Hematologic Effects of Levothyroxine in Iron-Deficient Subclinical Hypothyroid Patients: A Randomized, Double-Blind, Controlled Study

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Context: In patients with coexisting iron-deficiency anemia and subclinical hypothyroidism, anemia does not adequately respond to oral iron therapy.

Objective: We studied whether iron-deficiency anemia might indicate treatment of subclinical hypothyroidism.

Design: Patients were assigned to a control or experimental group: 240 mg/d oral iron alone (iron group) or 240 mg/d oral iron plus 75 μg/d levothyroxine (iron/levothyroxine group). Levels of hemoglobin, hematocrit, red blood cell count, serum iron levels, ferritin, total iron-binding capacity, TSH, and free T_4 were measured before and after treatment.

Setting: The study was conducted at a university hospital outpatient clinic.

Patients: Fifty-one patients with coexisting iron-deficiency anemia and subclinical hypothyroidism participated in the study.

Intervention: Patients were treated as described above in either the iron group or the iron/levothyroxine group.

Main Outcome Measure: A clinically satisfactory increase in hemoglobin was regarded as successful.

Results: Mean hemoglobin levels increased by 0.4 g/dl in the iron group [95% confidence interval (CI) 0.2–0.7, $P = 0.001$], whereas it increased by a mean of 1.9 g/dl in the iron/levothyroxine group (95% CI 1.5–2.3, $P < 0.0001$). The increase in serum iron was greater in the iron/levothyroxine group by a mean of 47.6 μg/dl (95% CI 34.5–60.6, $P < 0.0001$). Increases in hemoglobin, red blood cells, hematocrit, and serum ferritin levels after treatment were statistically significantly greater in the iron/levothyroxine group ($P < 0.0001$). Starting hemoglobin and increase in hemoglobin were negatively correlated in the iron/levothyroxine group ($r = -0.531$, $P = 0.006$).

Conclusions: Subclinical hypothyroidism should be treated in iron-deficiency anemia patients when both conditions coexist. This would provide a desired therapeutic response to oral iron replacement and prevent ineffective iron therapy. **(*J Clin Endocrinol Metab* 94: 151–156, 2009)**

Subclinical hypothyroidism is defined as an elevated serum TSH level in the setting of normal total or free T_4 and T_3 levels (1). It is a common clinical problem with an overall prevalence of 4–10% in the general population and up to 20% in women older than 60 yr (2). There are controversies mainly about screening, evaluating, and managing subclinical thyroid dysfunction. Thus, a consensus development panel was held in September 2002 to develop an evidence-based approach to var-

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Abbreviations: δ (Δ), Amount of changes; CI, confidence interval; FT_4, free T_4; Hb, hemoglobin; Hct, hematocrit; RBC, red blood cells; TIBC, total iron binding capacity.

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ious unresolved clinical issues regarding subclinical thyroid disorders (3). This led to another panel in 2004 (1) because data in several areas were inconclusive. The 2004 panel disagreed in three areas, one of which was routine treatment of patients with subclinical hypothyroidism with TSH levels between 4.5 and 10 mIU/liter.

Possible consequences of subclinical hypothyroidism are cardiac dysfunction (4) or adverse cardiac end points (including atherosclerotic disease and cardiovascular mortality) (5); elevation in total and low-density lipoprotein cholesterol (6); systemic hypothyroid symptoms (7); neuropsychiatric symptoms (8); and progression to overt, symptomatic hypothyroidism (9). Unfortunately, data regarding these potential consequences of untreated subclinical hypothyroidism are controversial and for most of them are insufficient to warrant treatment.

Anemia is a relatively frequent finding in overt hypothyroidism (10). Anemia that normalizes in response to T_4 replacement, even in the presence of normal serum iron, vitamin B12, and folate is found in up to 25% of hypothyroid patients (10). There are limited studies about such a relation between subclinical hypothyroidism and anemia. Anemia is not listed among the consequences of untreated subclinical hypothyroidism. One study has reported sideropenia to be a common finding in women with subclinical hypothyroidism and suggests routinely determining ferritin levels in such patients (11). Another study reported no change in hemoglobin (Hb) or hematocrit (Hct) levels upon restoration of euthyroidism in women with subclinical hypothyroidism (12).

