Original Research
Turk J Endocrinol Metab 2019;23:38-46

The Effect of Treatment of Iron Deficiency Anemia on Thyroid Volume

Demir Eksikliği Tedavisinin Tiroid Volümü Üzerine Etkisi

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Abstract

Objective: Iron and iodine, which are the two important micronutrients, are still deficient in a large number of women worldwide. This study aimed to examine the thyroid volumes of iron deficient, anemic women before and after correction of the anemia in a mildly iodine deficient environment.

Material and Methods: Sixty six women aged 18-45 years were prospectively enrolled in this study. Inclusion criteria included serum hemoglobin (Hb) level <11.0 g/dL, ferritin level <13 ng/mL, thyroid hormones within normal reference ranges and negative thyroid antibodies. Oral iron supplement (567 mg ferrous sulfate, twice a day) for six months was prescribed and strongly recommended. All patients were re-evaluated at the end of the iron treatment.

Results: Initially, the median (minimum/maximum) Hb and ferritin levels of patients were 10.2 g/dL (5.6/11.1) and 3.95 ng/mL (0.44/10.7), respectively. Six months later, median Hb and ferritin values increased significantly to 13.15 g/dL (9.3/15.6) (p<0.001) and 19.575 ng/mL (3.74/79) (p<0.001) respectively. Median thyroid volume decreased significantly from 15.705 mL (7.15/54.2) to 13.212 mL (6.11/52.8) (p<0.001). The patients were grouped according to the improvements in Hb and ferritin levels, initial thyroid gland volume, and response to the treatment. The reduction in thyroid gland size, at the end of the treatment, was more significant in patients with improvement in both Hb and ferritin levels as compared to those with improvement only in Hb levels (p<0.05).

Conclusion: Iron may be responsible for efficient organification of iodine, active iodine utilization from thyroglobulin, and control of hyperkinetic blood-flow to the thyroid gland. The findings of this study support that other than iodine, iron supplementation has a significant effect on the regression of thyroid volume in women with iron deficiency anemia.

Keywords: Iron; iodine; anemia; goiter; thyroid hormones

Özet

Amaç: Demir ve iyot, iki önemli mikro besin olup, dünya genelinde yaygın olarak kadınlarda hâlen eksiklikleri görülmektedir. Bu çalışmada, hafif iyot eksikliği bölgesindeki demir eksikliği anemisi bulunan kadınların, aneminin düzelmesinden önce ve sonra tiroid volümlerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya; yaş aralığı 18-45 yıl olan, 66 kadın hasta katılmıştır. Çalışmaya dâhil edilme kriterleri; serum hemoglobin (Hb) düzeyi <11,0 g/dL, ferritin düzeyi <13 ng/mL, tiroid hormonlarının normal sınırlarda ve tiroid antikorlarının negatif olması olarak belirlenmiştir. Her hastaya ağızdan demir desteği (567 mg ferrous sülfat, günde iki kez) reçete edilmiş ve kuvvetle önerilmiştir. Tüm hastalar demir tedavisi sonrası yeniden değerlendirilmiştir.

Bulgular: Başlangıçta hastaların medyan (minimum/maksimum) Hb ve ferritin düzeyleri sırasıyla, 10,2 g/dL (5,6/11,1) ve 3,95 ng/mL (0,44/10,7) idi. Altı ay sonra, Hb düzeyleri 13,15 g/dL (9,3/15,6) (p<0,001) ve ferritin düzeyleri 19,575 ng/mL (3,74/79) (p<0,001) ile anlamlı artış gösterdi. Medyan (minimum/maksimum) tiroid volümü de tedavi öncesi 15,705 mL (7,15/54,2) iken, tedavi sonrası 13,212 mL (6,11/52,8) (p<0,001) ile anlamlı azalma gösterdi. Hastalar ayrıca, Hb ve ferritin değerindeki iyileşmeye, tedavi başlangıcındaki tiroid bezi büyüklüğüne ve tedavi yanıtına gore karşılaştırıldılar. Tedavi sonunda tiroid bezi volümündeki gerileme, Hb ve ferritin değerinde iyileşme gösterenlerde, yalnız Hb değeri düzelenlere göre daha belirgin idi (p<0,05).

