

Iron deficiency anemia in patients with subclinical hypothyroidism benefits substantially by the addition of low-dose levothyroxine to iron replacement, as compared with iron replacement alone

Cinemre H, Bilir C, Gokosmanoglu F, Bahcebasi T. Hematologic effects of levothyroxine in iron-deficient subclinical hypothyroid patients: a randomized, double-blind, controlled study. *J Clin Endocrinol Metab* 2009;94:151-6.

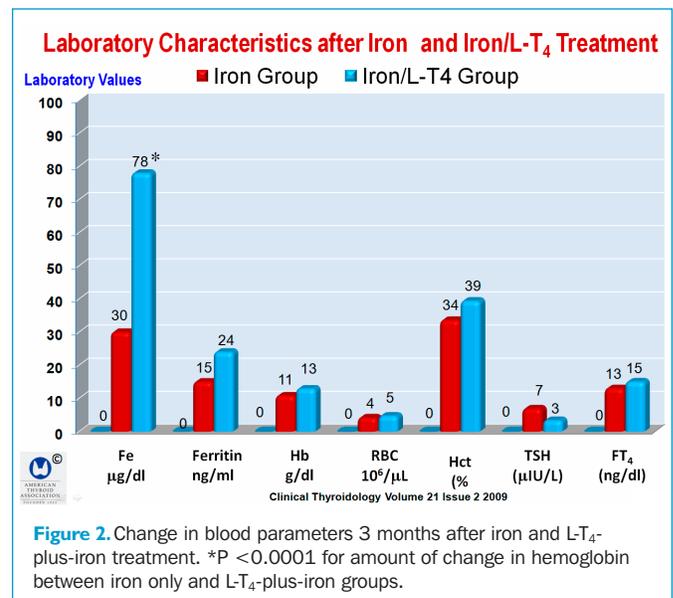
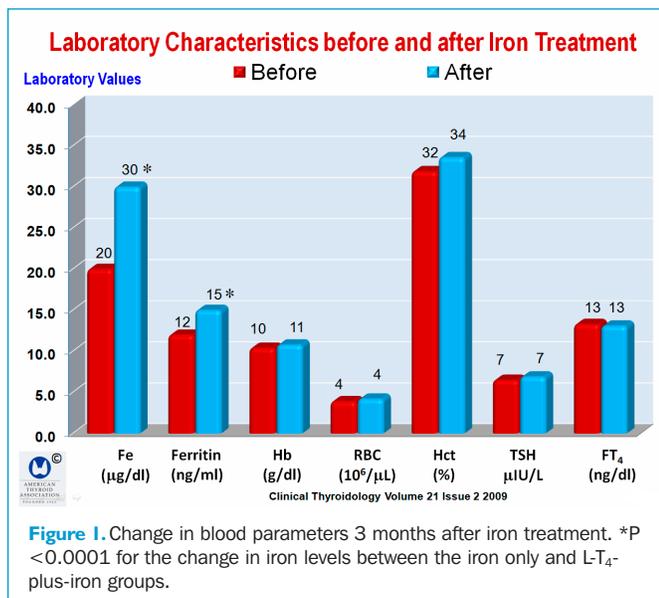
SUMMARY

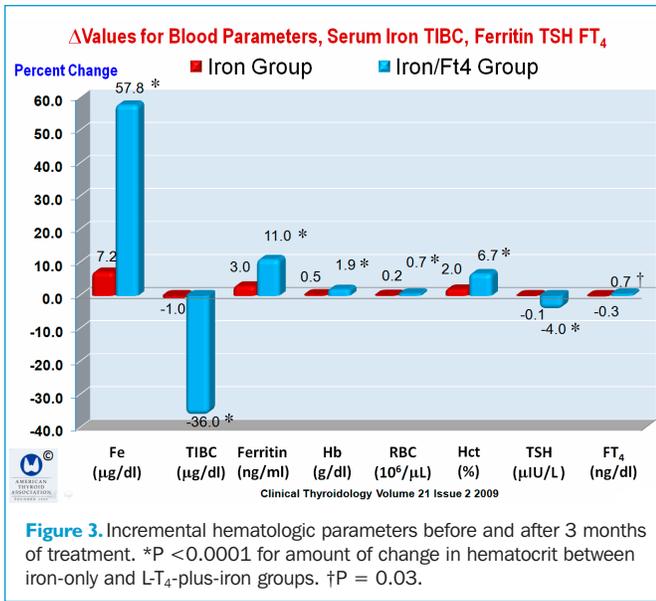
BACKGROUND Patients with untreated overt hypothyroidism frequently have concomitant anemia. Treatment of the underlying thyroid disorder will typically improve the anemia, without any other specific hematologic intervention (1). Nearly 30% of patients with subclinical hypothyroidism (SH) may also have coexistent anemia (2). The anecdotal experience of the authors of the study under discussion is that there is a group of patients with anemia and SH who are resistant to oral iron supplementation. This study seeks to determine whether the addition of levothyroxine (L-T₄) to the standard iron replacement regimen will be more effective in ameliorating the hematologic condition.