In our clinical practice, we have seen patients with a so-called diagnosis of iron-deficiency anemia who had received long-term iron therapy. Some of these patients stopped seeing their physician but continued to take iron, whereas others continued taking oral iron therapy, although they had no response. Interestingly, subclinical hypothyroidism was more common among these nonresponders.

We designed this randomized, double-blind, controlled study to address the question of whether subclinical hypothyroidism is associated with unresponsiveness to iron replacement therapy in iron-deficient, subclinical hypothyroid patients and whether thyroid replacement would reverse this.

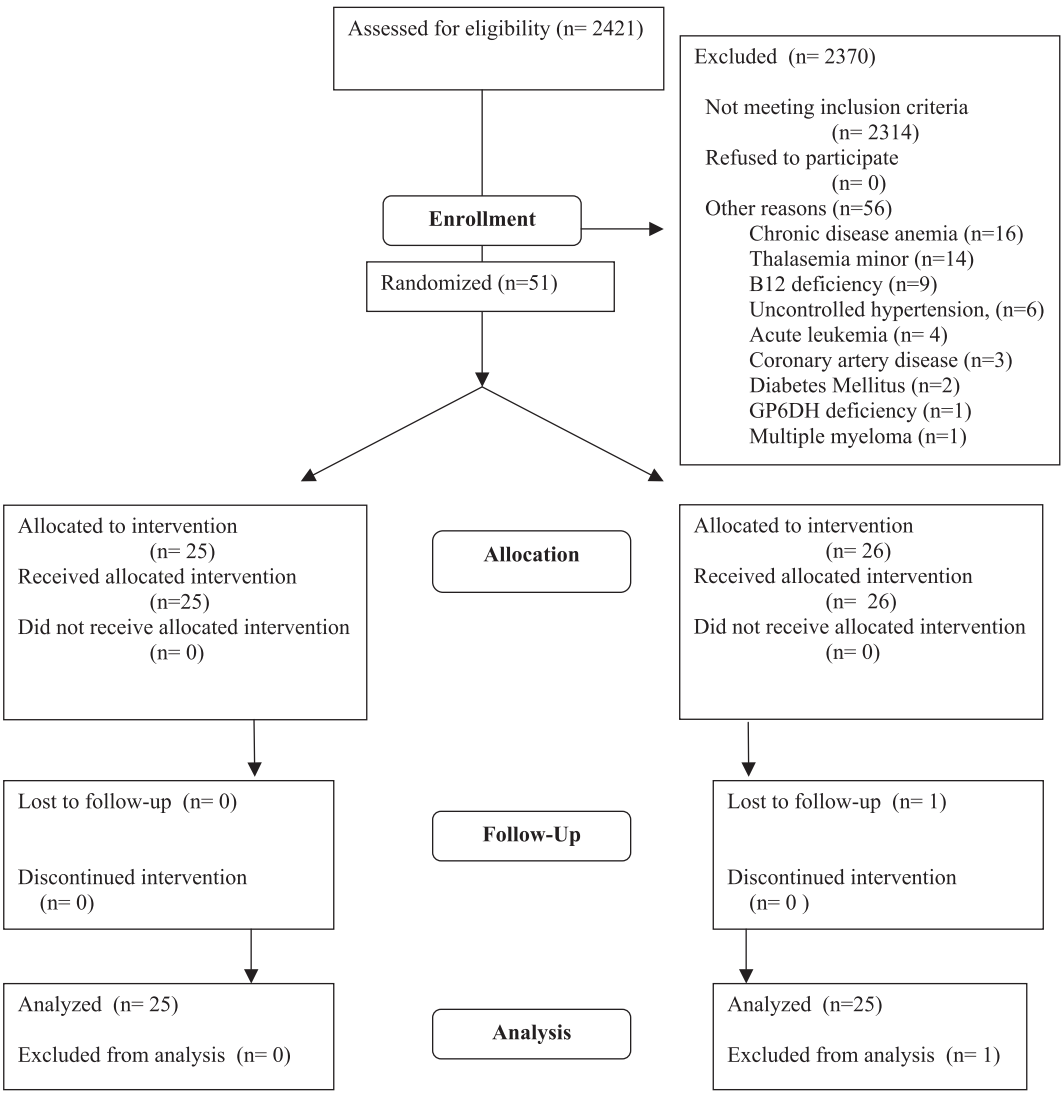

FIG. 1. Flow chart of the study. GP6DH, Glucose-6-phosphate dehydrogenase.

