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Evaluation of Anemia Frequency and Types in Patients with Subclinical and Clinical Hypothyroidism in the Endemic Goiter Region

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ABSTRACT

Objectives: Hypothyroidism is a disease that occurs as a result of thyroid hormone deficiency or rarely, due to ineffectiveness at the tissue level. While the prevalence of clinical hypothyroidism is reported to be 2-5% worldwide, of subclinical hypothyroidism it is 4-8.5%, with the prevalence of subclinical hypothyroidism in women over 60 years of age being 14-20%. Hypothyroidism affects many organs and systems in the body, one of which is the hematopoietic system. Thyroid hormone deficiency plays a role in the development of microcytic, normocytic and macrocytic anemia. The frequency of anemia in patients with hypothyroidism varies between 20-60%. In this study, our aim was to determine the regional prevalence of subclinical and clinical hypothyroidism in adult patients in our region and to evaluate the frequency and types of anemia in patients with hypothyroidism.

Method and Material: This study was conducted prospectively between 01.12.2012 and 01.05.2013 in the Faculty of Medicine, Endocrinology outpatient clinic. Included in the study were 96 patients who had subclinical hypothyroidism, 30 patients who had clinical hypothyroidism, and 100 healthy controls. Normal fT4 and fT3, high TSH values were used for the diagnosis of subclinical hypothyroidism, and low fT4 and/or fT3, high TSH values were used for the diagnosis of clinical hypothyroidism. The diagnosis of anemia was based on subclinical hypothyroidism, clinical hypothyroidism, and control group Hb value < 13g/dl in men and < 12g/dl in women.

Results: In our study, we found the prevalence of subclinical hypothyroidism to be 3.6%, and of clinical hypothyroidism to be 1.1%. We found the rate of anemia to be 30.2% in the subclinical hypothyroid patient group, 40% in the clinical hypothyroid patient group, and 25% in the control group. A statistically significant difference was shown between the clinical hypothyroidism group and the control group based on the frequency of anemia ($p = 0.033$). There was no statistical difference in the frequency of anemia between the subclinical hypothyroidism group and the control group ($p = 0.0586$). A statistically significant difference was found between the patient group (subclinical + clinical hypothyroidism) and the control group in terms of the frequency of anemia ($p = 0.049$). In the subgroup analysis of 66 anemic patients in the patient and control groups, in both groups the most common type of anemia was anemia of chronic disease, but there was no statistical difference between the groups in terms of anemia of chronic disease ($p = 0.223$).

Conclusion: We found that there was an increase in the frequency of anemia in patients with hypothyroidism and that the most common anemia subtype in hypothyroidism was anemia of chronic disease (normocytic).

Keywords: Anemia, Subclinical hypothyroidism, Clinical hypothyroidism

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Hypothyroidism is a disease that occurs because of thyroid hormone deficiency or, albeit rarely, ineffectiveness at the tissue level. Its prevalence varies from between communities, depending on demographic characteristics such as age, gender, race, and geographic region. While the prevalence of clinical hypothyroidism is reported to be 2-5% globally, the prevalence of subclinical hypothyroidism is reported to be 4-8.5%, and in women over 60 years of age 14-20%. [1] In hypothyroidism, there is a slowdown of the body's metabolism and all organs and systems are thus affected. Anemia occurs as a result of primary involvement of the hematopoietic system by multiple mechanisms. [2] Studies have reported the incidence of anemia in hypothyroidism to be 20-60%. [3] Anemia seen in hypothyroidism can be of hypochromic microcytic, normochromic normocytic or macrocytic type. The most common type of anemia is normochromic normocytic anemia. In hypothyroidism, depending on the metabolic slowdown, the need for oxygen in the body decreases, resulting in physiological hypoerythropoetinemia occurring in order to normalize the hematocrit level and normochromic normocytic anemia occurs. Macrocytic anemia in hypothyroidism can also develop due to malabsorption of vitamin B12 and/or folic acid. 4

