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Clinical Pathology & Research Journal
ISSN: 2642-6145

Evaluation of Anemia in Thyroid Dysfunctions Anemia in Thyroid Dysfunctions: Retrospective Cross-Sectional Study

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Investigation Paper
Volume 6 Issue 1
Received Date: September 23, 2022
Published Date: October 18, 2022
DOI: 10.23880/cprj-16000149

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Abstract

Objective: Evaluation of Anemia in Thyroid Dysfunctions Anemia in Thyroid.

Materials and Methods: The study analyzed 145 medical records of patients diagnosed with thyroid disorders (102 women and 43 men), receiving care between January 2011 and February 2018 at the University Hospital of Florianópolis, Brazil, selected with thyroid disorder ICD.

Results: Obtained by analyzing the medical records and assessing laboratory parameters: thyroid-stimulating hormone (TSH), free thyroxine (FT4), mean corpuscular volume (MCV), red blood cell distribution width (RDW), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hemoglobin values (Hb), red blood cell count (RBC), hematocrit values (Hct), cytomorphological erythrocyte changes, serum iron, and ferritin. Most patients were diagnosed with primary hypothyroidism, followed by primary hyperthyroidism. Hemoglobin values were present in 95.9% of patients with hypothyroidism and 89.6% of those with hyperthyroidism. Patients whose hemoglobin values were below 12 (for women) or 13 g/dl (for men) were classified as anemic. The frequency of anemia was 41.0% of patients – 76.3% had some type of hypothyroidism, while 29.7% had some type of hyperthyroidism.

Conclusion: Normocytic and normochromic anemia was observed in both thyroid disorders. In hyperthyroidism, values neared microcytosis. Red blood cell counts were statistically different between males with hypothyroidism and hyperthyroidism. Hypothyroidism was statistically related to diabetes, systemic arterial hypertension, and cardiovascular diseases.

Keywords: Thyroid Disorders; Anemia; Hematologic Changes; Thyroid Hormones

Abbreviations: TSH: Thyroid-Stimulating Hormone; MCV: Mean Corpuscular Volume; RDW: Red Blood Cell Distribution Width; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; Hb: Hemoglobin; RBC: Red Blood Cell; Hct: Hematocrit; IQR: Interquartile Range; WHO: World Health Organization; IL-6: Interleukin 6; MDD: Major Depressive Disorder.

Introduction

Thyroid dysfunctions (hypothyroidism and hyperthyroidism) are commonly diagnosed in primary healthcare and are among the most frequent diseases. Such dysfunctions can either manifest clinically or be verified in the laboratory, with abnormal results that suggest subclinical conditions, such as subclinical hyperthyroidism and hypothyroidism [1].

Hypothyroidism is a clinical condition that results from insufficient or absent thyroid circulating hormones, named T_4 (thyroxin) and T_3 (triiodothyronine), which are necessary to supply normal organic function. Hyperthyroidism, in its turn, is a hyper metabolic condition caused by increased thyroid gland function and consequently increased circulating concentrations of free T_3 and T_4 [2]. The most common cause of hypothyroidism is the self-immune destruction of the thyroid gland, in which antibodies can destroy the gland or block thyroid hormone synthesis. Another cause of hypothyroidism is the surgical removal of the thyroid, in the treatment of hyperthyroidism, hypothalamic-pituitary insufficiency, and I^- deficiency [3]. As for hyperthyroidism, the most common cause is diffuse thyroid hyperplasia associated with Graves' disease, hyper functioning multinodular goiter, and hyper functioning thyroid adenoma [3].

About 21% to 60% of hypothyroid patients have anemia, due to reduced cell production, lack of erythropoietic stimulation, and less need for organism oxygenation [4]. Anemia presents insidious signs and symptoms (e.g., fatigue, weakness, and dyspnea), which is why it is easily unnoticed and often underestimated [5]. Hence, these symptoms can be associated with clinical signs of hypothyroidism (i.e., lethargy, tiredness, and intolerance to cold) [6].

Anemia is characterized by a decreased hemoglobin index in blood circulation, at lower concentrations than in healthy people of the same age, sex, and physiological characteristics (such as pregnancy). It may result from factors such as defective erythrocyte production; shorter erythrocyte survival in the blood flow, due to either hemolysis or blood loss from other mechanisms; increased retention of normal erythrocytes in the abnormal (enlarged) spleen; increased sequestration of normal or abnormal erythrocytes (as in sickle cell disease) in the spleen (hepatic sequestration also occurs, though less often); or interaction with hemoglobinopathies [7].

