The relationship between iron status and thyroid hormone concentration in iron-deficient adolescent Iranian girls

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Original Article

Extensive data from animal and human studies indicate that iron deficiency impairs thyroid metabolism. The aim of this study was to determine thyroid hormone status in iron-deficient adolescent girls. By stepwise random sampling from among all public high schools for girls in Lar and its vicinity in southern Iran, 103 out of 431 iron deficient subjects were selected. Urine and serum samples were collected and assayed for urinary iodine and serum ferritin, iron, total iron binding capacity (TIBC), thyroid stimulating hormone (TSH), thyroxine (T4), triiodothyronine (T3), free thyroid hormones (fT4 and fT3), triiodothyronine resin uptake (T3RU), reverse triiodothyronine (rT3), selenium and albumin concentrations. Hematological indices for iron status confirmed that all subjects were iron-deficient. There was a significant correlation between T4 and ferritin (r= 0.52, P<0.001) and between TSH and ferritin (r=-0.3, P<0.05). Subjects with low serum ferritin had a higher ratio of T3/T4 (r= -0.42, P<0.01). Using stepwise regression analysis, only ferritin contributed significantly to the rT3 concentration (r=-0.35, P<0.01). The results indicate that the degree of iron deficiency may affect thyroid hormone status in iron-deficient adolescent girls.

Key Words: Thyroid hormones, iron deficiency, serum ferritin, adolescent girls, Iran.

Introduction

More than 2 billion people, mainly young women and children, are iron-deficient.¹ Over 90% of affected individuals live in developing countries.² Iron deficiency anemia has adverse health consequences for all age groups. In older children and adults it reduces work capacity and output and impairs immune function,³ and is also known to be associated with reduced reproductive capacity.⁴ The consequences of iron deficiency are more serious for women. Iron deficiency can be defined as occurring when the body’s iron stores become depleted and a restricted supply of iron to various tissues becomes apparent,⁵ and it results in the depletion of iron-dependent intracellular enzymes participating in many metabolic pathways.⁶ Studies in animals and humans have shown that iron deficiency with or without anemia impairs thyroid hormone metabolism. Nutritional iron deficiency has been shown to significantly lower the circulating levels of both thyroxine and triiodothyronine in rats,⁷⁸ and to reduce conversion of T4 to T3.⁹ Iron deficiency also impairs thyroid metabolism in human studies. Martinez-Torres and co-workers¹⁰ reported 10% lower T3 levels in human subjects with moderate to severe iron deficiency anemia, and Beard and his co-workers¹¹ showed that in iron-deficient-anemic subjects, serum T3 and T4 levels were significantly decreased. In addition, iron deficiency results in increased sympathetic activity, as evident by increased plasma and urinary catecholamine concentrations,¹²-¹⁴ increased turn-over rates of norepinephrine in sympathetically innervated tissues, and decreased tissue norepinephrine content.¹⁵-¹⁶ The study of Smith and his co-workers¹⁷ has confirmed findings in iron deficiency, where increased sympathetic nervous system activity¹³-¹⁴ was coupled with overt hypo-thyroidism.¹⁸ On the other hand, iron deficiency may significantly reduce circulating levels of T4-5’deoiodinase in rats,¹⁷ the enzyme responsible for the conversion of T4 to T3, resulting in diminished conversion of T4 to T3.¹⁹ As shown by national reports on anemia in Iran,¹⁹ the prevalence of iron deficiency among 15 to 49-years-old fe-males is 39%.

The aim of the present study was to investigate thyroid hormone status in iron-deficient adolescent girls living in Iran.
southern Iran, where iron deficiency is quite prevalent. An intervention study was conducted in a group of 103 iron deficient adolescent girls living in Southern Iran. This report provides data on their thyroid hormone status prior to the intervention and its relationship with the degree of iron deficiency.