Hypochromic microcytic anemia occurs as a result of menorrhagia caused by hormonal imbalances and iron malabsorption due to thyroid hormone deficiency. Macrocytic anemia develops due to impaired absorption of vitamin B 12 as a result of IF (Intrinsic Factor) deficiency and antibody development against gastric parietal cells in pernicious anemia, which can be seen together with autoimmune diseases of the thyroid. [2, 5]

In this study, our aim was to determine the prevalence of subclinical and clinical hypothyroidism in adult patients in our region and to evaluate the frequency and types of anemia in patients with hypothyroidism.

METHODS

This study was conducted prospectively between 01.12.2012 and 01.05.2013 in the Faculty of Medicine, Endocrinology outpatient clinic. The patients included in the study were selected from among the patients who applied to the endocrinology outpatient clinic between 01.12.2012 and 01.05.2013 for varying reasons. Thyroid function tests were performed and clinical and subclinical hypothyroidism diagnoses were made. 100 randomly selected healthy individuals with normal thyroid function were determined as the control group. Hemogram, iron, total iron binding capacity, ferritin, vitamin b12 and folate measurements were performed to determine the frequency and subtypes of anemia in 100 healthy control subjects with clinical and subclinical hypothyroidism. The Architect i 2000 (Abbott, USA) device was used to measure biochemical parameters, Architect c 1600 (Abbott, USA) device to measure iron and total iron binding capacity, and the Cell-Dyn Ruby (Abbott, USA) device for complete blood count.

Those who use thyroid hormone medication or have pre-existing thyroid disease, coronary artery disease, diabetes mellitus, uncontrolled hypertension, chronic kidney failure, recent acute bleeding (gastrointestinal-genitourinary-respiratory etc.), receiving anemia treatment, steroid treatment, hemolytic anemia, or hematological malignancies were excluded. Twelve of 108 patients with subclinical hypothyroidism and 5 out of 35 patients with clinical hypothyroidism were excluded from the study because they met one or more of the exclusion criteria.

Normal fT4 and fT3, as well as high TSH values, were used for the diagnosis of subclinical hypothyroidism, and low fT4 and/or fT3, high TSH values were used for the diagnosis of clinical hypothyroidism. Anemia was defined as Hb value < 13 g/dl in males and < 12 g/dl in females in the patient and control groups. In the determination of subgroups of patients with anemia, serum iron was defined as low in iron deficiency anemia, high serum total iron binding capacity and low ferritin value. In anemia of chronic disease, serum iron was low, serum total iron binding capacity was low, ferritin value was normal or high, and vitamin B 12 and folate values were defined as normal. It was defined as low serum vitamin B 12 level, high MCV value (> 100 fL) (macrocytosis) in anemia due to vitamin B 12 deficiency, and low serum folate level and high MCV value (> 100 fL) (macrocytosis) in folic acid deficiency.

Data were analyzed with the IBM SPSS Statistics 21.0 (SPSS, Inc, Chicago, IL, USA) package software. Continuous variables are given as mean ± standard deviation and categorical variables as numbers and percentages. T test was used to compare two groups, and One Way Anova method was used to compare more than two groups. The differences between the categorical variables were analyzed by Chi-square analysis. A $p < 0.05$ was considered statistically significant.

RESULTS

Clinical hypothyroidism was found in 30 (1.1%) of 2653 patients who applied to the outpatient clinic, and subclinical hypothyroidism was found in 96 (3.6%) patients. Demographic characteristics and mean laboratory values of the patient and control groups are given in Table 1.