Sonuç: Demir; iyotun etkin organifikasyonundan, tiroglobinde iyotun etkin kullanımından, tiroid bezinin hiperkinetik kan akımının kontrolünden sorumlu olabilmektedir. Çalışmamız da demir eksikliği anemisi olan kadınlarda, demir tedavisinin, artmış tiroid volümünün düzelmesine belirgin katkısı olduğunu desteklemektedir.

Anahtar kelimeler: Demir; iyot; anemi; guatr; tiroid hormonları

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Received: 09/07/2018 **Received in revised form:** 04/12/2018 **Accepted:** 22/12/2018 **Available online:** 20/03/2019

DOI: 10.25179/tjem.2018-62120

Introduction

The present scenario of the extent of iodine deficiency (ID) holds immense importance worldwide. Great efforts, especially with salt iodinization, are being made in order to prevent and eliminate health problems as well as social and economic consequences related ID (1). According to the World Health Organization (2004) data, 664 million people on an average are at risk for illnesses due to ID, in Europe and Eastern Mediterranean (2). Turkey is a severe to mild iodine deficient area; improvement in iodized salt consumption in the area has decreased the prevalence of ID in national surveys, as compared to that in 1997 and 2002 (i.e., 58% and 38.9%, respectively) (3).

Iron deficiency (IRD), another major public health problem, has several effects on the neural development, immune capacity as well as intellectual and physical performance in both, adult population and children (4, 5). Globally, the prevalence of IRD anemia has fallen from 33% to 29% during 1995-2011 in non-pregnant women (6). The Health Statistics 2013 Report by Ministry of Health indicates that 9.8% of the Turkish women experienced IRD anemia and the risk for IRD was higher among women between 15-49 years of age (7). These rates were supported with those from another study from Ege University, which showed that the prevalence of IRD was 15.6% while that of IRD anemia was 10.3% (8).

Combined iodine and iron deficiency are related to low socioeconomic conditions, inadequate food intake, poor quality diet, and poor bioavailability (9, 10). Furthermore, the women of the reproductive age group are at a greater risk for these micronutrient deficiencies because of increased physiological needs (11, 12). IRD also affects iodine metabolism, and thus thyroid metabolism (13). IRD can cause hyperkinetic flow in the thyroid gland and a decreased enzymatic activity of the heme-dependent thyroid peroxidase (TPO) (13). This study was aimed to investigate whether iron replacement therapy changes thyroid hormone metabolism and thyroid gland volume in females with IRD anemia.

Material and Methods

This prospective study was conducted for approximately 18 months in the Department of Internal Medicine, Ankara University, Ibni Sina Hospital. The female patients matching the inclusion criteria were evaluated and the inclusion criteria were Age: 18-45 years, Hemoglobin (Hb) <11.5 g/dL and Mean Corpuscular Volume (MCV) <80 fl, Mean Corpuscular hemoglobin (MCH) <27 pg in complete blood count, Peripheral Blood Smear: hypochromic and microcytic erythrocyte morphology, serum iron <35 µg/dL, serum iron binding 245-450 µg/dL or >450 µg/dL, saturation of transferrin <13%, ferritin < 10 ng/mL, normal thyroid function tests [sensitive thyroid stimulating hormone (sTSH) 0.35-5.5 mIU/mL, free thyroxine (fT4) 10-23 pmol/L, free triiodothyronine (fT3) 2.8-7 pmoL/L], negative thyroid autoantibodies [Anti-Thyroglobulin (Anti-Tg) <60 U/mL, Anti-Thyroid peroxidase (Anti-TPO) <60 U/mL]. The exclusion criteria were as follows: Microcytic and hypochromic anemia due to causes other than iron deficiency; patients who needed to be treated urgently because of cancer, heart failure, acute gastrointestinal bleeding; abnormalities of thyroid function tests and positive thyroid auto- antibodies; heterogeneous gland structure of thyroid glands in ultrasonographic imaging and co-existence of any chronic illness. All participants were given detailed information about the research in advance, and then made to sign the informed consent forms. The study protocol was approved by the Ankara University Ethical Committee and this study was carried out according to the principles of the Conference of Helsinki.