Materials and methods
Subjects
The study was carried out in the province of Lar and its vicinity in southern Iran (800 meters above sea level), an area in which iron deficiency is prevalent. In the first step, 431 iron-deficient subjects (with or without anemia) were selected by stepwise random sampling among 2038 students in grades 1 to 4 from the Lar high school for girls and its vicinity. In the second step 103 subjects who fulfilled all of the inclusion criteria were chosen. Criteria for case inclusion were: a) absence of any systemic disease, except for iron deficiency without anemia (hemoglobin >12mg/dl, serum ferritin <12µg/l and transferrin saturation <16%); b) serum albumin within the normal range: 3.5 to 5.5g/dl; c) urinary iodine >100µg/l; d) body mass index >19 kg/m²; e) age within the range of 14 to 18-years-old.

The number of cases which did not meet these criteria was 328: 203 for anemia, 23 for abnormal serum albumin levels, 17 for low levels of iodine in the urine, 59 for low body mass index, and 26 for an age out of the defined range. Anemic girls were offered iron supplementation. Demographic data, menstruation, any concurrent illness were collected by interviews and anthropometric physical characteristics of the 103 adolescent girls included in the study are shown in Table 1. The mean body mass index of subjects was within the normal reference range. Anthropometric data indicated a normal population excluding undernourished girls. The prevalence of stunting was low (height-for-age <- 2 z-scores: 6%).

Hematological and biochemical parameters of the study are shown in Table 2. Hematological indices for iron status show that all subjects were iron-deficient. Median urinary iodine was 120.0µg/l (range:100-280). Plasma selenium levels indicated that deficiency of this micronutrient was not a problem among subjects. There were a significant association between plasma T4 and TSH only with serum ferritin (r = 0.52, P<0.001 and r=-0.3, P<0.05 respectively). The statistical model showed that when the serum ferritin concentration was used as an independent variable, subjects with lower ferritin had a higher T3 to T4 ratio (r = -0.42, P< 0.01).

Further investigation into the changes in rT3 concentration in these subjects was carried out using multiple regression analysis in which the independent variables included were: urinary iodine, TSH, T4, T3, T3/T4 ratio, transferrin saturation, ferritin and selenium. Using a stepwise regression procedure, only ferritin contributed significantly to the rT3 concentration (r=-0.34, P<0.01) (figure 1); thus, subjects with lower iron stores also had a higher reverse triiodothyronine concentration.

Biochemical analyses
10 ml fasting venous blood samples were drawn from the arm. Blood was collected in two tubes; 2 ml were placed in the EDTA tube for measurement of hemoglobin and hematocrit, and 8 ml in another tube for determination of serum albumin, TIBC, iron, ferritin, selenium, total and free thyroxine, total and free triiodothyronine, thyro-tropin, T3RU and reverse triiodothyronine. Furthermore, urine samples were collected from the same subjects and on the same occasion as blood sampling for measurement of urinary iodine. Hemoglobin was measured using the cyanomethemoglobin method, while serum iron, TIBC, and albumin were measured by the colorimetric method (Zist Chimie company lot. no.11-514, lot. no. 12-515 and lot. no. 10-502, respectively).
Table 1. Characteristics of selected subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>X±SD</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>15.8 ± 1.4</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>50.9 ± 4.9*</td>
<td>41</td>
<td>63</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>155.0 ± 5.0*</td>
<td>140</td>
<td>167</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.0 ± 1.5*</td>
<td>19.0</td>
<td>25.6</td>
</tr>
<tr>
<td>Height-for-age (z-scores)</td>
<td>-0.98 ± 0.74*</td>
<td>-3.39</td>
<td>0.79</td>
</tr>
<tr>
<td>Weight-for-age (z-scores)</td>
<td>-0.30 ± -0.52*</td>
<td>-1.73</td>
<td>0.82</td>
</tr>
</tbody>
</table>