When evaluated in terms of anemia frequency, in the subclinical hypothyroid patient group anemia was detected in 29 (30.2%) of 96 patients, in 12 (40%) of 30 patients in the clinical hypothyroid patient group, and in 25 (25%) of 100 patients in the control group. A statistically significant difference was found between the clinical hypothyroidism group and the control group in terms of the frequency of anemia ($p = 0.033$). There was no statistically significant difference in the frequency of anemia between the subclinical hypothyroidism group and the control group ($p = 0.058$). A statistically significant difference was however found between the patient group (subclinical+clinical hypothyroidism) and the control group in terms of the frequency of anemia ($p = 0.049$).

According to the gender subgroup, anemia was detected in 27 (32.9%) of 82 female patients and 2 (14.3%) of 14 male patients in the subclinical hypothyroidism group. In the clinical hypothyroidism group, anemia was present in 10 (40%) of 25 female patients and 2 (40%) of 5 male patients. In the control group, 19 (27.1%) of 70 female patients and 6 (20%) of 30 male patients had anemia. Anemia was detected in 37 (34.5%) of 107 female patients and 4 (21%) of 19 male patients with hypothyroidism. When all groups were taken into account, 56 (84.9%) of 66 anemic patients were female and 10 (15.1%) were male.

Causes of anemia in the patient and control groups

When the patients with anemia were examined in terms of anemia subtype, 6 out of 12 anemic patients in the clinical hypothyroidism group had anemia of chronic disease (50%), while iron deficiency anemia was found in 5% (41.7%) and B12 deficiency anemia was found in 1 (8.3%). 14 of 29 anemia patients in the subclinical hypothyroidism group were found to have anemia of chronic disease (48.3%), 12 of them had iron deficiency anemia (41.4%), 2 of them had B12 deficiency anemia (6.9%) and one had folate deficiency anemia (3.4%). Of 25 anemia patients in the control group, 13 (52%) had anemia of chronic disease, 11 (44%) had iron deficiency anemia, and 1 had B 12 deficiency anemia (4%) (Fig. 1).

When the three groups were compared with these data in terms of the causes of anemia, no statistical difference was found ($p = 0.178$ for chronic disease anemia, $p = 0.215$ for iron deficiency anemia, $p = 0.500$ for B12 deficiency and p value could not be cal-

Table 1. Demographic characteristics and laboratory values of the patient and control groups

	Clinical Hypothyroidism	Subclinical Hypothyroidism	Control Group	*P* value
Number	30	96	100	-
Gender (male/female)	5/25	14/82	30/70	0.025
Age	44.60 ± 14.48	34.97 ± 13.34	44.28 ± 17.60	< 0.001
TSH	36.16 ± 31.80	6.97 ± 2.41	1.43 ± 0.82	< 0.001
FT3	2.44 ± 0.47	3.16 ± 0.44	---	< 0.001
FT4	0.53 ± 0.16	1.01 ± 0.14	---	< 0.001
MCV	83.18 ± 6.08	79.67 ± 8.99	82.96±3.64	0.153
Anti TG positivity	76.6	75	---	0.412
Anti-TPO positivity	73.3	67.7	---	0.216
Hemoglobin	12.53 ± 1.13	12.59 ± 1.62	12.98 ± 1.33	0.114
Hematocrit	36.94 ± 3.35	37.49 ± 3.99	37.64 ± 3.66	0.672
Vitamin B12	337.07	271.93	315.53	0.058
Folic acid	7.57 ± 3.15	7.70 ± 3.31	7.63 ± 3.00	0.976
Iron	76.93 ± 32.68	79.78 ± 36.98	82.62 ± 38.04	0.726
Ferritin	53.50 ± 92.32	48.46 ± 52.41	64.03 ± 62.59	0.224

