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Characterization of the anemia associated with Graves' disease

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SUMMARY

Background—Graves' disease (GD) is associated with hyperthyroidism. Thyrotoxicosis adversely affects multiple organ systems including hematopoiesis. Anemia occurring specifically in GD has not been systematically studied previously.

Objective—To define the prevalence and characteristics of the anemia associated with GD.

Design—Eighty Seven newly diagnosed patients with GD were recruited. Hematologic indices, thyroid function and inflammatory parameters were examined at presentation and following successful treatment.

Setting—Tertiary care academic referral center.

Results—Thirty three percent of subjects presented with anemia. The prevalence of anemia not attributable to other causes (GD anemia) was 22%. GD anemia affected 41.6% (10/24) of men compared to 17.5% of women (11/63). Mean EPO levels (15.5 ± 5.3 mIU/ml) were within normal reference limits but significantly higher ($P=0.004$) than those of the non-anemic controls. Hgb correlated inversely with EPO ($P=0.05$) and CRP ($P=0.04$) levels, a relationship that persisted after multivariate adjustment for TT3 or TT4. With antithyroid therapy for 16 ± 6.3 weeks, Hgb levels normalized in 8/9 subjects with GD anemia (10.7 ± 0.8 g/dl to 13.5 ± 1.3 g/dl, $P=0.0001$). After correction of Hgb, mean MCV and TIBC were significantly increased and median ferritin and mean Epo were significantly decreased.

Conclusions—GD anemia is common, resembles the anemia of chronic disease and is associated with markers of inflammation. It corrects promptly with the return to the euthyroid state following treatment.

Keywords

anemia; autoimmune; Graves' disease; thyrotoxicosis

INTRODUCTION

Graves' disease (GD) is an autoimmune disease associated with hyperthyroidism. Its prevalence is estimated to be 2.5% among women and 0.23% among men¹. Both thyrotoxicosis and the underlying autoimmunity of GD affect multiple tissues and their functions, including hematopoiesis^{2,3}. An association between thyrotoxicosis and anemia has been reported previously but the mechanisms involved remain poorly understood.

Alterations in erythrocytes purported in thyrotoxicosis are sometimes contradictory and include increased erythropoiesis and red cell mass, abnormal iron incorporation, 2,3-DPG levels, Hgb, shortened erythrocyte survival, and ineffective iron utilization^{2,3}. Anemia associated specifically with GD has not been studied previously in a prospective manner utilizing a large cohort. Anemia associated with chronic disease or inflammation is commonly seen in malignant, infectious, and autoimmune conditions⁴. It can occur within days of illness onset and its pathogenesis may result from the actions of cytokines⁵. Ford and Carter suggested that the hematologic changes associated with thyrotoxicosis might relate to the underlying immunologic disturbance in GD².

Here we report a novel study that for the first time examines in a prospective and adequately powered manner the prevalence of anemia in subjects newly diagnosed with GD, including kinetics of its reversal following resolution of thyrotoxicosis. Our findings disclose that the anemia is not only related to thyroid hormone excess but is also associated with markers of inflammation.

METHODS

Study subjects

Patients who presented to the endocrine clinic at Harbor-UCLA Medical Center with newly diagnosed GD were enrolled after obtaining informed consent, as approved by the Institutional Review Board. The diagnosis was established on the basis of standard clinical and laboratory criteria. Subjects were included if they were already treated with β -blockers but were excluded if thionamides or corticosteroid therapy had been initiated. Ninety-eight patients were prospectively screened and enrolled. Of these 98 subjects, 1 patient manifested “silent” thyroiditis, 2 were euthyroid, and 8 failed to undergo a complete blood count (CBC) and were therefore excluded. The remaining 87 subjects comprise the study group. Of these 87 subjects, 64 were unselected, and newly diagnosed with GD who presented consecutively. The remaining 23 subjects were selected because they were newly-diagnosed with the combination of GD and anemia. The study group was divided into those presenting with anemia (Group A) and those with normal RBC mass (Group B). Table 1 contains patient characteristics at presentation. Euthyroidism was achieved with thionamide therapy alone or in combination with radioactive iodine treatment or surgical thyroidectomy followed by thyroid hormone replacement. A group of control subjects (10 females and 9 males) without hyperthyroidism or any known autoimmune disease, presented for a routine health visit. They were randomly recruited from the primary care clinic, and were utilized for comparison of hematologic parameters with those of patients with GD.