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Patients and Methods

Patients

The study population was selected from 2421 patients who presented to the internal medicine outpatient clinic at Duzce University in Duzce, Turkey, for the first time, between June and September 2007. Of the 2421 patients, 2314 failed to meet the inclusion criteria, which were presence of newly diagnosed anemia and coexisting subclinical hypothyroidism.

Exclusion criteria were multifactorial anemia or anemia due to other reasons, including hemolytic anemias; iron-deficiency anemia requiring urgent intervention; cardiac ischemia, severe anemia, gastrointestinal or genitourinary losses due to malignancy and/or acute/subacute blood losses from the respiratory, gastrointestinal, or genitourinary system; prior thyroid disorder and/or treatment history; and presence of any comorbid disease like renal insufficiency/failure, coronary heart disease, uncontrolled hypertension, diabetes mellitus, or any endocrine system disease other than subclinical hypothyroidism.

Thus, 107 patients were left with anemia and subclinical hypothyroidism, 56 of which were excluded due to other reasons (Fig. 1). The remaining 51 patients who had diagnoses of iron-deficiency anemia and subclinical hypothyroidism were consecutively assigned to the treatment groups. All but one patient who was lost to follow-up completed the study, and data from 50 patients formed the basis of the analysis.

Study protocol

The study protocol was approved by the Duzce University Hospital Ethical Committee. Written, informed consent was obtained from all patients. A history was taken, and a physical examination was done on each patient. Baseline fasting blood urea nitrogen, creatinine, glucose, serum electrolyte, TSH, free T_4 (FT_4), aspartate aminotransferase, alanine aminotransferase, total bilirubin, direct bilirubin, total protein, and albumin levels were measured, and a complete blood count and differential as well as a urine analysis was done. A Roche Hitachi (Indianapolis, IN) modular analytics E170 system was used for thyroid assays. Serum chemistry was studied using a Modular P800 system (Roche Hitachi, Indianapolis, IN), and complete blood count and differentials were analyzed with a Roche Sysmex XT-2000i (Roche Diagnostic Corporation, Indianapolis, IN). Serum TSH and FT_4 levels were remeasured 3–4 wk after treatment to rule out transient subclinical hypothyroidism. Creatinine clearance for each patient was calculated using the Cockcroft-Gault equation, and renal insufficiency or failure was ruled out in all patients. All patients had peripheral blood smear examination, including stool guaiac $\times$ 3, and stool examination for leukocytes, parasites, and ova. Colonoscopy, esophagogastroduodenoscopy, gynecological, and genitourinary examinations were performed as necessary at the appropriate departments. Our gastroenterology team ruled out pernicious anemia/atrophic gastritis in all patients. None of the patients had malabsorption, inflammatory bowel disease, or colon cancer.

Each patient who presented to our outpatient clinic with the results of these studies and had diagnosis of iron deficiency anemia and subclinical hypothyroidism had been directed to one of the investigators who had access to the detailed information of the study. The clinician prepared either ferrous sulfate 80 mg or ferrous sulfate 80 mg plus 25 μg levothyroxine contained in identical capsules and placed 84 capsules in identical containers, which were numbered as no. 1 or no. 2. The containers were placed in the treatment room. Iron-deficiency anemia was suggested as being associated with menstrual bleeding, hemorrhoids, excessive black tea consumption, and other dietary factors or as being undetermined. Upon decision for iron replacement therapy, the same investigator directed each patient to a second assigned investigator. Thus, the sequence was generated by completing the evaluation studies and consecutive presentations to the second investigator. The second investigator assigned the patients consecutively to the first or second treatment group by starting with container no. 1, which contained oral iron only. He went on successively with next box number each time.