The patients diagnosed with IRD anemia, who met the inclusion criteria and voluntarily agreed to participate in the study, were examined for thyroid hormones (fT4, fT3, sTSH), thyroid auto-antibodies (Anti-Tg, Anti-TPO), urinary iodine concentration (UIC), and measurement of thyroid gland volume by ultrasonography. All the eligible patients were found to be euthyroid and tested negative for thyroid auto-antibodies. These values of basal examination were recorded and defined as the values before the treatment. A ferrous sulfate formulation (567 mg) equivalent to 100 mg elemental iron per capsule was prescribed and recom-

mended twice a day up to the patient's tolerance. The same preparation was taken throughout the treatment of iron deficiency by all the patients and no iodine-containing multivitamin preparation was not used.

All the patients were informed about the side effects of oral iron therapy. Following completion of the six-month-treatment, Hb level, iron status, thyroid hormones, UIC and ultrasonographic volume measurement of thyroid gland were repeated. These values were defined as the end of treatment values. Thyroid gland measurement was taken by the same researcher via ultrasonography using General Electric Logic 200 Pro Ultrasound with high-frequency (7 MHz) linear probe (GE Medical Systems, Milwukee, WI, USA). As soon as a nodule on the thyroid gland was detected, thin needle aspiration was applied; the size of the nodule was also followed before and after the treatment. The volume of the thyroid lobe was calculated from the measurements of the maximal depth, the maximal width, and the maximal length of each lobe and multiplied by π/6. Total thyroid volume was found by the sum of the volumes of right and left lobe. Thyroid volume >16 mL in women was regarded as goiter (3).

At the end of the treatment, the patients were grouped according to the improvements in Hb and ferritin values found by the end of the study (sufficient improvement/insufficient improvement) and thyroid gland volume at the beginning of the study (goitrous/non-goitrous). All parameters were compared for each group.

The samples of blood and urine were obtained from each participant in the morning after an overnight fast. All sera were immediately analyzed for TSH, fT4, fT3 and thyroid auto-antibodies based on chemiluminescence immunoassay (Beckman kits, Beckman Coulter, Inc, Miami, FL, USA) (Immulite 2000 Immunoassay System, Siemens Healthineers, Erlangen, Germany). Urinary iodine excretion was measured using an ammonium persulfate method based on the Sandell-Kolthoff reaction. Hb, MCV and MCH were measured using Beckman Coulter STKS Hematology Analyzer. Serum iron status was measured by Beckman Coulter CX7 based on ferrozine colorimetric reaction. Serum ferritin level was measured using ferritin enzyme immunoassay test kits.

Statistical Evaluation

Statistical evaluation was done by SPSS 25.0 (IBM Corporation, Armonk, New York, United States) and PAST 3 (Hammer Q, Harper. D.A.T, Ryan P.D, Paleontological statistics). Mardia (Dornik and Hansen omnibus) test was used for the analysis of multivariate normally distributed data while variance homogeneity was evaluated by Boxnm test. The independent samples t-test with the Bootstrap results and the Mann-Whitney U test with the Monte Carlo simulation technique were used for the comparison of the two independent groups according to the quantitative data. The paired samples t-test with the Bootstrap results and Wilcoxon Signed Ranks test with Monte Carlo simulation technique were used to compare the two repetitive measurements of dependent quantitative variables. General Linear Model-Repeated ANOVA was used to investigate the interaction of repeated quantitative measurements of the variables. Quantitative variables have been expressed as mean±SD (Standard Deviation) and median (minimum/maximum) in the text and tables. The variables were examined at 95% confidence level and the p-value was considered significant when less than 0.05.

Results

The study participants included females aged 35.6±8.4 years. As shown in Table 1, all patients had iron deficiency anemia at the beginning of the treatment; improvements in all hematological parameters were observed at a significant level, after the treatment ($p<0.001$). Ferritin values in the 17 patients were observed to be below the normal level at the end of the treatment.

Before the treatment, thyroid function tests were at a normal level and thyroid auto-antibodies were negative in all patients. Their median UIC was 82.5 µg/L (1/450). The total thyroid volume of the patients was measured to be 16.705 mL (7.15/54.2) before the treatment. The total thyroid volume of 30 patients was measured above 16 mL, and therefore they were said to be goitrous. A nodule was found on the right lobe of eight patients and on the left lobe of nine patients. Thyroid cancer was not detected in any patient during the thin needle aspirations. After continuing iron therapy for six months, no significant change was observed

Table 1. The patients' iron deficiency parameters and thyroid parameters, and comparison between baseline and after treatment values.