Laboratory investigation

C-reactive protein (CRP) levels were measured using the ROCHE COBAS MIRA S analyzer and CRP reagent kit (Cat.# 999-27001) and calibrator set (Cat.# 997-27041) from Wako Chemicals (Richmond, VA). Erythropoietin (EPO) levels were measured by Quest Diagnostics (San Juan Capistrano, CA) utilizing a chemiluminescent immunoassay by Diagnostic Product Corporation (Los Angeles, CA).

Statistical analysis

All continuous measurements except ferritin are summarized as mean $\pm$ standard deviation and compared between groups with 2-sided t-tests. Due to its skewed distribution, ferritin is summarized with quartiles and compared between groups with Kruskal-Wallis tests. Percentages are compared between groups with Fisher’s exact tests. Pearson correlations are used to measure associations between continuous measurements. Multivariate adjustment for group differences in means and for correlations is made using multiple regression. Due

to skewness in some measures, non-parametric Spearman correlations were also calculated and provided the same conclusions as Pearson correlations. A data analysis plan, including statistical methods and specification of all measurements to be examined was developed prior to data analysis. All of these are included in this report. A 0.05 level of significance is used without mathematical correction for multiple comparisons. The study includes a sufficient number of subjects to provide (1) a margin of error on the estimate of prevalence of anemia in GD patients to be no greater than $\pm 15\%$, and (2) 80% power to detect a shift in the distribution of any characteristic in anemia patients that is at least 15% of the reference range for non-anemic GD patients.

RESULTS

Prevalence of anemia at presentation

Of the 87 GD subjects comprising the study group, 64 were unselected and consecutively enrolled and are used to establish the prevalence of anemia in our population. Forty-five of 64 (70.3%) subjects were female with a mean age of 37.5 ± 11.3 yr (mean $\pm$ SD). Twenty-one of 64 (33%) were anemic. The diagnosis of anemia was established based on Hgb levels below the lower limit of the reference range for our assay (females 11.9-14.9 /dl, males 13.9-16.9 g/dl). Of these 21 subjects, a secondary cause of anemia could be established in 7 patients. Therefore, the prevalence of anemia without an obvious secondary cause (GD anemia) was 14/64 (21.9% [95% CI: 12.5% to 34.0%]).

Characterization of anemia at presentation

Thirty-one patients presented with anemia, having a mean Hgb of 11.3 ± 1.2 g/dl. Another cause could be identified in 10 of these 31 patients. Seven were iron-deficient, 1 carried the diagnosis of thalassemia minor, 1 with hereditary hemochromatosis, and another with coincident rheumatoid arthritis and anemia of chronic disease. We focused on the 21 subjects with GD anemia (Hgb 11.6 ± 1.2 g/dl) (Table 2) in which no other cause could be identified by history, physical exam, blood chemistries, or hematologic assessment. The mean MCV was $80.3 \text{ fL} \pm 3.8$, slightly below the lower limits of normal (females < 81.5 , males < 82.2 fL). Median ferritin, mean TIBC, and EPO levels (15.5 ± 5.3 mIU/ml, reference range 4.1-19.5 mIU/ml) were within normal reference limits. However, these EPO levels are inappropriately low for subjects with anemia. By comparison, anemic patients with a secondary cause ($n=10$) presented with a Hgb of 10.6 ± 1.0 g/dl, MCV $74.4 \text{ fL} \pm 12.1$, median ferritin 14 ng/ml, TIBC $366 \mu\text{g/dl} \pm 115.3$ and EPO $101.7 \text{ mIU/ml} \pm 203.1$ (Table 2). Interestingly, while 80% (8/10) of patients presenting with secondary anemia were female, the distribution of males and females was nearly equivalent among those with GD anemia (48% vs 52%). Males comprised only 28% (24/87) of the overall cohort. Thus GD anemia affected 41.6% (10/24) of men presenting with autoimmune hyperthyroidism compared to 17.5% of women (11/63). The 56 patients from Group B who presented without anemia exhibited Hgb concentrations of 13.5 ± 1.0 g/dl while MCV, TIBC, ferritin and EPO levels were within normal limits (Table 2).