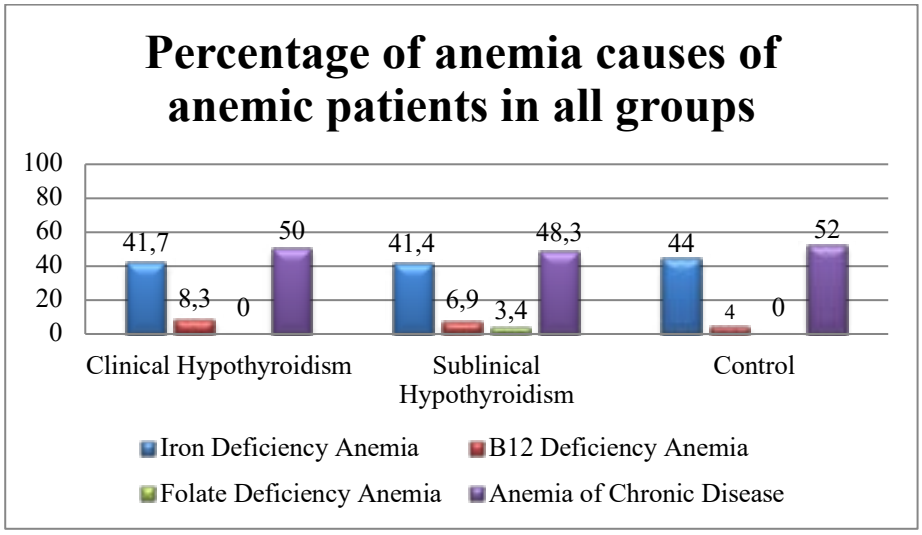

Fig. 1. Percentage of causes of anemia in anemic patients in all groups (%)

culated for folate deficiency).

In the distribution of the causes of anemia, of the 41 anemic patients in the patient group (subclinical + clinical hypothyroidism), chronic disease anemia was seen in 20 patients (48.8%), iron deficiency anemia in 17 patients (41.5%), B12 deficiency anemia in 3 patients (7.3%), and folate deficiency anemia in 1 patient. (2.4%). When the patient (subclinical+clinical hypothyroidism) and control groups were compared in terms of anemia causes, no statistical difference was found between them (p = 0.223 for chronic disease anemia, p = 0.257 for iron deficiency anemia, p= 0.317 for B12 deficiency anemia and p value could not be calculated for folate deficiency).

The most common type of anemia in clinical hypothyroidism, subclinical hypothyroidism and control groups was anemia of chronic disease (50%, 48.3%, 52%, respectively) and the second most common type of anemia was iron deficiency anemia (41.7%, 41.4%, 44%, respectively). The mean laboratory values of anemic patients in all three groups are given in Table 2.

Anemia type distribution according to the erythrocyte size of 66 anemic patients in the clinical hypothyroidism, subclinical hypothyroidism, and control groups was analyzed. It was found that among 12 anemic patients in the clinical hypothyroidism group, 2 patients (16.7%) had microcytic anemia and 10 patients (83.3%) had normocytic anemia, among 29 anemic patients in the subclinical hypothyroidism group, 10 patients (34.5%) had microcytic anemia and 19 patients (65.5%) had normocytic anemia, and among 25 anemic patients in the control group, 5 patients (20%) had microcytic anemia and 20 patients (80%) had normocytic anemia. In the patient group (subclinical + clinical hypothyroidism) of 41 anemic patients, 12 (29.3%) with microcytic anemia and 29 (70.7%) with normocytic anemia were detected. The most common type of anemia according to erythrocyte size in the patient and control groups was normocytic anemia. There was no statistically significant difference between the patient group (subclinical+clinical

Table 2. Laboratory values of anemia patients in all groups

	Clinical hypothyroidism (n:12)	Subclinical hypothyroidism (n:29)	Control Group (n:25)	*P* value
MCV	83.18 ± 6.08	79.67 ± 8.99	82.96 ± 3.64	0.509
Hematocrit	34.27 ± 1.30	33.37 ± 3.21	34.07 ± 2.08	0.736
Hb	11.61 ± 0.58	10.75 ± 1.26	11.65 ± 0.64	0.017
Ferritin	38.04 ± 51.30	23.23 ± 28.66	42.24 ± 61.64	0.436
Vitamin B12	272.50 ± 141.05	260.93 ± 93.90	328.36 ± 158.54	0.272
Folate	7.80 ± 2.45	7.80 ± 2.41	7.74 ± 3.78	0.839
Iron	54.42 ± 29.47	63.31 ± 42.26	69.80 ± 34.36	0.430

hypothyroidism) and the control group in terms of the frequency of microcytic anemia and the frequency of normocytic anemia ($p = 0.257$ and $p = 0.068$, respectively).

