

Anemia in Graves' disease is common and resembles the anemia of chronic disease

Gianoukakis AG, Leigh MJ, Richards P, Christenson PD, Hakimian A, Fu P, Niihara Y, Smith TJ. Characterization of the anaemia associated with Graves' disease. Clin Endocrinol (Oxf) 2009;70:781-7.

SUMMARY

BACKGROUND Anemia sometimes develops in patients with Graves' disease; the cause of this anemia is uncertain. The aim of this study was to define the prevalence and characteristics of anemia associated with Graves' disease.

METHODS The study subjects were patients with newly diagnosed Graves' disease treated in the Endocrine Clinic at Harbor-UCLA Medical Center. A total of 98 patients were initially recruited for the study if they had anemia based on standard clinical and laboratory criteria and were already being treated with β -blockers. Patients who had been treated with thionamides or corticosteroids were excluded from the study, as were patients who had silent thyroiditis, were euthyroid, or did not have a complete blood count. The remaining 87 patients comprise the study group, which was then divided into two groups: those with anemia (group A) and those without anemia (group B). Ten women and 9 men without hyperthyroidism or any known autoimmune disease were randomly recruited from the primary care clinic to serve as controls (Figure 1).

RESULTS A total of 31 patients (36%) were in group A, and 56 (64%) were in group B. There were 12 men and 19 women in group A and 12 men and 44 women in group B (Figure 2). The mean age was 37 years (range, 19 to 53) in group A and 36 (range, 19 to 63) in group B. Of the 87 patients in the study group with Graves' disease, 64 (74%) were sequentially removed from the study group to form another cohort to establish the prevalence of anemia within the study population; 45 of this group (70.3%) were women with a mean (\pm SD) age of 37.5 ± 11.3 years, 21 of whom (33%) had anemia, with a hemoglobin (Hgb) level below the lower reference limits of 11.9 to 14.9 for women and 13.9 to 16.9 for men (Figure 1). Of the 21 patients with anemia and Graves' disease, a secondary

cause of anemia was established in 7 (33%). As a result, the prevalence of anemia with no cause other than Graves' disease was 14 of 64 patients (21.9%; 95% confidence interval [CI], 12.5 to 34%) (Figure 1). Graves' disease with anemia affected 10 of 24 men (41.6%), as compared with 11 of 63 women (17.5%) (Figure 1).

Of the 21 patients with Graves' anemia, mean erythropoietin (EPO) levels were 15.5 ± 5.3 mIU/ml, which was within normal reference limits (4.1 to 19.5 mIU/ml) as compared with 11.4 ± 5 mIU/ml in the non-Graves' anemia patients ($P = 0.004$) (Figure 3). With

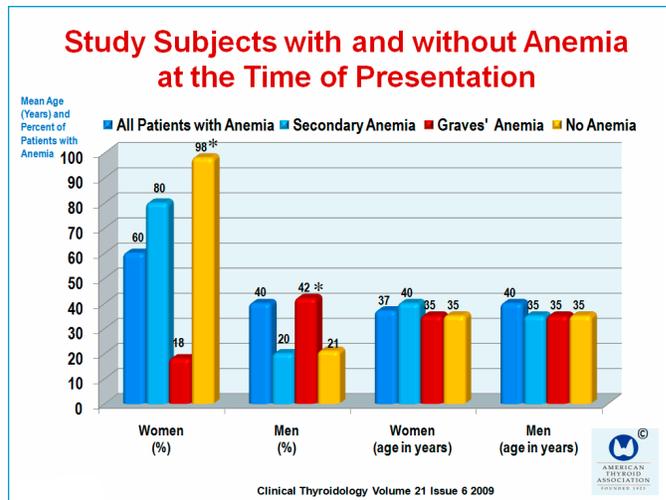


Figure 2. Women were more likely than men (98% vs. 21%) to have anemia. Most of the women in the study were in mid-life.

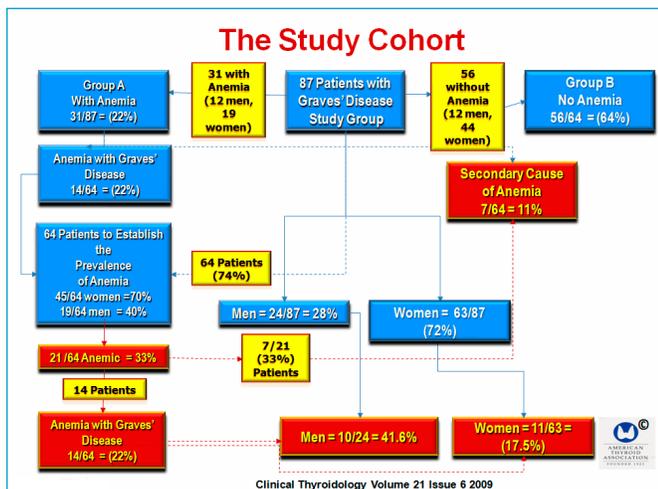


Figure 1. The study cohort comprised patients with Graves' disease and anemia and patients with Graves' disease and secondary causes of anemia. A greater percentage of men (41.6%) than women (17.5%) had anemia with Graves' disease. This figure shows the flow of the study.