We next compared the 21 GD anemic patients with those 56 without anemia with regard to MCV, ferritin, TIBC and EPO levels (Table 2). While mean MCV did not differ between the two groups, those presenting with GD anemia exhibited significantly lower mean TIBC ($p < 0.0001$) and higher mean EPO ($P = 0.004$) levels. Interestingly, the GD anemia group exhibited marginally higher ferritin levels, although not achieving statistical significance ($P = 0.09$).

Correlation of GD anemia at presentation with thyroid hormone, anti-thyroid Ab, and inflammatory marker levels

When comparing thyroid hormone levels and anti-thyroid Ab status [anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-TG), thyroid stimulating immunoglobulin (TSI)] in the two groups, GD anemic and non-anemic subjects differed only with regard to TT4 ($26.1 \pm 9.6 \mu\text{g/dl}$ vs $20.4 \pm 7.6 \mu\text{g/dl}$, $P=0.02$), as shown in Table 2.

We then examined CRP and ferritin, markers of inflammation, in the two groups. Mean CRP ($5.5 \pm 5.6 \text{ mg/dl}$ vs $2.7 \pm 4.9 \text{ mg/dl}$) and median ferritin levels (133 vs. 87) were substantially but not significantly higher in the GD anemic group ($P=0.07$ and $P=0.09$ respectively, Table 2). Since no correlation was observed between CRP and thyroid hormone levels ($P>0.85$), group differences for CRP were essentially unchanged in multivariate analyses that adjusted for T3 ($P=0.04$) or for TT4 ($P=0.08$).

Correlation at presentation of Hgb with thyroid hormone, anti-thyroid Ab, and inflammatory marker levels

TT4, TT3, and CRP levels as well as the presence of anti-thyroid Abs were also examined for associations with levels of Hgb in the combined group of GD anemic and non-anemic subjects (Table 3). TT4 and TT3 levels at presentation were not significantly correlated with Hgb levels (Table 3, Fig. 1A). Hgb correlated inversely with CRP (Table 3, Fig. 1B) and remained so after multivariate adjustment for TT3 or TT4, but Hgb was not correlated with ferritin levels (Table 3). TIBC correlated positively ($P=0.0005$) while EPO levels correlated inversely ($P=0.05$) and this relationship remained essentially unchanged after multivariate adjustment for TT3 ($P=0.004$ and $P=0.05$, respectively) and TT4 ($P=0.01$ and $P=0.06$, respectively). The presence of anti-thyroid Abs (anti-TPO, anti-TG and TSI) failed to correlate with Hgb levels at presentation (data not shown).

Impact of restoration to the euthyroid state on hematologic parameters

Hematologic parameters were examined at the time subjects first became euthyroid, as was established by normalization of TT4 and/or TT3. Fourteen previously anemic (9 with GD anemia and 5 with a secondary cause) subjects who became euthyroid within 26 weeks of initial presentation and 36 non-anemic patients were included in this analysis. Of the 14 anemic subjects, 10 were treated with anti-thyroid medications alone while 4 received radioactive iodine in addition. Subjects received no additional therapy for their anemia. Interestingly, Hgb levels normalized in 8/9 subjects with GD anemia ($10.7 \pm 0.8 \text{ g/dl}$ to $13.5 \pm 1.3 \text{ g/dl}$, $P=0.0001$). The mean Hgb level achieved post euthyroidism in these 8 subjects (7 female, 1 male) was $13.6 \pm 0.73 \text{ g/dl}$ for females and 15.5 g/dl in the male. These levels are comparable to those found in control subjects without hyperthyroidism or autoimmune disease [$13.8 \pm 0.65 \text{ g/dl}$, range= 12.6 - 14.8 g/dl (females), $15.2 \pm 1.08 \text{ g/dl}$, range= 13.6 - 16.9 g/dl (males)]. Hgb levels increased more modestly in the 5 subjects with secondary cause-associated anemia, changes that failed to reach statistical significance ($10.4 \pm 1.3 \text{ g/dl}$ to $11.6 \pm 1.9 \text{ g/dl}$ $P=0.08$) (Table 4). In contrast to those with GD anemia, those with secondary anemia failed to correct (8/9 vs 0/5, $P=0.003$). After GD anemia subjects increased their Hgb, their mean MCV and TIBC were significantly increased and their median ferritin and mean Epo were significantly decreased (Table 4). Hemograms were also performed on 36 non-anemic patients once they became euthyroid. Compared to those with GD anemia, the non-anemic subjects manifested a small but statistically significant increase in Hgb ($0.36 \pm 0.9 \text{ g/dl}$ $P=0.02$) and MCV ($3.97 \pm 3.2 \text{ fL}$ $p<0.0001$) (Table 4). Decreasing TT4 and TT3 levels following treatment correlated with increasing Hgb in the combined group of GD anemic and non-anemic subjects (Table 4, Fig 2A). A similar inverse correlation existed between changes in Hgb and EPO levels ($r=-0.48$, $P=0.04$). TT4 and TT3 levels were coupled to those of Hgb over short time intervals. Intermittently