Variable Median (Min./Max.)	Before Treatment (N=66)	After Treatment (N=66)	P
Iron deficiency variables			
Hb (mg/dL)	10.2 (5.6/11.1)	13.15 (9.3/15.6)	<0.001[a]
Iron (mcg/dL)	19 (2/93)	71 (14/238)	<0.001[a]
Iron binding capacity (mcg/dL)	429 (280/524)	312 (237/435)	<0.001[a]
Saturation of transferrine (%)	5 (0.6/21)	22.65 (4.2/63.6)	<0.001[a]
Ferritin (ng/mL)	3.95 (0.44/10.7)	19.575 (3.74/79)	<0.001[a]
Thyroid variables			
fT3 (pmol/L) (Mean±SD.)	4.91±0.98	5.17±0.91	0.066[b]
fT4 (pmol/L)	15.55 (11.4/22.5)	16.4 (5.97/22.8)	0.019[a]
sTSH (mIu/mL)	1.6 (0.5/4.08)	1.475 (0.509/6.55)	0.467[a]
UIC (Mg/L)	82.5 (1/450)	118 (12/450)	0.119[a]
Thyroid gland volume (mL)	16.705 (7.15/54.2)	13.212 (6.11/52.8)	<0.001[a]

[a] Wilcoxon sing Test (Monte Carlo). [b] Paired T Test (Bootstrap). Min.: Minimum; Max.: Maximum; SD.: Standard deviation.

in fT3, sTSH, and UIC values. However, the fT4 value was 15.55 pmol/L (11.4/22.5) before the treatment, which increased to16.4 pmol/L (5.97/22.8) after the treatment. The total thyroid volume decreased to 13.212 mL (6.11/52.8). These results were statistically significant (p<0.05) (Table 1).

The patients were grouped according to the improvements in Hb and ferritin values. Forty-nine patients showed sufficiently improved values in both, Hb and ferritin levels (improved IRD group), while 17 patients only had improved values of Hb levels (unimproved IRD group), even beyond ferritin levels, at the end of the treatment (Table 2). They were compared on the basis of the thyroid volume change. While the median thyroid volume was 16.24 mL (7.15/54.2) in the improved IRD group before the treatment, it decreased to 13.65 mL (6.11/58.8) after the treatment. The median thyroid volume was 14.4 mL (8.297/29.17) in unimproved IRD group before the treatment, it decreased to 12.9 mL (7/31.857) after the treatment. There was a significant difference among the groups with regard to the thyroid volume change in favor of improved IRD group (p=0.048) (Table 3, Figure 1).

The patients were grouped according to the volume of the thyroid gland at the beginning of the study. Goitrous patients and non-goitrous patients were compared with their response to oral iron therapy. The median thyroid volume of 30 patients in the goitrous group was 19.65 mL (16/54.2) before treatment, which decreased to 16.525 mL (7.76/58.8) after the treatment. The median thyroid volume of 36 patients in the non-goitrous group was 13.045 mL (7.15/15.934) before the treatment, which decreased to 10.84 mL (6.11/16.73) after the treatment. There was no difference in terms of reduction of thyroid gland volume between the groups (p=0.117). The analysis of values of their thyroid and iron deficiency variables before and after the treatment, between these two groups, showed no significant difference (Table 2, Table 3).

Discussion

This study was carried out to point out the changes in thyroid gland volume and thyroid hormone metabolism after oral iron therapy in women with IRD anemia. The study revealed that the thyroid gland volumes of women with IRD anemia regressed significantly after the oral iron replacement therapy. fT4 level also increased after the treatment, without any changes in sTSH and fT3 levels. Interestingly, the reduction in the thyroid gland size was more significant in patients showing improvement in both, Hb, and ferritin levels than those showing improvement only in Hb levels.

Of the school age children, 20-30% have both, iron deficiency and goiter, in northwest Africa (14). In India, it was found that 15% of the teenage pregnant women have goiter

Table 2. The comparisons of non-goitrous group and goitrous group, and unimproved IRD group and improved IRD group according to iron deficiency parameters.

