and anxiety in women with reproductive age. Similarly, Noorazar et al. found a significant correlation between depressive symptoms and hemoglobin levels.<sup>9</sup>

Fatigue is one of the most common symptoms of IDA. While IDA is known to be associated with fatigue, there is still an inadequate evidence of such an association in women with reproductive age.<sup>10,11,25</sup> Patterson et al. showed that self-reported fatigue was significantly higher in women aged 18-50 years with iron deficiency.<sup>25</sup> In the other study, Patterson et al. also showed that the total fatigue score was significantly higher in women aged 18-50 years with iron deficiency.<sup>10</sup> Similar to the results of these studies, we detected that level of fatigue was increased in IDA group compared to controls. We also detected that education, levels of serum iron, ferritin, and hemoglobin levels were significantly associated with fatigue.

There is evidence that iron plays an essential role in the optimal functioning of skeletal muscles. Iron is present in slow red fibers in muscles and is responsible for oxygen storage in myoglobin.<sup>26</sup> We assessed physical functioning of the subjects using HAQ-

DI. Physical functioning in women with IDA was worse than the controls. In addition, serum iron, ferritin, and hemoglobin levels were found to be correlated with physical functioning. To our knowledge, there is no study to evaluate the physical function using a specific assessment tool in subjects with IDA.

There is a widely belief that IDA has effects on quality of life and chronic fatigue. Only a few studies in the literature investigated this belief.<sup>10,25</sup> In the present study, physical and mental health of adult women with IDA were found to be significantly impaired in comparison to controls. In correlation analysis, we detected that serum iron, ferritin, and hemoglobin levels were significantly correlated with both physical and mental health quality. Correlatively to our results, Rangan et al. detected that anemic subjects scored significantly impaired on the General Health Questionnaire (mental health assessment) than non-anemic subjects.<sup>27</sup> Patterson et al. reported that physical and mental health were significantly impaired in women aged 18-50 years with ID.<sup>25</sup> In another study, Patterson et al. reported that while mental health scores were significantly lower in women 18 to 50 years of age in ID group, no significant difference in physical health scores were found.<sup>10</sup> These results indicate that adult women with ID or IDA have limitations on general health and decreased health quality. As iron is an important component of many enzymes involved in cellular energy metabolism and neurotransmitter synthesis, inadequate energy production and alterations in neurotransmitter metabolism may be the underlying mechanisms of decreased quality of life.<sup>10,25</sup>

This study had some limitations. First, we did not evaluate the effects of iron supplementation on cognition. Several studies detected an association between iron supplementation and cognitive improvement.<sup>10,25</sup> Second, we did not assess iron-deficient women without anemia. Iron deficiency and IDA may have different effects on cognitive functions. Third, only female subjects were recruited for the study. However, it seems that there are not any substantial different effects of IDA on cognitive functions depending on the sex.<sup>5</sup>

In conclusion, this study demonstrated that IDA negatively affects cognition, physical functioning, quality of life, fatigue, and symptoms of anxiety and depression in reproductive-age women. Early detection and treatment of IDA is essential to prevent cognitive impairment and to improve quality of life in adult women. Further studies with a larger sample size are needed to replicate the results of this study in women of reproductive age.

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