The effects of iron deficiency anemia on the thyroid functions

Demir eksikliği anemisinin tiroid fonksiyonları üzerine etkisi

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ABSTRACT

Objectives: The aim of the present study was to investigate the effect of iron deficiency anemia and iron treatment on the thyroid functions.

Materials and methods: In this study, 42 patients and 38 healthy individuals were studied. Iron deficiency anemia was diagnosed by measurement of serum ferritin and complete blood counts. Free Triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine, total thyroxine, thyroid stimulating hormone (TSH) and cortisol levels were measured in blood samples before treatment and after two months of treatment with iron in patients group and after 12 hours of starvation in healthy controls.

Results: Before iron treatment, secondary hypothyroidism (35.7%) and subclinical hypothyroidism (16.6%) were found in patient group. Before the treatment TSH levels in the patient group were higher than the control group (p=0.001). FT3 values were not different between patient and the control groups (p>0.05). Before the treatment FT4 levels were significantly lower than the control group (p<0.001) and FT4 values significantly increased after treatment (p=0.001). Cortisol levels before treatment were significantly higher than the control group (p=0.001). Cortisol levels were significantly decreased after iron treatment in the patient group (p<0.001).

Conclusions: Secondary and subclinical hypothyroidism were found in iron deficiency anemia. Hormonal changes returned to normal values with iron supplementation. J Clin Exp Invest 2010; 1(3): 156-160

Key words: Iron deficiency, anemia, thyroid functions, secondary and subclinical hypothyroidism, iron supplementation

ÖZET

Amaç: Bu çalışmanın amacı demir eksikliği anemisinin tiroid fonksiyonları üzerine etkisi ve demir tedavisi sonrası değişiklikleri belirlemektir.

Gereç ve yöntem: Bu çalışma, 42 hasta ve 38 sağlıklı birey ile yapıldı. Demir eksikliği anemisi tanısı serum fer-ritin ve tam kan sayımı yapılarak kondu. Hasta grubunda tedavi öncesi ve iki aylık tedavi sonunda ve kontrol grubunda ise 12 saat açıktan sonra kan örnekleri alınarak serbest triiyodotironin (ST3), serbest tiroksin (ST4), total triiyodotironin (TT3), total tiroksin (TT4), tiroid stimule edici hormon (TSH) ve kortizol değerleri çalışıldı.

Bulgular: Hasta grubunda demir tedavisi öncesi, olguların %35.7’sinde sekonder ve %16.6’sında subklinik hipotiroidi bulundu. Hasta grubunda tedavi öncesi, TSH düzeyi kontrol grubuna göre anlamlı düzeyde yüksekti (p=0.001). ST3 düzeyleri hasta ve kontrol grupları arasında farklı de-ğildi (p>0.05). Tedavi öncesi ST4 düzeyleri, kontrol grubuna göre, anlamlı düştü (p<0.001). ST4 düzeyleri teda-vi sonrasında anlamlı şekilde yükseldi (p=0.001). Hasta grubunda demir tedavisi öncesi anlamlı şekilde yüksek olan kortizol düzeyinin tedavi sonrasında anlamlı olarak düştüğü belirlendi (p<0.001).


Anahtar kelimeler: Demir eksikliği, anemi, tiroid fonksiyonları, sekonder ve subklinik hipotiroidi, demir tedavisi

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**INTRODUCTION**

Apart from thyroid diseases, thyroid functions are affected by acute or chronic diseases such as chronic renal failure, diabetes mellitus, acute myocardial infarction, postoperative period, long-term starvation, heart failure, infections, cirrhosis, and stress. In recent years studies carried out in human and animals have suggested that iron deficiency can affect the thyroid hormone metabolism and peroxidase enzyme which is catalyzed initial steps of thyroid hormone synthesis is dependent on the iron. The studies carried out in rats have indicated that iron, T4 and T3 levels in circulation were significantly decreased during conversion of thyroxine (T4) to triiodothyronin (T3). However, effects of iron deficiency anemia on thyroid function-related studies are mostly based on animal studies and results are contradictory.

The aim of this prospective study was to determine thyroid functions changes before and after iron treatment in patients with iron deficiency anemia and to compare the data with healthy control subjects.