	Thyroid gland volume status			IRD		
	Non-goitrous	Goitrous		Unimproved IRD	Improved IRD	
Variable Median (Min./Max.)	(n=36)	(n=30)	P Goitrous	(n=17)	(n=49)	P IRD
Hb (mg/dL)						
Before	10.25 (6.1/11.1)	10.11 (5.6/11)	0.741	10.2 (6.5/10.9)	10.2 (5.6/11.1)	0.510
After	12.95 (9.3/15.4)	13.5 (10.4/15.6)	0.348	12.4 (10.4/15.1)	13.5 (9.3/15.6)	0.001
Alteration (After-Before)	3.05 (1.2/8.4)	3.6 (1/8.8)	0.275	2.9 (1/5.1)	3.4 (1.2/8.8)	0.047
Iron(mcg/dL)						
Before	19 (3/93)	18.5 (2/52)	0.193	17 (7/93)	19 (2/65)	0.441
After	71 (14/219)	71 (14/238)	0.599	41 (14/106)	72 (17/238)	0.002
Alteration (After-Before)	49 (-21/215)	57 (6/217)	0.215	24 (-21/89)	56 (-3/217)	0.002
Iron binding capacity (mcg/dL)						
Before	397.5 (294/522)	437.5 (280/524)	0.319	439 (317/522)	412 (280/524)	0.407
After	317.5 (237/398)	306 (273/435)	0.340	336 (289/398)	309 (237/435)	0.013
Alteration (After-Before)	-84 (-257/61)	-126.5 (-220/14)	0.238	-97 (-183/-17)	-105 (-257/61)	0.788
Saturation of transferrine (%)						
Before	5.4 (0.6/21)	4.35 (0.9/13)	0.106	4.4 (1.2/21)	5.2 (0.6/13)	0.271
After	21.95 (4.2/61.7)	23.5 (4.6/63.6)	0.726	13.9 (4.2/26.6)	26 (5.8/63.6)	<0.001
Alteration (After-Before)	14.25 (-0.2/58.3)	19.8 (1.6/56.7)	0.439	7.3 (-0.2/22.7)	21 (1.6/58.3)	<0.001
Ferritin(ng/mL)						
Before	4 (0.44/10.7)	3.7 (1.3/10)	0.524	3.2 (0.44/10.7)	4.11 (1/10)	0.100
After	16.9 (4/77)	20.5 (3.74/79)	0.185	8 (3.74/11.02)	24 (14/79)	<0.001
Alteration (After-Before)	13.47 (-0.02/70.79)	16.875 (1.05/72.72)	0.107	4.1 (-0.02/8.83)	21 (13/72.72)	<0.001

Mann Whitney U Test (Monte Carlo); Min.: Minimum; Max.: Maximum; SD.: Standard deviation; IRD: Iron deficiency.

and iron deficiency (15). In Iran, among 2917 school age children, 80% children were having ferritin concentrations <10 mg/dL and also goiter; however, only 20% children with ferritin concentrations >10 mg/dL had goiter (16). Two studies from Turkey reported that neither multinodular goiter nor iodine deficiency showed any correlation with iron status (17, 18). Erdogan et al. detected median UIC to be 26 µg/L in 1997-1999, 90 µg/L in 2002 and 135 µg/L in 2009 during the follow-up monitoring surveys in school age children in Ankara (19). In the present study, the UIC levels of patients were found to be similar at the beginning and end of the treatment, being 82.5 µg/L (1/450) and 118 µg/L (12/450), respectively. Goiter was observed in 45.4% patients out of all the subjects with IRD anemia in this study. In the subgroup analysis, median UIC levels of individuals with goiter were found to be lower than those of non-goitrous patients. All patients benefited from oral iron replacement therapy, especially in terms of regression in thyroid gland size, although median UIC levels did not change significantly either in the goitrous or non-goitrous group. It is striking that iron, apart from iodine, has an effect on thyroid volume. Zimmermann performed a study on children between 6-12 years of age in Cote d'Ivore of North Africa where iron and iodine deficiency were seen together, which was in support of the present study (20). In the study, 51 patients having only goiter and 53 patients having both, goiter and iron deficiency anemia, were followed for 30 weeks under only iodine replacement therapy. In patients having only goiter, thyroid volume decreased by 22% till the 10th week and further by 45% till the 30th week (20). However, in the patients with both goiter and iron deficiency together, thyroid volume decreased by 20% till the 10th week and did not decrease any further between weeks 10-30 (20). After the 30th week, iron replace-

Table 3. The comparisons of non-goitrous group and goitrous group, and unimproved IRD group and improved IRD group according to thyroid parameters.