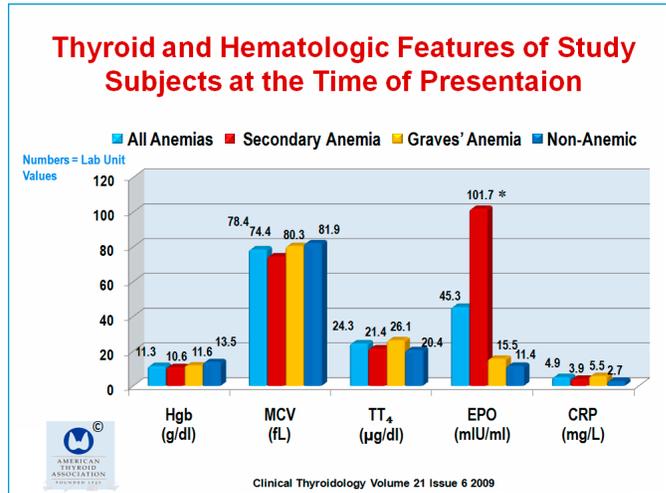


Figure 3. Hemoglobin (Hgb), mean corpuscular volume (MCV), total thyroxine (TT₄), C-reactive protein (CRP), and erythropoietin (EPO) levels are shown in patients with Graves' anemia, in those with secondary anemias, and in patients without anemia * $P < 0.005$ comparing EPO levels with secondary anemia and Graves' disease with anemia. fL = femtoliter

Change in Hematologic Parameters during Restoration of Euthyroidism (1)

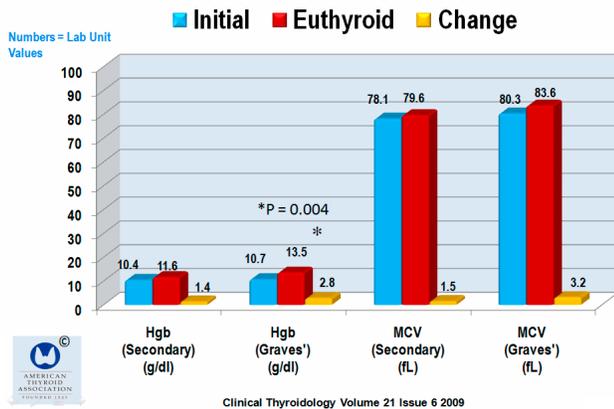


Figure 4. This figure shows the change in hematologic parameters during restoration of euthyroidism. Hgb = hemoglobin; MCV = mean corpuscular volume.

antithyroid therapy for 16 ± 6.3 weeks, Hgb levels became normal in 8 of 9 patients (89%) with Graves' disease and anemia (10.7 ± 0.8 to 13.5 ± 1.3 g/dl, $P = 0.0001$) (Figure 4). After the Hgb returned to normal, mean corpuscular volume (MCV) and total iron-binding capacity (TIBC) increased significantly, and median ferritin and mean erythropoietin (EPO) decreased significantly (Figure 4). C-reactive protein (CRP) and ferritin, which are markers of inflammation, were not significantly higher in group A than in group B ($P = 0.09$). Total T_4 (TT_4) and total T_3 (TT_3) were not significantly correlated with Hgb levels; however, Hgb correlated inversely with CRP, and remained so after multivariate analysis, but not with ferritin levels. TIBC correlated positively with Hgb ($P = 0.0005$), while EPO levels correlated inversely with Hgb ($P = 0.05$). After patients with Graves' anemia had a significant increase in their Hgb, mean MCV, and TIBC levels, median ferritin, and mean EPO levels decreased significantly ($P = 0.0004$, 0.02 , 0.03 , and 0.04 , respectively) (Figure 5).

COMMENTARY

This study by Gianoukakis et al. of anemia in 87 patients with newly diagnosed Graves' disease found that 33% had anemia. However, about one third had secondary causes of anemia that were not due to Graves' disease. Most patients suffering from chronic infections, inflammatory diseases, and some malignancies have a mild to moderate anemia termed anemia of chronic disease or anemia of inflammation. Patients with this type of anemia generally have low serum iron, low to normal transferrin, and high to normal serum ferritin concentrations. The anemia is caused by increased inflammatory cytokines, especially interleukin-6 (1).

