

Thyroid Hormones Status in Iron Deficient Adolescent Girls

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Abstract

Background: Iron deficiency is the most common single-nutrient deficiency disease in the world and is a major concern for about 15% of the world population. It has been shown that iron deficiency may affect thyroid hormones.

Objective: To determine thyroid hormone status in iron deficient adolescent girls.

Methods: A cross-sectional study was carried out in Lar Province and its' vicinity in South of Iran. By a stepwise random sampling from all public girls' high schools in Lar and its' vicinity, using World Health Organization (WHO) criteria, 94 iron deficient subjects were selected. Urine and serum samples were collected and assayed for urinary iodine and serum ferritin, iron, TIBC, TSH, T₄, T₃, FT₄, FT₃, T₃RU, rT₃, selenium and albumin concentrations.

Results: Hematological indices for iron status confirmed that all of subjects were iron deficient. There was a positive correlation between plasma T₄ and serum ferritin (p<0.001). Subjects with low serum ferritin had a higher T₃/T₄ ratio (p<0.001). Using a stepwise regression analysis, it was found that among the variables studied, only ferritin contributed significantly to rT₃ concentration (p<0.004).

Conclusion: Iron deficiency may impair thyroid hormone status in iron deficient adolescent girls.

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Keywords • Thyroid hormones • iron deficiency • serum ferritin

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Introduction

Iron deficiency is the most common single-nutrient deficiency disease in the world. It is a major problem for about 15% of the world population.¹ As estimated, 30% to 60% of women and children in developing countries have iron-deficiency anemia.² Iron deficiency occurs when the body's iron stores become depleted and a restricted supply of iron to various tissues becomes apparent³ which results in the depletion of iron-dependent intracellular enzymes participated in many metabolic pathways.⁴ Studies in animals and humans have been shown that iron deficiency anemia impairs thyroid hormones metabolism. Nutritional iron deficiency has been shown to significantly lower the circulating levels of both thyroxine and

M H. Eftekhari, S A. Keshavarz, M. Jalali, N. Saadat, et al triiodothyronine in rats⁵⁻⁸ and also in humans.⁹ The two initial steps of thyroid hormone synthesis are catalyzed by a heme-containing enzyme, thyroperoxidase.⁸⁻¹¹ Severe iron deficiency may lower the activity of this enzyme and thus, may interfere with the synthesis of thyroid hormones.¹² Furthermore, low concentration of thyroid hormones in iron-deficient anemic animals may be due to low turnover of the plasma pool of T₃. In most organs, the plasma concentration of T₃ determines the binding of T₃ to nuclear receptors and its metabolic activity.¹³⁻¹⁴ Beard and his co-workers showed that T₃ disposal from the plasma pool and its irreversible loss from the circulation is significantly slowed in iron deficiency states.¹⁵ In addition, iron deficiency results in an increased sympathetic activity, as is evident by increased plasma and urinary catecholamine concentrations,¹⁶⁻¹⁷ increased turnover rates of norepinephrine in sympathetically innervated tissues,^{7,18} and decreased contents of tissue norepinephrine.^{7,18} The study of Smith and his co-workers¹⁹ confirms these findings in iron deficiency, where increased sympathetic nervous system activity^{16,17} was coupled with overt hypothyroidism.¹⁵ On the other hand, iron deficiency significantly reduces circulating levels of T₄-5' deiodinase in rats,¹⁵ the enzyme responsible for conversion of T₄ to T₃, which results in diminished conversion of T₄ to T₃. As was shown in the National reports on anemia in Iran,²⁰ the prevalence of iron deficiency among 15- to 49-year-old females is 39%. The aim of the present study was to investigate thyroid hormone status in iron-deficient adolescent girls, in southern Iran, where iodine-deficiency is moderately and iron-deficiency is quite prevalent.²¹⁻²²

Patients and Methods

Subjects:

A cross-sectional study was carried out in Lar Province and its' vicinity in South of Iran (altitude: 800 meters above sea level), an area where iron deficiency is prevalent. In the first step, 431 iron deficient subjects (with or without anemia) were selected by stepwise random sampling from grades 1 to 4 high-school girls of Lar and its' vicinity. In the second step, 94 subjects who fulfilled all the inclusion criteria were chosen. The inclusion criteria were: a) absence of any systemic diseases, except iron deficiency according to the WHO criteria²³ (*i.e.*, serum iron < 40 µg/dl, TIBC > 400 µg/dl, serum ferritin < 12 µg/dl and hemoglobin > 12 mg/dl), b) serum albumin within the normal range of 3.5 to 5.5 g/dl, c) body mass index > 19 kg/m², d) age between 14 and 18 years.