	Thyroid gland volume status			IRD		
	Non-goitrous	Goitrous		Unimproved IRD	Improved IRD	
Variable Median (Min./Max.)	(n=36)	(n=30)	P Goitrous	(n=17)	(n=49)	P IRD
fT3 (pmol/L) Mean±SD.						
Before	5.01±0.96	4.79±1.01	0.264[c]	4.54±0.99	5.04±0.95	0.074[c]
After	5.07±1.04	5.30±0.73	0.426[c]	4.83±1.02	5.29±0.85	0.114[c]
Alteration (After-Before)	0.06±1.19	0.40±1.01	0.059[b]	0.29±1.19	0.25±1.11	<0.001[b]
fT4 (pmol/L)						
Before	15.95 (12.7/22.5)	15.25 (11.4/19.7)	0.075[a]	15.5 (12.7/22.5)	15.6 (11.4/19.7)	0.971[a]
After	17.2 (11.2/20.4)	16.05 (5.97/22.8)	0.266[a]	16.4 (5.97/19)	16.4 (10.2/22.8)	0.290[a]
Alteration (After-Before)	0.3 (-5/4.9)	1.1 (-7.63/7.5)	0.579[a]	0 (-7.63/3.1)	1.1 (-5/7.5)	0.117[a]
sTSH(mIu/mL)						
Before	1.785 (0.8/4.08)	1.185 (0.5/2.35)	<0.001[a]	1.6 (0.5/3.1)	1.6 (0.57/4.08)	0.986[a]
After	1.74 (0.689/6.55)	1.235 (0.509/2.77)	0.001[a]	1.57 (0.668/4.49)	1.47 (0.509/6.55)	0.730[a]
Alteration (After-Before)	-0.03 (-1.45/2.89)	0.13 (-1.62/0.94)	0.619[a]	0.14 (-1.45/2.33)	0.06 (-1.62/2.89)	0.804[a]
UIC (Mg/L)						
Before	98 (1/420)	58.5 (1/450)	0.024[a]	80 (10/180)	84 (1/450)	0.798[a]
After	138 (12/450)	88 (14/450)	0.024[a]	87 (34/450)	127 (12/450)	0.265[a]
Alteration (After-Before)	2.5 (-293/270)	12 (-141/351)	0.829[a]	-5 (-129/270)	13 (-293/351)	0.808[a]
Thyroid gland volume (mL)						
Before	13.045 (7.15/15.934)	19.65 (16/54.2)	<0.001[a]	14.4 (8.297/29.17)	16.24 (7.15/54.2)	0.129[a]
After	10.84 (6.11/16.73)	16.525 (7.76/58.8)	<0.001[a]	12.9 (7/31.857)	13.65 (6.11/58.8)	0.488[a]
Alteration (After-Before)	-1.485 (-5.09/4.61)	-2.685 (-11.79/5.52)	0.117[a]	-1.3 (-9.74/4.61)	-1.98 (-11.79/5.52)	0.048[a]

[a] Mann Whitney U Test(Monte Carlo), [b] General Linear Model Repeated Anova (Wilks' Lambda), [c] Independent Samples T Test(Bootstrap). Min.: Minimum; Max.: Maximum; SD.: Standard deviation; IRD: Iron deficiency.

ment therapy was supplemented to this group and thyroid volume was observed to decrease to 38% that of the initial volume (20). This finding suggested that iron plays a role in thyroid metabolism (21-24). Zimmermann performed another study in 166 school aged children with goiter and iron deficiency and followed them for 20 weeks (23). One group of children was administered iron while the rest received placebo. In the group that received iron treatment, the reduction of thyroid volume was twice as much as it was in the placebo group (23). It supported the fact that thyroid volume is unquestionably influenced by iron status (25). The thyroid gland is a highly vascularized gland and blood flow influences an important part of the thyroid gland volume. IRD anemia exerts a hyperkinetic flow in the thyroid gland. It is proposed that the apparent elevation of blood volume on the thyroid vessel bed causes an increase in thyroid volume. This mechanism may be responsible for the decrease in volume after oral iron therapy (16, 20). On the other hand, patients in whom both Hb and ferritin values improved sufficiently, showed a more significant reduction in thyroid volume than in the patients having still low ferritin value at the end of the treatment. It was thus emphasized that iron may be an independent beneficial factor for thyroid gland volume.