In a study by Das et al. (2) the bone marrow showed erythroid hyperplasia in all patients with hyperthyroidism. The authors postulated that thyroid hormones stimulate erythropoiesis, sometimes leading to erythrocytosis, provided there is no deficiency of hematopoietic nutrients.

Change in Hematologic Parameters during Restoration of Euthyroidism (2)

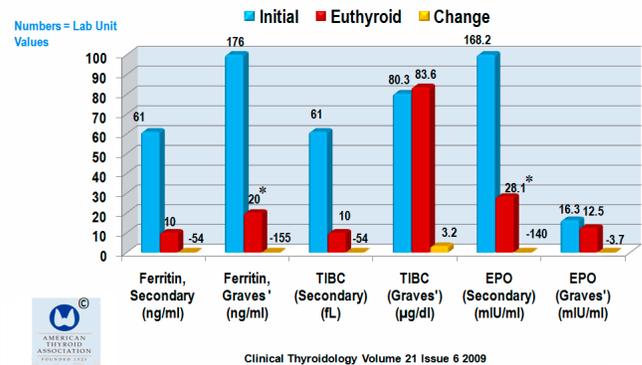


Figure 5. The levels of ferritin and total iron-binding capacity (TIBC) and erythropoietin (EPO) were significantly elevated after patients with anemia and Graves' disease were treated with antithyroid drugs or radioiodine.

With antithyroid therapy for 16 ± 6.3 weeks, Hgb levels became normal in 8 of 9 patients with Graves' anemia, increasing from 10.7 ± 0.8 to 13.5 ± 1.3 g/dl ($P = 0.0001$) (Figure 4). In patients with Graves' disease without anemia, there was a small but statistically significant increase in Hgb (0.36 ± 0.9 g/dl, $P = 0.02$) and MCV. The TT_4 and TT_3 levels correlated with an increasing Hgb in patients with Graves' disease anemia and patients with anemia of other causes. In addition, a similar inverse correlation existed between changes in Hgb and EPO levels ($P = 0.04$) (Figure 5). There was no correlation between changes in Hgb and CRP levels. Patients treated with 2.5 to 40 mg of methimazole or 50 to 600 mg of propylthiouracil did not experience worsening hematologic parameters.

CONCLUSION Anemia in Graves' disease is common and resembles the anemia of chronic disease.

In a study of 239 patients with uncomplicated hyperthyroidism, Nightingale et al. (3) found that the hemoglobin concentration was less than 12.0 g/dl in 37 (18%) of 207 women and less than 13.0 g/dl in 9 of 32 (28%) of men. Although some of the patients had iron deficiency, many did not. After treatment, the hemoglobin increased by an average of 0.5 g/dl in patients who had not had anemia at the time of diagnosis. The authors concluded that a small decline in hemoglobin is usual in hyperthyroidism and may sometimes be sufficient to cause a mild anemia. There was a reduction in MCV in patients with hyperthyroidism who had neither anemia nor reduced transferrin saturation. After treatment of hyperthyroidism, the MCV increased an average of 6 fl. Thus, a reduction in MCV, even within the normal range, is a common finding in hyperthyroidism.

Gianoukakis et al. found that with antithyroid therapy, the Hgb levels returned to normal in 8 of 9 patients, with Graves' disease anemia, and mean MCV and TIBC increased significantly, while median

ferritin and mean EPO decreased significantly. Hgb correlated inversely with CRP and remained so after multivariate analysis with adjustment for TT_3 or TT_4 . Although men comprised only 28% of the cohort, Graves' disease anemia affected 41.6% of men as compared with 17.5% of women. While this seems somewhat counterintuitive, others have also found this to be the case (3).

Still, despite the erythropoietic effects of thyroid hormone, most patients with thyrotoxicosis have normal levels of Hgb. Gianoukakis et al. postulate that the approximately 6% increase in blood volume that occurs in hyperthyroidism may

serve to partially counterbalance the erythropoiesis induced by thyrotoxicosis. Why anemia develops in a subgroup of patients is not known. Although some patients with Graves' disease have vitamin B12 deficiency, the authors of this study did not find a secondary cause for the anemia. Nonetheless, Gianoukakis et al. detected a slight but significant ($P < 0.01$) increase in the levels of Hgb after improvement of hyperthyroidism in the group without anemia. Others have made similar observations, suggesting that thyrotoxicosis routinely decreases Hgb levels (3,4).

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