Demographic data, history of menstrual habits, any concurrent illness, consumption of any medications, vitamin and mineral supplementations were

collected by interviews and anthropometric indices were determined for each subject. Anthropometric assessments included measurement of weight and height. Body weight was measured to the nearest 0.1 kg (using a Seca 713 scale) while subjects were minimally clothed. Body mass index was calculated by dividing weight (kg) by square of height (m²).

Food intake pattern was evaluated by a 24-hour dietary recall questionnaire. Using a food processor software modified by incorporating Iranian food composition table, the amount of macro- and micro-nutrients intake were calculated.

Biochemical analyses:

Ten-ml fasting venous blood samples were drawn from the arm. Blood was collected in two tubes; a 2-ml aliquot placed into EDTA tube for measurement of hemoglobin and hematocrit and an 8-ml aliquot in another tube for determination of serum albumin, TIBC, iron, ferritin, selenium, total and free thyroxine, total and free triiodothyronine, thyrotropin, T₃RU and reverse triiodothyronine. Furthermore levels. Ten-ml urine samples were collected for measurement of urinary iodine level.

Iron deficiency was considered to be present if the Hb concentration was >12 g/dl, serum iron < 40 µg/dl, ferritin <12 µg/dl and TIBC > 400 µg/dl. Hemoglobin was measured using the cyanomethemoglobin method.²⁴ Serum iron²⁵, TIBC²⁶, and albumin²⁷ were measured manually by calorimetric methods (using Zist Chimie Co. kits; Cat. No.11-514, Cat. No. 12-515 and Cat. No. 10-502, respectively). Serum ferritin, T₄, T₃, TSH, FT₄, FT₃, T₃RU and rT₃ were determined by radioimmunoassay²⁸ (Belgium, Zen Tech for rT₃ and American DSL for the rest). Urinary iodine level was measured by digestion method²⁹ and selenium by using atomic absorption method³⁰.

Statistics:

Normally-distributed data were expressed as mean±SD. Multiple regression analysis was used to test for possible correlation(s). All statistical analyses were computed using SPSS version 10 for Windows[®] (SPSS Inc., Chicago, 2000).

Results

Physical characteristics of the 94 adolescent girls

Table 1: Characteristics of selected subjects			
Characteristics (n=94)	Mean±SD	Min	Max
Age (year)	15.8±1.4	14	18
Weight(kg)	50.7±5.8	40	66
Height(cm)	156.0±4.9	140	167
BMI(kg/m ²)	20.8±1.9	16.9	25.6

Table 2: Normal values for thyroid hormone indices*		
Index	Min	Max
TSH(μ U/ml)	0.5	5.1
TT ₄ (μ g/dl)	3.4	13.6
TT ₃ (ng/dl)	61	219
FT ₄ (pg/ml)	8.0	20.0
FT ₃ (pg/ml)	1.5	5.0
rT ₃ (ng/dl)	20	50
T ₃ RU(%)	30	40

*As indicated by the manufactures of the assay kits

included in the study are shown in Table 1. The mean body mass index of most of subjects were within the normal range, only 6% having a low BMI (<19 kg/m²). Anthropometric data indicated a normal population excluding chronically undernourished girls. Table 2 shows normal values for thyroid hormone indices.

Hematological and biochemical parameters of population are shown in Table 3. Hematological indices for iron status showed that all the subjects were iron deficient. Mean \pm SD urinary iodine level was 10.3 \pm 6.8 μ g/dl and only 5.3% of the studied sample had urinary iodine <5 μ g/dl. Plasma level of selenium indicated that deficiency of this micro-nutrient was not a problem among the studied subjects.

As might be expected from the fact that thyroid hormone measurements were related to iron status, there were only significant positive correlation between plasma T₄ and serum ferritin ($r = 0.52$, $p < 0.001$). Also the statistical analysis showed that when serum ferritin concentration was used as independent variable, subjects with low serum ferritin had a higher ratio of T₃ to T₄ ($r = 0.4$, $p < 0.001$).

To further study the changes of rT₃ concentration in these subjects, a multiple regression analysis in with independent variables of urinary iodine, TSH, T₄, T₃, ferritin and selenium was carried out. Using a stepwise regression procedure, it was found that only the ferritin level contributed significantly to rT₃ concentration ($r = 0.35$, $p = 0.004$) (Figure 1), i.e., subjects with lower iron stores had greater changes in circulating reverse triiodothyronine concentration.