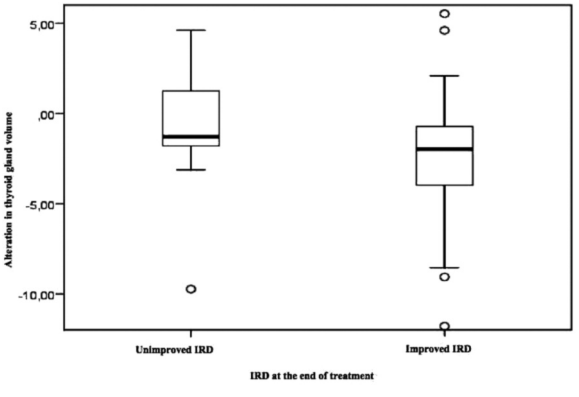

Figure 1: Comparison of the alteration in total thyroid gland volume between unimproved IRD and improved IRD groups.
IRD: Iron deficiency.

It is obvious that TSH is a trophic factor for the thyroid gland. When the whole group was considered, an increase in fT4 level was seen with oral iron therapy; however, fT3 and sTSH levels did not change even at the end of the treatment. The correction in the iron status may have been related to the better organification of iodine, better utilization of tyrosine residues in thyroglobulin and thus formation of more efficient T4. The TPO is a heme protein with a prosthetic group of ferriprotoporphyrin IX comprising iron in its structure. The iodine reacts with tyrosine residues in thyroglobulin through the activity of TPO; this step is essential for thyroid hormone synthesis. IRD may decrease TPO enzyme activity and result in hypothyroxinemia (26). Hess et al. found that the TPO activity, in the thyroid gland, determined by the guaiacol assay in rats, which were fed on an iron deficient diet containing 3, 7 and 11 mcg iron/g, was decreased by 33, 45, and 56%, respectively (23). However, no further information on which serum iron level and which hemoglobin level may change this enzyme activity is available. Hu et al. found that total serum T4 levels were positively related to liver iron, serum ferritin, serum iron and Hb concentration in rats with IRD (27). Khatiwada et al. studied 227 school children aged 6-12 years in Nepal and found that the risk of having hypothyroidism (overt and subclinical) in anemic and iron deficient children was 5.513 and 1.939, respectively, as compared to the children who were non-anemic and had iron in sufficient amounts (28). Yu et al. reported that fT4 levels were significantly lower in both, 3340 pregnant and 1052 non-pregnant women with IRD (29). The study from Eftekhari in Iranian adolescents with IRD showed that despite an increase in fT3 and fT4 concentrations, the TSH concentration remained unaffected by iron supplementation (30). Recently, Maldonado-Araque et al. confirmed the association between IRD, hypothyroxinemia, and hypotriiodothyroninemia in Spanish general adult population (31). The results suggested that several mechanisms are involved in IRD and thyroid hormone metabolism. Iron deficiency may alter the control of hypothalamus-hypophysis-thyroid axis, modify nuclear thyroid hormone binding and hepatic thyroid hormone turnover and impair oxygen transport to the thyroid gland. These mechanisms jointly contribute to change in thyroid hormone metabolism and thyroid gland volume in patients with IRD (27-31).

The studies on micronutrient deficiencies are frequently performed on pregnant women, infants or school age children. The strength of this study was that healthy women participated and it comprised a homogenous group with iodine and iron deficiency. However, the study should also have included patients with sufficient UIC. Further molecular research is necessary to determine the effects of iron on enzymes related to thyroid hormone metabolism.

To conclude, the study found a significant reduction in thyroid gland volume in women with IRD anemia consistently when the iron was replaced. Thus, iron supplementation is not only beneficial for IRD anemia but also ameliorates increased thyroid gland volume. In societies where iron and iodine deficiency are seen together especially in young women, iron therapy and iodine supplementation are inevitable. It is suggested that thyroid gland volume and functions must be evaluated once again after iron therapy.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Murat Faik Erdoğan; Design: Diğdem Özer Etlik, Murat Faik Erdoğan; Control/Supervision: Diğdem Özer Etlik; Data Collection and/or Processing: Diğdem Özer Etlik; Diğdem Özer Etlik; Analysis and/or Interpretation: Diğdem Özer Etlik; Literature Review: Diğdem Özer Etlik; Writing the Article: Diğdem Özer Etlik; Critical Review: Murat Faik Erdoğan; Materials: Diğdem Özer Etlik.

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