* N = 100

Table 2. Hematological and biochemical parameters of selected subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean ± SD</th>
<th>Min.</th>
<th>Max.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (mg/dl)</td>
<td>12.5 ± 0.3</td>
<td>12.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>37.6 ± 1.3</td>
<td>35.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Iron (µg/dl)</td>
<td>32.2 ± 3.1</td>
<td>26.0</td>
<td>38.0</td>
</tr>
<tr>
<td>TIBC (µg/dl)</td>
<td>442.0 ± 12.0</td>
<td>421.0</td>
<td>476.0</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>7.3 ± 8.8</td>
<td>7.3</td>
<td>8.8</td>
</tr>
<tr>
<td>Ferritin (µg/l)</td>
<td>8.9 ± 1.0</td>
<td>7</td>
<td>11.5</td>
</tr>
<tr>
<td>Thrytropin (mLU/ml)</td>
<td>2.5 ± 0.6</td>
<td>1.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Total thyroxine (µg/dl)</td>
<td>8.7 ± 0.7</td>
<td>7.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Free thyroxine (pg/ml)</td>
<td>10.6 ± 1.4</td>
<td>8.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Total triiodothyronine (ng/dl)</td>
<td>136.0 ± 18.0</td>
<td>110.0</td>
<td>177.0</td>
</tr>
<tr>
<td>Free triiodothyronine (pg/ml)</td>
<td>2.7 ± 0.4</td>
<td>1.6</td>
<td>3.7</td>
</tr>
<tr>
<td>T3 resin uptake (%)</td>
<td>27.6 ± 3.3</td>
<td>20.6</td>
<td>33.5</td>
</tr>
<tr>
<td>T3/T4 ratio</td>
<td>15.8 ± 2.3</td>
<td>11.6</td>
<td>23.4</td>
</tr>
<tr>
<td>Reverse triiodothyronine (ng/dl)</td>
<td>42.5 ± 6.0</td>
<td>26.0</td>
<td>56.0</td>
</tr>
<tr>
<td>Albumin (gr/dl)</td>
<td>3.6 ± 0.2</td>
<td>3.2</td>
<td>3.9</td>
</tr>
<tr>
<td>Selenium (µg/dl)</td>
<td>27.7 ± 7.5</td>
<td>15.0</td>
<td>43.0</td>
</tr>
<tr>
<td>Urinary iodine (µg/l)</td>
<td>120.0†</td>
<td>100.0</td>
<td>280.0</td>
</tr>
</tbody>
</table>

† Median

Discussion

Children and adolescents differ from adults in many aspects, but especially in that they continue to grow. The thyroid gland is one of the most important organs for optimal growth. Normal thyroid status is dependent on the presence of many trace elements for both the synthesis and metabolism of thyroid hormones. Iodine is most important as a component of the hormones thyroxine and 3,3,5-tri-iodothyronine (T3). Selenium is essential for normal thyroid hormone metabolism, which is involved with selenium-containing iodothyronine deiodinases that control the synthesis and degradation of the biologically active thyroid hormone T3.29,30 Additionally, selenoperoxidases and thioredoxin reductase protect the thyroid gland from peroxides produced during the synthesis of hormones.31 Observation of mean levels of selenium in serum and urinary iodine levels in the studied population provides evidence that the subjects studied do not have any deficiency of these elements.