Discussion

Anemia is the most common hematologic ailment of adolescent girls, especially in developing countries. More than two billion people, mainly young women and children, mostly in developing countries, are iron deficient.²³ The present study explores the possibility that iron deficiency might impair thyroid metabolism, as was previously reported in animal and human studies.⁸⁻¹¹ Our findings show

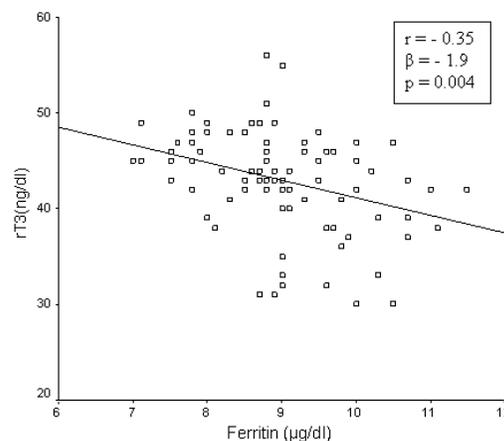


Fig 1: Correlation between serum ferritin and rT₃ concentration

that depletion of iron stores may decrease T₄ levels and suggests that an alteration in thyroid hormone status in these people could be a reflection of disturbed activities of iron-dependent enzymes such as thyroperoxidase that impairs thyroid metabolism. The initial steps of thyroid hormone synthesis are catalyzed by a heme-containing thyroid peroxidase. As such, severe iron deficiency may lower thyroperoxidase activity and thus may interfere with the synthesis of thyroid hormones.¹² Recently, Hess and co-workers,³¹ have shown that thyroid peroxidase activity is significantly reduced in iron deficiency anemia. Previous studies have shown that iron deficiency in both animals and humans, impairs thyroid hormone metabolism. In rats, it decreases hepatic thyroxine 5'-deiodinase, a selenium-containing protein, impairs conversion of T₄ to T₃ in the periphery, and blunts the TSH response to thyrotropin-releasing hormone (TRH).^{11,32} In adults, iron deficiency is accompanied by reduced serum T₄ and T₃ and increased TSH concentrations, as compared to healthy controls.⁸⁻¹¹ In contrast, our findings are suggestive of only a significantly positive correlation between serum ferritin level and T₄ concentration and a significantly negative correlation between serum ferritin and T₃/T₄ ratio which are not consistent with other studies that indicated that iron deficiency reduces circulating levels of T₃.

In many organs, the plasma concentration of T₃ determines its binding to nuclear receptors and its metabolic activities.^{13,14} Beard *et al*, showed that in rats, T₃ disposal from the plasma pool and irreversible loss from the systemic circulation was significantly slowed in iron deficiency.¹⁵ Moreover Bianco and Silva demonstrated that peripheral deio-

Table 3: Hematological and biochemical parameters of selected subjects

Parameters (n=94)	Meant±SD	Min	Max
Hemoglobin(mg/dl)	12.5±0.3	12.0	13.0
Hematocrit(%)	37.6±1.3	35.0	40.0
Albumin(gr/dl)	3.6±0.2	3.2	3.9
Iron (µg/dl)	33.6±3.6	24.0	39.0
TIBC(µg/dl)	441.9±11.6	421.0	476.0
Ferritin (µg/dl)	8.9±1.0	7.0	11.5
Total Thyroxine (µg/dl)	8.7±0.7	7.0	10.0
Total Triiodothyronine (ng/dl)	136.2±18.0	110.0	177.0
Tyrotropin (µU/ml)	2.5±0.6	1.0	4.8
Free thyroxine (pg/ml)	10.6±1.4	8.0	15.0
Free triiodothyronine (pg/ml)	2.7±0.4	1.6	3.7
T ₃ Resin Uptake	27.6±3.3	20.6	33.5
T ₃ /T ₄ ratio	15.8±2.3	11.6	23.4
Reverse triiodothyronine (ng/dl)	42.5±5.8	26.0	56.0
Selenium (µg/dl)	27.7±7.5	15.0	43.0
Urinary iodine(µg/dl)	10.3±6.8	2.0	28.0

dination in iron deficiency state, was compensated by decreased utilization and or disappearance of T₃ from the plasma pool.³³ Our findings support the hypothesis that an increase in rT₃ is related to changes in iron status and that an increased level of rT₃ was inversely correlated with changes in plasma ferritin concentration. Iron deficiency decreases plasma concentrations of T₃ and T₄ and increases hepatic rT₃ deiodination, suggesting that the iron deficient animals tend to metabolize thyroid hormones via a deactivating pathway.³⁴ Presumably, a small fraction of T₄ is converted to T₃ and a larger proportion is metabolized to a physiologically inactive metabolite, rT₃.

It is not yet clear how iron deficiency exerts its effects on deiodinase activity. Kaplan and Utiger³⁵ have shown that the outer ring deiodinase activity is not affected by either ferrous or ferric ions in an incubation method *in vitro*. This of course, does not rule out the possibility that iron needs to be incorporated into the enzyme during synthesis.

Although in this study other indices that might influence thyroid status have not been measured, considering that iron deficiency is a nutritional and readily treatable disease condition that influences the thyroid hormone status, a combined fortification of salt with iron and iodine, may be justified.

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