compliant subjects exhibited excursions in their Hgb levels coinciding with changing TT3 levels (Figure 3).

No correlation was found between changes in Hgb and changes in CRP levels (Fig. 2B). Note in Fig 2B that although the 5 GD anemic subjects exhibited a remarkably strong association, only the patient with the greatest Hgb increase showed substantial CRP decrease. One non-anemic subject had an anomalous CRP of 31 mg/dl at presentation.

Treatment with antithyroid drugs

Thirty patients with anemia at presentation received antithyroid medication. They received either methimazole or propylthiouracil, with daily doses ranging from 2.5-40 mg and 50-600 mg, respectively. In none of these patients did either drug worsen hematologic parameters. CBC's were available for 14 previously anemic patients who had achieved euthyroidy. Mean Hgb improved from 10.6 g/dl $\pm$ 1.0 to 12.8 g/dl $\pm$ 1.8 ($P=0.0001$). Only 1/14 of these patients exhibited worsening of their anemia (0.8 decrease in Hgb) while treated with anti-thyroid medication.

DISCUSSION

Here we studied 87 newly diagnosed patients with GD and found the overall prevalence of anemia to be 33%, a finding congruent with previous reports⁶⁻⁸. These earlier studies included hyperthyroidism from several different etiologies and were either small or retrospective. GD is substantially more frequent among females of childbearing age. Our cohort reflects this gender and age distribution. Interestingly, and for unclear reasons, men presented more frequently with GD anemia among our study subjects. GD anemia resembled that associated with chronic disease. Normalization of Hgb following treatment of thyrotoxicosis was accompanied by increases in MCV and TIBC while ferritin and EPO levels decreased. This correction occurred within a median of 16 weeks from initiation of anti-thyroid therapy and correlated with normalizing TT4, TT3 and TSH levels. GD anemia corrected in 8/9 (89%) patients but in none of those with secondary anemia. Agranulocytosis and pancytopenia can complicate thionamide therapy^{9, 10}. Fourteen anemic subjects in this study were treated with thionamides. After correction of hyperthyroidism, Hgb levels improved in all but one. Thus, thionamides may be safely administered to patients presenting with anemia and autoimmune hyperthyroidism with periodic monitoring of CBC.

Thyroid hormone stimulates erythropoiesis leading to marrow erythroid hyperplasia and an increased red cell mass^{2, 3}. The mechanisms underlying these actions remain unclear but evidence for both direct¹¹ and indirect effects on erythroid precursors^{12, 13} have been reported. The hormones may increase Epo levels directly¹³ or through increased oxygen demand². Das *et al* studied 21 patients with hyperthyroidism of which 5 were anemic⁶. The authors found increased erythropoiesis with erythrocytosis and elevated serum Epo levels in these patients. They concluded that Epo provoked these effects. However, in a rodent model, both LT3 and its calorigenically inactive isomer, DT3, increased erythrocyte iron utilization while only LT3 stimulated oxygen consumption¹⁴. Thus, the calorigenic and erythropoietic actions of thyroid hormone may be uncoupled. Thyroxine promotes heme synthesis and degradation in liver,¹⁵⁻¹⁸. It shifts the Hgb dissociation curve to the right², facilitating tissue oxygen delivery, suggesting that a secondary elevation of Epo may not represent the sole compensatory mechanism. In our study, patients with GD anemia presented with Epo levels within the normal range (Table 2). These were reduced following correction of thyrotoxicosis and correlated inversely with increasing Hgb levels. Thus, relatively modest changes in Epo levels which remain within the normal range might impose biologically important consequences in red cell mass. Another indirect effect of thyroid hormone on erythropoiesis is mediated through release of erythroid specific stimulating factors from