**MATERIALS AND METHODS**

In this study, 42 patients with iron deficiency anemia and 38 healthy control groups were recruited. The number of cases in both groups was statistically sufficient for comparison. The study subjects were informed about the purpose of the study, and written consent was taken from each of them. Ethical approval was obtained from the Local Ethics Committee. The patients taken to the study did not have known thyroid disease. The diagnosis of iron deficiency anemia based on; hemoglobin concentration less than 13.5 g/dL in male, less than 12 g/dL in female, mean corpuscular volume (MCV) less than 76 fL, ferritin concentration less then 10 μg/L in male and postmenopausal woman and less than 5 μg/L in premenopausal woman. Subclinical hypothyroidism was considered, when TSH levels elevated but FT4 and FT3 levels are normal. Secondary hypothyroidism was considered when TSH level normal or below normal and FT4 level is low.

The blood was drawn into two different ten milliliters’ tubes containing EDTA. Patients were hungry at the time of blood draw. Hemoglobin was measured in patient and control group. Other blood samples were centrifuged at 5000 rpm for 10 minute. Free triiodothyronine (FT3), free thyroxine (FT4), total triiodothyronine (TT3), total thyroxine (TT4), Tiroid stimulating hormone (TSH), cortisol and ferritin were measured by chemiluminescence metod in BIO DPC Immulite 2000 analyser using BIO DPC Immulite (USA) kit. Normal values of study parameters are: FT3 (1.8-4.71 pg/mL), FT4 (0.8-1.90 ng/dL), TT3 (84-172 ng/dL), TT4 (4.5-12.5 ng/dL), TSH (0.4-4 IU /mL), serum iron (SI) level (37-157 mg/dL), total iron binding capacity (TIBC) (274-497 mg/dL), ferritin (11-67 pg/dL) and cortisol (5-25 ng/dL).

The hemoglobin concentration was measured by the cyanmethemoglobin method in Coulter® LH 750 Hematology Analyzer (USA) using Lyse S III Diff Reagent (Ireland). Serum iron levels and total iron binding capacity was measured by ferrozin methods in Roche Cobas Integra 800 analyzer using Roche Cobas integra Iron II (USA) and Roche Cobas Integra UIBC (USA) kit, respectively. 42 patients with iron deficiency anemia received oral iron sulfate 200 mg/day. None of the patient was treated with an iron before this study. At the end of the second month of iron treatment, whole blood count, FT3, FT4, TT3, TT4, TSH, serum iron level, total iron binding capacity and ferritin measurements were repeated.

**Statistical analysis**

A computer statistical program was used (SPSS vs. 10.0) to analyze the data. Kolmogorov-Smirnov test was used to examine distribution pattern of the measured data. Patients and control group parameters and the relations between the parameters were compared using “Independent-Samples T” test and “Mann-Whitney U” test, according to normally or not-normally distributed data respectively. Non parametric “Wilcoxon” test was used for comparison of patients’ values between before and after iron treatment. Mean values and standard deviations were presented. P value less than 0.05 was considered as statistically significant.

**RESULTS**

Mean ages were 35.8±8.6 years (range 20-52; 9 male, 33 female) in patients group and 33.2±7.5 (range: 20-46; 8 male, 30 female) years in control group. There was no statistical difference between
age of the patients and control group (p>0.05). After two month of iron supplementation hemoglobin and hematocrit values were reached normal levels in iron deficiency patient.

Before iron therapy, TSH levels were significantly higher compared with the control group (p<0.001) (Table 1). In terms of TSH levels, between after iron treatment and control groups no significant differences were found (p>0.05) (Table 2). TSH levels were decreased after iron treatment (p<0.001) (Table 3).

FT4 levels in the patient group before the iron treatment were significantly low according to the control group (p<0.001) (Table 1), but there was no significant difference after the treatment (p=0.118) (Table 2). FT4 levels were significantly different between before and after iron the treatment (p<0.001) (Table 3).

A total of 15 patients, 12 female and 3 male, had FT4 levels below the normal limits and TSH levels were normal or over the normal limits. Although secondary hypothyroidism was observed in these patients, simultaneous cortisol levels were within normal limits (Table 1,3).