Patients were instructed to take the capsules on an empty stomach, 1 h before meals, three times daily. Patients also received instructions for diet including adding 60–70 g/day of red meat to their diet and avoiding consuming excess amounts of black tea. Patients were instructed to report, by phone or by coming to the clinic, any adverse effects they experienced. All patients had Hb and Hct remeasured in 1–1.5 months. Only one 27-yr-old woman in the first group was offered iv iron treatment because her Hb level had increased slightly from 6.5 to 6.8 g/dl after 4 wk of therapy; however, she decided to continue on oral therapy; her serum iron and ferritin levels increased despite continuing metroragy.

All patients had fasting serum iron, ferritin, total iron binding capacity (TIBC), transferrin saturation, TSH, FT_4, Hb, Hct, and red blood cell levels re-measured after 12 wk; the study was then terminated. No new medications, other than those stated, were used during the study. Four patients in the iron group who were asymptomatic but responded to oral iron slightly were followed up with further treatment as necessary. The remaining 21 asymptomatic patients with mild anemia were offered further management. Data collection was completed by the end of December 2007.

Statistics

Data with normal distribution are reported as means and SDs, whereas medians and interquartile ranges are used for markedly nonnormal distributed data. Accordingly, nonparametric tests were used for data with nonnormal distributions. The Kruskal-Wallis test was used to demonstrate that both groups had been selected from the same population. Baseline characteristics also were compared using independent samples *t* test, the χ^2 test, or Mann-Whitney *U* test. Paired samples *t* test or the Wilcoxon signed rank test was used to compare two repeating measurements in the same group. To compare the efficiency of two different treatments, amount of changes [δ (Δ)] in parameters were calculated by subtracting after treatment measurement, values from before treatment values for both groups. An independent samples *t* test or a nonparametric Mann-Whitney *U* test was used to compare the groups. For nonparametric tests, 95% confidence intervals (CIs) were calculated for the difference in population medians. To evaluate correlations between parameters in the groups, the Pearson product moment correlation analysis (r) was calculated. All *P* values are two tailed, and statistical significance was set at $P < 0.05$. Statistical Product and Services Solutions software (version 15.0; SPSS Inc., Chicago, IL) was used for the statistical analyses.

Results

Baseline characteristics and laboratory data for the treatment groups are shown in Table 1. Median age, sex, and prevalence of additional medical problems did not differ between the groups. Thyroglobin and/or thyroid peroxidase antibodies were positive in seven patients in the iron group and eight patients in the iron/levothyroxine group. None of the patients had anti-TSH antibodies. Thyroid ultrasound examination was consistent with Hashimoto's disease in five of thyroglobin and/or thyroid peroxidase antibody-positive patients in the iron and iron/levothyroxine groups. The remaining antibody-positive patients in both groups demonstrated atrophic glands on ultrasonography. All patients with negative antibodies had normal thyroid ultrasonography results except one who had an atrophic thyroid gland. Subclinical hypothyroidism in these patients was quite a frequent finding in our practice, which is located in a mild iodine-deficiency prevalent region.

Patients did not have physical findings related to hypothyroidism including goiters. All but one patient in the iron group denied symptoms related to anemia. About one third of all the

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TABLE 1. Laboratory and clinical characteristics of 50 patients with coexisting iron deficiency anemia and subclinical hypothyroidism, before and after three months of treatment