METHODS Patients were selected from an Internal Medicine outpatient clinic at Duzce University in Turkey. New patients with anemia and SH who were seen from June through September 2007 were screened for underlying causes of anemia. Patients were excluded from the study if they had anemia due to other causes or other comorbid diseases, such as renal insufficiency, coronary heart disease, uncontrolled hypertension, or diabetes mellitus. To rule out other secondary causes of anemia, renal function was checked and peripheral-blood smears were performed. Each patient had three stool guaiac tests. Patients were also examined for signs and symptoms of malabsorption, colon cancer, and inflammatory bowel disease. In all, 51 patients who had iron deficiency anemia were eligible for the study and were randomly assigned to receive either 80 mg of ferrous sulfate (FeSO₄) orally (iron-only group) or 80 mg of FeSO₄ plus 25 μg of levothyroxine (L-T₄-plus-iron group) in identical capsules. Patients were instructed to take their capsules three times daily on an

empty stomach 1 hour prior to meals. Diet instructions included 60 to 70 g/day of red meat and avoidance of excessive amounts of black tea. Four to six weeks after initiation of the intervention, hemoglobin (Hb) and hematocrit (Hct) were measured. After 12 weeks, ferritin, total iron-binding capacity (TIBC), transferrin saturation, fasting serum iron (Fe), thyrotropin (TSH), free T₄ (FT₄), Hb, Hct, and red-cell (RBC) levels were remeasured and the study was terminated.

RESULTS One of the 51 patients enrolled in the study was lost to follow-up. Among the remaining 50 patients, 25 were in the iron-only group, and 25 were in the L-T₄-plus-iron group. There were 22 men and 3 women in each group, with a mean age of 38 years (range, 27 to 50) and 35 (range, 29 to 55) in the iron group and L-T₄-plus-iron group, respectively. Baseline laboratory values were similar in the two groups. Patients did not have physical findings of hypothyroidism, and all but one patient reported no symptoms related to the anemia. There was no significant difference in the presence of serum antithyroid peroxidase or antithyroglobulin antibodies between the two groups. The two groups were similar in baseline hematologic status and thyroid-function indexes. Baseline mean (±SD) Hb was 10.4±1.58 and 12.9±0.93 g/dl, mean Hct 31.9±4.7 and 31.9±4.7%, mean RBC count 3.9±0.66 and 3.27±2.77 10⁶ cells/μL, and mean serum TSH 6.5±1.24 and 7.4±1.65 μIU/ml in the iron-only group and L-T₄-plus-iron group, respectively (P = nonsignificant for all). There were no adverse effects of treatment in either group. Mean Hb increased by 0.4 in the iron-only group and by 1.9 g/dl in the L-T₄-plus-iron group (P<0.0001). Likewise, the change in RBCs, Hct, iron, transferrin saturation, ferritin, and FT₄ were significantly





higher in the L-T₄-plus-iron group than in the iron-only group. The decrease in TIBC and TSH after treatment was greater in the L-T₄-plus-iron group than in the iron-only group. There was a significant negative correlation between baseline Hb and the change in Hb in the L-T₄-plus-iron group, such that the more anemic patients were observed to have a greater hematologic response to the L-T₄-plus-iron than patients with higher starting Hb levels (Figures 2 and 3). Serum TSH normalized in 23 of the patients in the L-T₄-plus-iron group, and was reduced in 2.

CONCLUSION Iron deficiency anemia in patients with subclinical hypothyroidism benefits substantially by the addition of low-dose L-T₄ to iron replacement, which yields greater improvement in hematologic parameters than iron replacement alone. Subclinical hypothyroidism should be treated in patients with iron deficiency anemia when the two conditions coexist. This would provide a desired therapeutic response to oral iron replacement and prevent ineffective iron therapy.

COMMENTARY

Subclinical hypothyroidism is a common endocrine disorder, affecting approximately 4.3% of the U.S. population (3). Significant controversy exists as to whether this condition should be treated with L-T₄ replacement therapy or simply followed expectantly until the development of overt hypothyroidism (4,5). This study by Cinemre et al. makes an argument in favor of early treatment for a subset of patients with SH. This is the first study to examine the effect of L-T₄ used jointly with iron supplementation on the hematologic parameters of patients with SH and iron deficiency anemia. It is interesting to note that FeSO₄ has been shown to bind to and reduce the efficacy of L-T₄ when the medications are taken simultaneously (6). In spite of this well-recognized drug-drug interaction, the patients in the combination group had significant improvements in their TSH after 3 months of treatment. In addition, the combined intervention revealed significant improvement in levels of Hb over iron therapy alone, rendering the majority of patients euthyroid while simultaneously reversing the anemia. In fact, patients on combined therapy with the worse anemia achieved higher gains in Hb than patients with milder hematologic deficiencies within the same group. The majority of patients in the iron-only group also had significant improvements in Hb but they remained anemic upon completion of the trial.

An earlier study (7) found no change in Hb/Hct in patients with SH after 48 weeks of L-T₄ therapy. Erythropoietin levels did increase, however. It is important to note that these patients were not anemic upon study entry, and as seen in the study by Cinemre et al., the greatest gains in Hb were made by those with lower baseline levels. It is thus conceivable that patients with a normal Hb at baseline would not see significant change in this particular hematologic parameter after L-T₄ therapy. The fact that the erythropoietin levels increased further supports the notion of a close association between thyroid dysfunction and hematopoiesis, though the exact mechanism of this relationship is not known. A recent study (8) showed that patients with subclinical hypothyroidism had significantly lower serum iron levels than euthyroid controls and L-T₄ replacement alone resulted in reversal of the iron deficiency. Taken together, these three studies suggest that iron deficiency and anemia are common among patients with subclinical hypothyroidism. Furthermore, treatment of the underlying thyroid disorder improves the hematologic profile. Though anemia is not identified as a potential consequence of untreated SH in the treatment guidelines (4,5), this study by Cinemre et al. expertly draws attention to this very important issue.

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