The present study explores the possibility that iron deficiency might impair thyroid metabolism as previously reported in animal and human studies.7-12,32 The two initial steps of thyroid hormone synthesis are catalyzed by heme–containing thyroid peroxidase.10-12 Severe iron deficiency may lower thryperoxidase activity and interfere with the synthesis of thyroid hormones.31 Recently Hess and his co-workers30 have shown that thyroid peroxidase activity is significantly reduced in iron deficiency anemia. In rats, it decreases hepatic thyroxine-5´-deiodinase, impairs conversion of T4 to T3 in the periphery, and blunts the TSH response to thyroid–releasing hormone (TRH).32,35 Only a few studies performed on humans exist on this subject. Results of these studies show that in adults, iron deficiency is accompanied by reduced serum T4 and T3, as compared to healthy controls.10-12 But in the study of Tienboon and Unachak,36 there was no statistical difference in thyroid hormones in the iron-deficient anemic children before resolution of anemia as compared to after. In contrast, although normal thyroid function, as defined by normal levels of thyroid indices was preserved in our subjects with iron deficiency, a positive and significant association between the serum ferritin level and the rT4 concentration, and a negative and significant association between ferritin and the T3/T4 ratio, as well as a negative and significant association between ferritin and TSH, suggest that thyroid status alterations could be due to a deficiency in iron-dependent enzymes such as thyroperoxidase that impair thyroid metabolism. In our study, there were no decreases in rT3 levels in parallel with decreased iron stores, which is not consistent with other studies that show that iron deficiency reduces circulating levels of T3. The low concentration of thyroid hormones in iron-deficient anemic animals may be due to a low plasma pool turnover of T3. In most organs, the plasma concentration of T3 determines its binding to nuclear receptors and metabolic activities.37,38 Beard et al., showed that in rats, T3 disposal from the plasma pool and irreversible loss from the system were significantly slowed down in iron deficiency.18 Moreover, Bianco and Silva demonstrated that peripheral deiodination in iron deficiency was
coordinated with decreased utilization or disappearance of T3 from the plasma pool.39

Our study provides support for the contention that an increase in rT3 is related to changes in iron status and that the increased level of rT3 is inversely correlated with changes in plasma ferritin concentration. Iron deficiency decreased plasma concentrations of T3 and T4 and increased in vitro hepatic rT3 deiodination, suggesting that iron-deficient animals tend to metabolize thyroid hormone via a deactivating pathway.40 Presumably, a small fraction of T4 was converted to T3 and a larger proportion metabolized to a physiologically inactive metabolite, rT3. It is not yet clear how iron deficiency exerts its effects on deiodinase activity. Kaplan and Utiger41 have shown that the outer ring deiodinase activity is not affected by either ferrous or ferric ions in an in vitro incubation method. This of course, does not rule out the possibility that iron needs to be incorporated into the enzyme during synthesis.

One explanation for the discrepancy among studies could be age differences in study subjects, since our study is the first to consider adolescent girls. Another explanation could be that only girls with moderate iron deficiency and without anemia were included. The exclusion of girls with anemia was motivated by our intention to conduct an iron supplementation intervention, in which we did not include anemic girls for ethical reasons. Therefore, we cannot reject the possibility that thyroid function might be impaired with more severe iron deficiency and anemia.

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References


Original Article

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铁离子水平与患有缺铁性疾病的伊朗女性青少年的甲状腺激素浓度之间的关系

大量的动物和人体实验表明缺铁能影响甲状腺激素的代谢。本研究的目的是测定患有缺铁性疾病的伊朗女性青少年的甲状腺激素浓度。我们对伊朗南部地区的 Lar 及其临近地区的所有公立中学的女生进行逐步随机取样，最后从 431 个患者中随机选了 103 个作为实验人员。收集 103 个实验人员的尿样和血清，分别测定其尿中的碘量，血清中的血清铁蛋白，铁离子，总铁结合量 (TIBC)，促甲状腺激素刺激激素 (TSH)，甲状腺素 (T4)，碘甲腺氨酸钠 (T3)，游离的甲状腺素 (fT4 和 fT3)，三碘甲腺原氨酸树脂摄取量 (T3RU)，反三碘甲腺原氨酸 (rT3)，硒以及白蛋白浓度。能够反应铁离子水平的血清指数表明所有的实验人员都是缺铁性患者。T4 和铁蛋白浓度之间 (r=0.52, P<0.001) 以及 TSH 和铁蛋白浓度之间 (r=-0.3, P<0.05) 有着紧密的联系。血清铁蛋白浓度低的患者的 T3/T4 的比值就相应较高 (r= -0.42, P<0.01)。通过逐步回归分析，我们发现只有铁蛋白能明显提高 rT3 的浓度 (r=-0.35, P<0.01)。结果表明患有缺铁症的女性青少年患者可能会影响体内甲状腺激素的水平。

关键词：甲状腺粉、缺铁症、血清铁蛋白、女性青少年、伊朗。