mononuclear cells¹². T4 may also act directly on erythrocyte precursors through a receptor with β 2-adrenergic properties that can be blocked by β -blockers^{19, 20}. At the time of enrollment, approximately 50% of non-anemic and 76% of anemic patients in our cohort were treated with β -blockers. It is possible that these agents might have played some role in their development of anemia. Another finding of interest was the higher CRP level associated with GD anemia and with lower Hgb levels at presentation. While the implications of this finding to the underlying pathogenesis of GD anemia remain uncertain, it suggests the possibility that some aspect of the inflammation driving the thyroid disease may also influence erythropoiesis in addition to the effects of thyrotoxicosis.

Despite the erythropoietic effects of thyroid hormone, most patients with thyrotoxicosis present with normal levels of Hgb. Blood volume is increased in hyperthyroidism by approximately 6%²¹ and this may serve to partially counterbalance the erythropoiesis induced by thyrotoxicosis. Furthermore, red cell life span may be shortened^{2, 3, 22} and some thyrotoxic patients may exhibit ineffective erythropoiesis^{23, 24}. Thyroxine may also influence iron incorporation into red cells but previous findings conflict^{14, 23, 24}. Why a subset of patients with hyperthyroidism, as in our cohort, should develop anemia is not understood. Some authors have suggested a “suppressive effect”^{8, 25} of supra-physiologic doses of thyroid hormone on erythropoiesis. Others have postulated a contribution of secondary causes⁶ including autoimmune associated vitamin B12 and iron deficiency²⁶. In our cohort only 10/31 (32.3%) anemic GD patients exhibited a secondary cause. Rivlin *et al* suggested that anemia occurred more frequently in patients whose hyperthyroidism was unusually severe or protracted²⁴, while Axelrod and colleagues found no such relationship²⁷. We did not observe a correlation between degree of hyperthyroidism and Hgb that ranged over normal and anemic levels, but newly diagnosed GD anemic subjects did present with higher mean TT4 than non-anemic subjects. It remains possible that thyrotoxicosis uniformly decreases Hgb in all subjects but relatively few become anemic. Nightingale *et. al.* found that Hgb levels of 131 non-anemic hyperthyroid patients increased 0.5g/dl ($P<0.01$) after up to 4 years following treatment⁷. Similarly, J. How *et. al.* reported a 0.68 g/dl ($p<0.01$) increase in 44 non-anemic hyperthyroid females after therapy²⁸. We too detected a significant Hgb increase of 0.36g/dl after correction of hyperthyroidism in our non-anemic cohort.

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Fig 1. Correlation between Hgb and TT4, TT3 and CRP levels at presentation

Scatter plot 1A displays the Pearson correlation (Spearman correlation= -0.19 , $P=0.12$) between Hgb and TT4 levels [TT3 in insert] in GD anemic ($\diamond$) and non-anemic ($\blacksquare$) subjects. The Pearson correlation between Hgb and CRP levels in these subjects is displayed in scatter plot 1B. [Spearman correlation= -0.38 , $P=.002$].

Fig 2. Correlation between changes in Hgb and TT4, TT3 and CRP levels following successful therapy

Scatter plot 2A displays the Pearson correlation (Spearman correlation= -0.42, $P=0.02$) between change (delta) in Hgb and TT4 levels [T3 in insert] of GD anemic (◇) and non-anemic (■) subjects. Scatter plot B displays the Pearson correlation (Spearman correlation= 0.25, $P=0.20$) between change (delta) in Hgb and CRP levels in these subjects.

Fig 3. Hgb levels correlate inversely with thyroid hormone levels

Panel A and B contain data from two newly diagnosed subjects presenting with GD anemia. The Hgb and TT3 levels are plotted along the ordinate and time (weeks) along the abscissa. TT3 levels fluctuated widely in these subjects as a consequence of intermittent compliance and were mirrored by coincident changes in Hgb.