	Iron group (n = 25)		Iron/levothyroxine group (n = 25)		Baseline comparisons between groups
	Before	After	Before	After	Z/t/χ^2, *P*
Male/female	22/3		22/3		1.000
Age, median (IR)	38 (27–50)		35 (29–55)		−0.311, 0.756
Other medical problems, n					
None	19		16		0.857, 0.354
Hypertension	3		5		
Hemorroides	3		4		
TPOAb and/or TgAb positive	7 (28%)		8 (32%)		0.095, 0.758
Fe, median or mean (SD), μg/dl	20 (15–38)	30 (17–45)	23.3 (10.37)	78 (26.43)	−0.282, 0.778
TIBC, mean (SD), μg/dl	386.9 (70.79)	380.2 (65.9)	378.9 (46.56)	342.9 (43.53)	0.472, 0.639
TS, median (IR) or mean (SD), %	5.5 (3–10.15)	11 (9.84)	8 (4–13.15)	21.8 (8.78)	−0.156, 0.876
Ferritin, median (IR) or mean (SD), ng/ml	12 (8.5–22)	15 (9–23)	11.64 (6.67)	24 (16–34)	1.317, 0.194
Hb, mean (SD), g/dl	10.4 (1.58)	10.8 (1.43)	10.9 (0.98)	12.9 (0.93)	−1.345, 0.185
RBC, mean (SD), 10^6 cells/μl	3.9 (0.66)	4.2 (0.59)	3.9 (0.43)	4.7 (0.29)	−0.076, 0.940
Hct, mean (SD), %	31.9 (4.7)	33.6 (4.7)	32.7 (2.77)	39.4 (3.08)	−0.715, 0.478
TSH, mean (SD), mIU/liter	6.5 (1.24)	6.9 (4.3)	7.4 (1.65)	3.4 (1.09)	−1.915, 0.061
FT_4, mean (SD), ng/dl	13.3 (1.66)	13.01 (2.73)	13.9 (1.65)	15.2 (2.06)	−1.299, 0.200

Baseline laboratory and clinical characteristics of 50 patients with subclinical hypothyroidism. The groups did not differ in age; sex; starting hematological and thyroid parameters; and serum iron, total iron binding capacity, transferrin saturation, ferritin levels. TPOAb, Thyroid peroxidase antibodies; TgAb, thryoglobulin antibodies; TS, transferrin saturation; Z/t/χ^2, Mann-Whitney *U* test Z-value, independent samples t-test, or chi-square test χ^2 value.

patients complained of occasional constipation. Three patients in the iron group and five patients in the iron/levothyroxine group had history of recurrent symptoms due to hemorrhoids. The two groups were similar in starting hematological parameters, iron studies, and thyroid status. Although there were eight patients with TSH values greater than 10 mIU/liter (12.1–19.0 mIU/liter) in the iron/levothyroxine group, baseline characteristics did not differ significantly between the groups (Table 1). The Kruskal-Wallis test on Hb, red blood cells (RBC), and Hct verified that the groups were selected from the same population of patients ($\chi^2 = 0.576$, $df = 1$, $P = 0.448$; $\chi^2 = 1.068$, $df = 1$, $P = 0.301$; and $\chi^2 = 0.002$, $df = 1$, $P = 0.961$, respectively). Serum TSH values became normal (0.27–4.2 mIU/liter) in 23 patients in the iron/levothyroxine group with a fixed dosage of 75 μg/d levothyroxine. TSH decreased to 5.1 and 5.8 mIU/liter in two patients. Both groups of patients tolerated the medications well without any adverse effects.

We found that Hb increased by a mean of 0.4 g/dl in the iron group (95% CI 0.2–0.7, $P = 0.001$), whereas it increased by a mean of 1.9 g/dl in the second group (95% CI 1.5–2.3, t = 9.8, $df = 25$, $P < 0.0001$). The amounts of increase in medians or means for RBC, Hct, Fe, transferrin saturation, ferritin, and FT_4; and the decrease in TIBC and TSH after treatment were greater in the iron/levothyroxine group than the iron group (Fig. 2). δ values were compared between the groups, and significant differences were found. δ iron was greater in the iron/levothyroxine group compared with the iron group by a mean of 47.6 (95% CI 35.7–59.4; $P < 0.0001$). The Δs of the other variables also were significantly higher in the iron/levothyroxine group (Table 2). We found several correlations, among which a significant negative correlation between starting Hb and ΔHb in the iron/levothyroxine group deserves mentioning (Pearson r = −0.531, $P = 0.006$).