Table 1. The laboratory values of the patient and control group before treatment.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-treatment Patients (n=42)</th>
<th>Controls (n=38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>10.0 ± 1.0</td>
<td>14.3±1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SI (mg/dL)</td>
<td>19.5±5.1</td>
<td>76.9±23.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIBC (mg/dL)</td>
<td>504.4±69.7</td>
<td>294.2±50.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ferritin (pg/mL)</td>
<td>4.54±3.51</td>
<td>63.6±47.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT3 (pg/mL)</td>
<td>3.48±1.13</td>
<td>3.73±0.49</td>
<td>0.384</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>0.91±0.46</td>
<td>1.36±0.18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH (IU/mL)</td>
<td>3.32±1.10</td>
<td>1.17±0.51</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TT3 (ng/dL)</td>
<td>82.3±28.7</td>
<td>91.0±19.1</td>
<td>0.133</td>
</tr>
<tr>
<td>TT4 (ng/dL)</td>
<td>7.31±2.15</td>
<td>7.51±1.19</td>
<td>0.479</td>
</tr>
<tr>
<td>Cortisol (ng/dL)</td>
<td>17.1±6.8</td>
<td>12.1±4.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>


Table 2. The laboratory values of the patients-after treatment and control group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients- After Treatment (n=42)</th>
<th>Control Group (n=38)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>13.3±1.3</td>
<td>14.3±1.1</td>
<td>0.100</td>
</tr>
<tr>
<td>FT3 (pg/mL)</td>
<td>3.16±0.93</td>
<td>3.73±0.49</td>
<td>0.550</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>2.38±0.94</td>
<td>1.36±0.18</td>
<td>0.118</td>
</tr>
<tr>
<td>TSH (IU/mL)</td>
<td>1.02±0.52</td>
<td>1.17±0.51</td>
<td>0.185</td>
</tr>
<tr>
<td>TT3 (ng/dL)</td>
<td>87.7±19.1</td>
<td>91.0±19.1</td>
<td>0.434</td>
</tr>
<tr>
<td>TT4 (ng/dL)</td>
<td>6.0±1.5</td>
<td>7.5±1.2</td>
<td>0.173</td>
</tr>
<tr>
<td>Cortisol (ng/dL)</td>
<td>12.0±4.3</td>
<td>12.1±4.6</td>
<td>0.632</td>
</tr>
</tbody>
</table>


Table 3. The laboratory values of the patient group before and after treatment.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Before treatment (n=42)</th>
<th>After treatment (n=42)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>10.0 ± 1.0</td>
<td>13.3±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FT3 (pg/mL)</td>
<td>3.48±1.13</td>
<td>3.16±0.93</td>
<td>0.082</td>
</tr>
<tr>
<td>FT4 (ng/dL)</td>
<td>0.91±0.46</td>
<td>2.38±0.94</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSH (IU/mL)</td>
<td>3.32±1.10</td>
<td>1.02±0.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TT3 (ng/dL)</td>
<td>82.3±28.7</td>
<td>87.6±19.1</td>
<td>0.318</td>
</tr>
<tr>
<td>TT4 (ng/dL)</td>
<td>7.31±2.15</td>
<td>6.02±1.54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cortisol (ng/dL)</td>
<td>17.07±6.76</td>
<td>12.04±4.33</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


While TT4 levels were significantly higher in patient group before the treatment compared with the after treatment (p<0.001) (Table 3), no significant differences were found in TT4 values in pre- and post-treatment period compared with the control group (p=0.479; p=0.173, respectively) (Table 1, 2).

There was no significant difference in FT3 and TT3 levels between patients and control groups (Table 1). There were no significant difference between before and after treatment values of FT3 and TT3 (p>0.05) (Table 3).

It was observed that cortisol levels were higher in patient group before treatment when compared with the control group (p=0.001) (Table 1). The cor-
Tisol levels were significantly decreased after iron treatment compared to pre-treatment measurement (p<0.001) (Table 3). After treatment levels did not show significant difference compared with control group (p=0.632; Table 2).