Table 1

Patient characteristics

	N=87	
	Group A (Anemic)	Group B (Non-Anemic)
N (%)	31 (36)	56 (64)
Sex:		
Male	12	12
Female	19	44
Mean age (yr) (range)	37 (19-53)	36 (19-63)

Table 2

Thyroid and hematologic parameters of study subjects at presentation

	Anemic		Non-Anemic	[†] P-value
	All	Anemia with 2 nd cause	GD Anemia	
N	31	10	21	56
Age	37	40	35	35
mean (range)	(19-53)	(20-50)	(19-53)	(19-63)
Sex: Male	12	2	10	12
Female	19	8	11	44
Mean±SD				
Hgb (g/dl)	11.3±1.2	10.6±1.0	11.6±1.2	13.5±1.0
MCV (fL)	78.4±7.8	74.4±12.1	80.3±3.8	81.9±5.3
Ferritin (11-306ng/ml)[*]	90 (35-219)	14 (4-84)	133 (77-293)	87 (43-193)
TIBC (245-400µg/dl)	308±88.6	366.1±115.3	277.7±52.1	349±58
EPO (4.1-19.5 mIU/ml)	45.3±122.5	101.7±203.1	15.5±5.3	11.4±5
TT4 (6.1-12.2 µg/dl)	24.3±8.6	21.4±5.9	26.1±9.6	20.4±7.6
TT3 (79-149 ng/dl)	557±315	479±266	606±341	497±275
CRP (0.5-3.0 mg/L)	4.9±5.5	3.9±5.3	5.5±5.6	2.7±4.9
% positive				
TSIG (%+)	26/29=90%	8/10=80%	18/19=95%	45/55=82%
Anti-TPO (IU/ml)	26/29=90%	9/10=90%	17/19=89%	50/54=93%
Anti-Tg (IU/ml)	22/29=76%	8/10=80%	14/19=74%	28/51=55%
				0.18

[†] Comparison between GD anemic and Non-Anemic subjects^{*} Median (1st – 3rd Quartiles)

Table 3

Correlation of Hgb levels with other parameters at presentation

	GD Anemia and Non-Anemic			P-value
	N	Range	Correlation	
TT4	67	7.1 – 49.3	-0.19	0.11
TT3	66	59.2 – 1282	-0.05	0.67
Ferritin	70	12.1 – 1085	-0.09	0.45
CRP	64	0.12 – 31.3	-0.26	0.04
EPO	73	3.4 – 57.0	-0.23	0.05
TIBC	70	201 – 489	0.40	0.0005

Table 4

Change in hematologic parameters during restoration of euthyroid state

	Anemia with 2 nd cause	GD Anemia	[†] <i>P</i> -value	Non-Anemic
N	5	9		36
Weeks	13.4±4	16±6.3	0.43	
Hgb (g/dl)				
Initial	10.4±1.3	10.7±0.8		13.3±1.0
Euthyroid	11.6±1.9	13.5±1.3		13.7±0.4
Change	1.4±1.3	2.8±1.3	0.07	0.36±0.9
MCV (fL)				
Initial	78.1±15.6	80.3±2.9		81.3±4.4
Euthyroid	79.6±16.2	83.6±3.9		85.2±4.4
Change	1.5±2.9	3.2±1.9	0.19	4.0 ±3.2
Ferritin (ng/ml) *				
Initial	61 (17-593)	176 (114-450)		
Euthyroid	10 (7-431)	20 (14-28)		
Change	-54 (-165- -8)	-155 (-426- -98)	0.14	
TIBC (µg/dl)				
Initial	296±86.1	247.6±49.8		
Euthyroid	410.3±124.5	328.3±67.3		
Change	114.3±49.2	96.8±71.7	0.72	
EPO (mIU/ml)				
Initial	168.2±284.1	16.3±5.2		
Euthyroid	28.1±13.3	12.5±5.8		
Change	-140.1±282.8	-3.7±4.3	0.33	
Hgb normalization	0/5 =0%	8/9 =89%	0.003	

With the exception of ferritin, results are expressed as mean±SD

* Median (1st – 3rd Quartiles)[†] Comparison between GD anemia and anemia with secondary cause

Table 5

Correlation of Hgb change to change in other parameters during restoration of euthyroid state.

	GD Anemia and Non-Anemia		
	N	Range	Correlation / P-value
TT4	31	-33.4 to 1.8	-0.46/0.01
TT3	30	-1166 to 12.8	-0.38/0.04
Ferritin	7	-544 to -50.8	-0.31/0.49
CRP	28	-26 to 15.4	0.09/0.66
EPO	19	-13.2 to 16.4	-0.48/0.04
TIBC	7	-103 to 185	0.75/0.05