Discussion

Our results indicate that iron-deficiency anemia did not respond to oral iron therapy adequately in subclinical hypothyroid patients. Addition of levothyroxine, on the other hand, caused a significant improvement of serum iron and blood count variables. These findings support our clinical observation regarding the presence of a group of patients resistant to oral iron because of their coexisting subclinical hypothyroidism. These patients might benefit from addition of levothyroxine to their treatment regimen, and this might be an indication for treating subclinical hypothyroidism in iron-deficiency anemia patients.

In this study, we tried to find a similar group of patients to test our hypothesis. This was hard in general because subclinical hypothyroidism is not so common, and anemia can have a broad

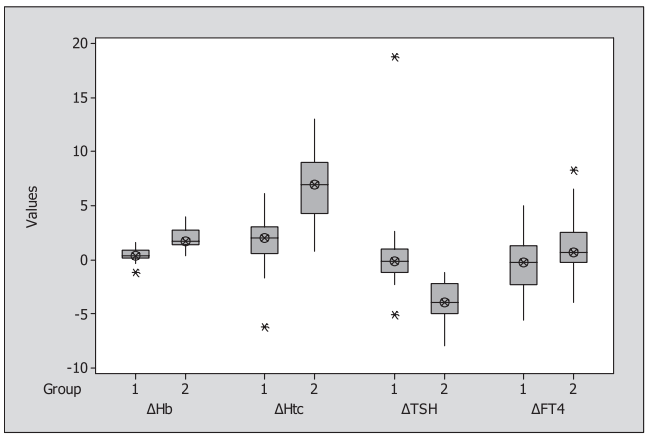

FIG. 2. ΔHb (grams per deciliter), ΔHct percent, ΔTSH (milliinternational units per liter), and ΔFT4 (nanograms per deciliter) in the iron and iron/levothyroxine groups. The amounts of changes after treatment were greater for all variables in the iron/levothyroxine group.

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TABLE 2. δ values for hematological parameters, serum iron, TIBC, TS, ferritin, TSH, and FT_4 in the iron and iron/levothyroxine groups

	Iron group	Iron/levothyroxine group	*P*
ΔFe, mean (SD), μg/dl	7.20 (9.23)	57.76 (27.98)	<0.0001
ΔTIBC, median (IR) or mean (SD), μg/dl	−1.0 (−19.5 to 19.5)	−36.04 (37.92)	0.001
ΔTS, mean (SD), %	2.0 (2.61)	15.64 (8.70)	<0.0001
ΔFerritin, median (IR) or mean (SD), ng/ml	3.0 (−1.5 to 7.5)	11.0 (9.5–21.5)	<0.0001
ΔHb, mean (SD), g/dl	0.46 (0.59)	1.92 (0.92)	<0.0001
ΔRBC count, mean (SD), 10^6 cells/μl	0.21 (0.29)	0.72 (0.33)	<0.0001
ΔHct, median (IR) or mean (SD), %	2.0 (0.55 to 3.0)	6.71 (3.28)	<0.0001
ΔTSH, median (IR) or mean (SD), mIU/liter	−0.1 (−1.2 to 0.95)	−3.97 (1.94)	<0.0001
FT_4, median (IR) or mean (SD), ng/dl	−0.27 (2.42)	0.7 (−0.2 to 2.5)	0.03

Statistical comparison of the amount of changes (Δs) in hematological parameters, TSH, and FT_4 after oral iron and oral iron plus levothyroxine treatment. There were significant differences in Δs of the all measured parameters between groups. TS, Transferrin saturation.

spectrum of causes. Even after finding iron deficiency as the cause of anemia, this would leave us with a wide variety of causes. The location of our clinic helped greatly regarding these issues because the coast of the Black Sea of Turkey is well known to be an endemic goiter region (13). This provided us with another advantage because there was a young female population presenting to our outpatient clinic to determine their blood and thyroid status. On the other hand, the advantage of this preponderance caused a disadvantage in the sex distribution. Upon completion of our study, we noted that there were three men in each group.