Anti TG and Anti TPO rates in the patient group

The mean Anti TG values of the patients in the subclinical hypothyroidism group were 109.26 IU/ml and the Anti TPO values were 325.74 IU/ml. The mean Anti TG values of the patients in the clinical hypothyroid group were 196.31 IU/ml and the Anti TPO values were 471.96 IU/ml. Of the 96 patients in the subclinical hypothyroidism group, the number with Anti TG positivity was 72 (75%) and of patients with Anti TPO positivity it was 65 (67.7%). Of the 30 patients in the clinical hypothyroidism group, the number with Anti-TG positivity was 23 (76.6%), and of patients with Anti-TPO positivity it was 22 (73.3%). Additionally, out of a total of 126 patients in the patient group (subclinical + clinical), the number of patients with Anti TG positivity was 95 (75.3%) and the number of patients with Anti TPO positivity was 87 (69%).

DISCUSSION

The frequency of clinical hypothyroidism in many large-scale studies has been reported as 1-2% in women and 0.1% in men, and it is less common than subclinical hypothyroidism. [6-8] In our study, the prevalence of subclinical hypothyroidism was 3.6% and the prevalence of clinical hypothyroidism was 1%. These results are similar to previous studies.

According to the data of the World Health Organization (WHO), the prevalence of anemia is reported as 24.8% globally, with a higher rate occurring in underdeveloped countries. [9] While in European countries the prevalence of anemia is around 14%, it reaches up to 25% in developing countries such as Turkey. 10 Similar to the literature, in our study the frequency of anemia in the control group was found to be 25%. In a study by Christ-Crain M *et al.*, it was reported that the frequency of anemia in hypothyroid patients varied between 20-60%. [3] In our study, we found the incidence of anemia in the patient group (subclinical hypothyroidism+clinical hypothyroidism) as 32.5%, compatible with the literature.

In a study by Mehmet E *et al*., it was observed that 86.5% of hypothyroid patients were female and 13.5% were male. 10 In our study, 84.9% of patients with hypothyroidism were female and 15.1% were male, and anemia was found in 34.5% of women with hypothyroidism and 21% of men with hypothyroidism. Considering all these results, it can be said that hypothyroidism is more common in women, and a risk factor for anemia is the presence of hypothyroidism.

Hashimoto's thyroiditis (Chronic Autoimmune Thyroiditis) is the most common cause of hypothyroidism in iodine-sufficient regions globally, and its frequency increases with age. [11] Anti TG is positive in 80-90% and Anti-TPO is positive in 90-100% in patients with chronic autoimmune thyroiditis. [12] In our study, Anti TG 75.3% and Anti TPO 69% were found positive in hypothyroid patients, which was consistent with the literature.

In a study by Chanchal Das *et al*. in India, they found that 31 (51.6%) of 60 hypothyroid patients had normochromic normocytic anemia. [13] In another study by Mehmet E *et al*., the rate of anemia of chronic disease was found to be 31% in patients with clinical hypothyroidism, and 24% in patients with subclinical hypothyroidism. [10] In our study, the most common type of anemia in hypothyroid patients was anemia of chronic disease (48.8%), and this rate was 48.3% in the subclinical hypothyroidism group and 50% in the clinical hypothyroidism group, which was consistent with the literature.