DISCUSSION

Some studies carried out in animals and human have indicated that iron deficiency is related to impaired thyroid functions. Either iron deficiency or anemia cause changes of thyroid hormone metabolism has been the topic of discussion. Some studies have suggested that T3 levels returns to normal limit after iron treatment but recovery of iron deficiency anemia by blood transfusion did not change T3 and T4 levels.12,13,14 Contrast to this view, increased levels of plasma T3 by blood transfusion in iron deficiency anemia have been reported.5 Animal studies showed that, basal T3 and T4 levels are low in rats with iron deficiency anemia compared with the control group and these levels returned to normal limits after iron supplementation.3,15

It has been reported that in rats on iron restricted diet, TT3 levels were 37% lower than iron-dextran administered group.14 Beard et al. have performed a study to compare mild anemic woman and non anemic woman and they found that T3 and T4 levels were significantly lower, TSH levels were significantly higher in anemic group, and they have demonstrated that T3 levels have been increased with iron therapy.16

The studies on iron deficiency anemia have reported reduced total T4 and T3. Also the converting of T4 to T3 has reduced and TSH has increased.6,7 In addition, Hess et al. have suggested that, iron deficiency prevent T3 to T4 conversion by reducing hepatic thyroxine deionized activity.17 This situation affects the thyrotropin releasing hormone (TRH) and plasma TSH level is reduced. These researchers have suggested that iron deficiency anemia changes thyroid metabolism by reduced oxygen transport and hypoxia, changing the impact on the metabolism of central nervous system or leading to modification of T3 binding capacity. Also, iron-dependent peroxidase which catalyzes the transfer of iodine to thyroglobulin is sensitive to decrease in iron level. So, iron deficiency can reduce transfer iodine to thyroglobulin.

In our study it was seen that TSH levels which was significantly higher than control group significantly decreased after treatment. Also total T4 levels were significantly higher in pre-treatment period compared to the post-treatment period. Gündüz et al. reported that, T3, T4 and TSH levels are higher in IDA group than control group in the study containing 32 patients with iron deficiency anemia and there were not significant difference between control group and after treatment group in terms of TSH and T4 levels.18 T3 levels also higher in post-treatment than control group. They explain this situation by reduction in T3 and T4 conversion in iron deficiency. Because of T3 and T4 levels have increased by adding iron, this mean that iron has an important role in enzyme structure.18

In our study, decreased levels of T4 and increased levels of T3 after treatment can be considered as result of inhibited peripheral T4 to T3 conversion. Animal studies showed that reduced peripheral T4 to T3 conversion and increased TT4 levels are associated with reducing liver 5-monodeiodinase activity.7,19 This finding was considered that, Iron element has a role in 5-monodiodinase enzyme which was responsible for T4 to T3 conversion.

Changes in TSH and thyroid hormone levels have been reported on studies related to non-thyroidal diseases.20,21 Kokei et al. found normal FT4 and higher TSH levels in animals with non-thyroidal diseases.22 In our study, secondary and subclinical hypothyroidism was determined in a significant portion of our patients (52%).

Kantrowitz et al. found that serum FT4 levels were significantly lower than control group in dogs with non-thyroidal diseases.20 In our study, FT4 levels were significantly lower before treatment than control group. FT4 levels were below normal values and TSH levels were normal or over normal limits in 35.7% of patients. Although, these patients had secondary hypothyroidism, synchronously measured cortisol levels were within normal limits. Thus, we suggested that, these cases shown euthyroid patient syndrome profile without hypophysal insufficiency.

In animal studies, Duntas et al. have suggested that there may be an increase in TSH levels with reduction in thyroid activity and this increase reduced after treatment.23 In our study, TSH levels were high.
and FT4 levels were normal in 16.6% of all patients. High TSH levels may be associated with decreasing inhibitor effect of T3 on TSH releasing result of reducing T3 to T4 converting. The existing literature provides limited knowledge about treatment of patient with euthyroid patient syndrome (EPS). Brent and Hershman have studied EPS patients in intensive care unit and suggested that T4 levels increases by L-thyroxine, but mortality has not change.24 Utiger suggested that T3 levels did not increase in patients with EPS by given thyroxine.25 Researchers suggest that EPS is a defense mechanism in patients having nonthyroidal diseases and thyroxine replacement could make disease worse.

In conclusion, the studies associated with thyroid function in iron deficiency anemia are limited and almost all of the data provided from animal experiments. This study performed on adults with iron deficiency anemia. This clinical study showed that, secondary and subclinical hyperthyroid developed in a significant portion of patients with iron deficiency anemia and these abnormalities can recover after iron replacement therapy without additional thyroid hormone replacement. Further studies are needed to highlight this topic.

REFERENCES