We found a significant increase in Hb in the iron/levothyroxine group after 12 wk of therapy. Besides a statistical significance, the amount of increase was clinically satisfactory in all patients. Although the Hb level was elevated significantly in the iron group, the improvement was not clinically satisfactory. Other hematological variables showed similar changes in both groups, and improvement was significantly better in the iron/levothyroxine group.

Animal and human studies show that thyroid hormones stimulate red cell production (14, 15). In hypothyroidism, the erythrocyte life span remains normal, and there is hypoproliferative erythropoiesis (14). There have been several suggestions to try to explain how thyroid hormones stimulate erythropoiesis. Increased metabolic rate and its related increase in oxygen demand have been the major explanations. The proposed mediator was erythropoietin. Consistent with this suggestion, Christ-Crain *et al.* (12) found elevated erythropoietin levels after levothyroxine therapy in subclinical hypothyroid women, but Hb and Hct did not change in that study. This is in contrary to our findings. The sex distribution was quite similar to our study, but their patients were older. More importantly, patient characteristics were different between the studies. Our patients also had iron-deficiency anemia. Thus, levothyroxine alone might not increase Hb or Hct in nonanemic, subclinical hypothyroid patients. This is supported by significant negative correlation between starting Hb and ΔHb in the iron/levothyroxine group, which might indicate a better hematological response in the more anemic patient with iron plus levothyroxine treatment. Finally, yet importantly, the reliability of Hb as an indicator of red cell mass during hypothyroidism (16) owing to a concomitant decrease in plasma volume (17) can be argued. This might be true for overt hypothyroidism, but our patients were euvolemic on detailed physical examination. None of them had edema, weight loss, or reported polyuria during therapy. Hence, better hematological variables could not be accounted for by plasma volume changes in our study.

Our results also indicate that hematologic improvement is closely associated with improved serum iron variables. This parallel change suggests that stimulation of erythropoiesis by thyroid hormones is not the sole mechanism, but thyroid hormone effects on iron metabolism are also involved.

Other evidence for the presence of other mechanisms comes from the experience of managing anemia related to chronic renal failure. There are increasing reports about treatment-resistant anemia in chronic renal failure patients. Erythropoietin resistance in the presence of hypothyroidism and even subclinical hypothyroidism have been reported in chronic renal failure. Furthermore, this resistance is resolved by treating subclinical hypothyroidism (18). These reports challenge the erythropoietin hypothesis because exogenous human erythropoietin alone failed to correct anemia in subclinical hypothyroid, chronic renal failure patients. Thus, it seems reasonable to conclude that thyroid hormones affect erythropoiesis in multiple ways including stimulating iron incorporation into erythrocytes (14) and increasing iron absorption (19) and by an inhibitory effect (15) or even by acting on its receptors to function as a switch between proliferation or differentiation of erythroid progenitors (20). There is no reason not to believe that these multiple mechanisms came into play in our study.

Another point worth mentioning is the presence of more complex interactions between thyroid hormones and iron metabolism. A considerable amount of data indicates that an iron deficiency impairs thyroid metabolism (21). Lower serum T_3 (22) or increased TSH and lower serum T_3 and T_4 levels have been reported (23) in iron-deficient humans. This might explain our clinical observation regarding the increased prevalence of subclinical hypothyroidism among iron-deficiency anemia patients. Zimmerman and Köhrle (21) pointed out this side of the interaction. Analogous to our study, they showed that coadministration of iron with iodine was more effective in the treatment and prophylaxis of goiter (24). Individuals in this region consume iodized salt. We did not see a significant change in TSH or FT_4 levels by oral iron, however, and we do not know the exact effect of this side of the interaction in our study.

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This is the first study to compare the hematological effects of levothyroxine in iron-deficient, subclinical hypothyroid patients. Our results show that patients with these coexisting disorders benefit significantly from treatment of their subclinical hypothyroidism. The endemic goiter region we studied had high prevalence of both disorders, which brought to light the benefit of treating subclinical hypothyroidism. We also found that resistance to oral iron treatment indicates the need to test for thyroid function, especially in regions with endemic goiter.

Acknowledgments

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