Iron deficiency anemia in hypothyroid patients occurs due to iron malabsorption or, in women, as a result of menorrhagia due to hormonal imbalance. In a study by Kosenli A *et al*., anemia was found in 85.7% of women with hypothyroidism and 14.3% of men with hypothyroidism, and it was demonstrated that a large percentage of anemia in women with hypothyroidism may be associated with menorrhagia. [14] In a study conducted by Mitra Kazemi J *et al*. investigating the effectiveness of hypothyroidism treatment on the frequency of anemia, it was found that 64 of 70 hypothyroid patients had improvement in hematological parameters after levothyroxine (st4) treatment. 15 In another randomized controlled double-blind study by Cinemre H *et al*., it was shown that female patients with subclinical hypothyroidism and iron deficiency anemia initially did not respond to oral iron replacement therapy, and then the addition of levothyroxine (st4) to the treatment increased serum iron levels, thus increasing the effectiveness of oral iron therapy and iron absorption in patients. [2] These results demonstrate that the presence of hypothyroidism should be evaluated in patients with anemia. In our study, the

rate of iron deficiency anemia in the subclinical hypothyroid patient group was 41.4%, the clinical hypothyroid patient group it was 41.7%, and the female sex ratio in the hypothyroid (subclinical + clinical) patient group was 84.9%. The rate of iron deficiency anemia in both patient groups was lower than in the control group. In our study, iron deficiency anemia was the second most common type of anemia after anemia of chronic disease.

The prevalence of vitamin B 12 deficiency increases with age. The most common cause of vitamin B 12 deficiency is malabsorption and insufficient intake. In a study by Mc Lean E *et al*., it was demonstrated that the prevalence of vitamin B 12 deficiency in Europe is between 1.6% and 10%. 16 In the Framingham study, the prevalence of vitamin B 12 deficiency in the elderly population was reported as 12%. 17 In our study, we found the prevalence of vitamin B 12 deficiency to be 4% in patients in the control group with a mean age of 44 years. In a study investigating the causes of anemia in patients with primary hypothyroidism, it was found that 6 (10%) of 60 patients with primary hypothyroidism had macrocytic anemia due to vitamin B 12 deficiency, and 3 of them had positive antiparietal cell antibodies that was related to pernicious anemia. [13] In another study, vitamin B12 deficiency was examined in patients with primary hypothyroidism, and it was observed that vitamin B12 levels were low in 46 (39.6%) of 116 hypothyroid patients (95 females, 21 males), while it was reported that the prevalence of anemia was not high in patients with vitamin B12 deficiency. [18] In our study, we found B12 vitamin deficiency in the hypothyroid patient group as 7.3%, and there was no significant difference compared to the control group.

Folic acid deficiency is very rare and occurs most often because of insufficient intake. Intestinal malabsorption can additionally also cause folate deficiency. 19 In thyroid hormone deficiency, along with folate malabsorption, folic acid deficiency occurs due to a decrease in the level of dihydrofolate reductase, which converts dihydrofolate to tetrahydrofolate (biologically active folic acid) at the liver level. [10] In our study, we found folic acid deficiency to be 2.4% in the patient group (subclinical+clinical hypothyroidism).

Anemia seen in patients with hypothyroidism can occur by various mechanisms. In this study, we found that there is an increase in the frequency of anemia in hypothyroidism and that the most common type of anemia is anemia of chronic disease (normocytic), which is consistent with the literature.

CONCLUSION

We found that there was an increase in the frequency of anemia in patients with hypothyroidism and that the most common anemia subtype in hypothyroidism was anemia of chronic disease (normocytic).

Authors' Contribution

Study Conception: KI, TA, EA,; Study Design: KI, TA, EA,; Supervision: KI, TA, EA,; Materials: KI, TA, EA,; Data Collection and/or Processing: KI, TA, EA,; Statistical Analysis and/or Data Interpretation: KI, TA, EA,; Literature Review: KI, TA, EA,; Manuscript Preparation: KI, TA, EA and Critical Review: KI, TA, EA.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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