Thus, anemia and thyroid dysfunction occur simultaneously, although the relationship between these clinical disorders is still unclear. The direct action of thyroid hormone regulation in hematopoiesis has been reported in the literature, as it directly stimulates the proliferation of erythrocytic precursors and kidney production of erythropoietin [8]. Different forms of anemia can develop in thyroid dysfunctions; normocytic anemia is the most common one, while macrocytic and microcytic anemia is less frequently found [9].

The coexistence of anemia with thyroid disease is an important clinical problem. Not only are thyroid hormones involved in erythropoiesis, but some factors and comorbidities also contribute to the course of anemia in thyroid diseases. For instance, other self-immune diseases can cause anemia – including pernicious anemia, in which parietal cells are attacked and vitamin B_{12} absorption is consequently decreased [10]. Moreover, other dysfunctions, such as celiac disease, may change nutrient absorption mechanisms, directly affecting intestinal integrity; thus, it may absorb fewer nutrients, such as iron, causing iron-deficiency anemia [11].

The objective of this research was to evaluation of Anemia in Thyroid Dysfunctions Anemia in Thyroid. Hematologic, biochemical, and hormonal data were analyzed and correlated with thyroid dysfunctions in patients diagnosed with hypothyroidism and its sub classifications and hyperthyroidism and its sub classifications.

Materials and Methods

Sample Characterization

This is a retrospective cross-sectional study conducted at a University Hospital, where individuals diagnosed with hypothyroidism and its sub classifications and hyperthyroidism and its sub classifications were assessed. The research was based on data from the International Statistical Classification of Diseases and Related Health Problems (ICD), collected from the medical records of outpatients and inpatients at the University Hospital of Florianópolis (Santa Catarina, Brazil) diagnosed with thyroid dysfunctions in their first visit. Those who met the inclusion criteria and whose medical records had entries dated from January 1, 2011, to February 28, 2018, were selected.

Inclusion and Exclusion Criteria

This study included male and female patients, with no restriction on age, diagnosed with hypothyroidism and its sub classifications and hyperthyroidism and its sub classifications, according to the ICD (ICD-10 E02-subclinical hypothyroidism, E03-other types of hypothyroidism, E05-thyrotoxicosis, and E06-self-immune thyroiditis and thyrotoxic thyroiditis), which was indicated in their medical

records as early as their first visit. Patients whose medical records could not be found and/or accessed in the system (passive file) or did not indicate the ICD that characterized their thyroid dysfunction were excluded from the study.

Data Collection

The study analyzed medical record data from patients with hypothyroidism and its sub classifications and hyperthyroidism and its sub classifications, at the University Hospital of Florianópolis, Brazil. Participants were selected through the Hospital computer system, based on pre-established ICD-10 diagnosis (E02, E03, E05, and E06) and period (January 1, 2011, to February 28, 2018). Records were individually checked to verify the patients' laboratory and clinical data. Those that met the inclusion criteria were analyzed, and the laboratory and other parameters of interest were collected.

Laboratory Parameters

The study analyzed research participants' laboratory parameters, including thyroid assessment parameters such as thyroid-stimulating hormone (TSH) and free thyroxine or free T_4 (FT_4). The following hematologic data were analyzed: mean corpuscular volume (MCV); red blood cell distribution width (RDW); mean corpuscular hemoglobin (MCH); mean corpuscular hemoglobin concentration (MCHC); hemoglobin values (Hb); red blood cell count (RBC); hematocrit values (Hct); and cytomorphological changes in the red cells. Other laboratory data were also considered, such as serum iron (Fe) and ferritin concentrations. Anemic and non-anemic patients were divided according to criteria from the World Health Organization (WHO) – the following Hb reference values (RV) were used to include patients in the anemic group: Hb < 13.0 g/dL (men); Hb < 12.0 g/dL (women). The other hematologic parameter RV were as follows: RBC (men: 4.50 to 6.10 x 10^6/mm^3; women: 4.00 to 5.40 x 10^6/mm^3); Hct (men > 39.0%; women > 36.0%); MCV (80 – 100 fL), MCH (26.0 – 34.0); MCHC (31.0 to 35.0); RDW (< 15%) (WHO, 2011). Biochemical parameters RV were as follows: Fe (35.0 to 150.0 µg/dL); ferritin (women: 10.0 to 291.0 ng/mL; men 22.0 to 322.0 ng/mL). Hormone parameter RV were as follows: TSH (0.4 to 4.5 µUI/mL) (HOLLOWELL et al., 2002); FT_4 (0.8 to 1.80 ng/dL) (DEMERS; SPENCER, 2002)

Statistical Treatment

Data were included and organized in Microsoft Excel® 2010 spreadsheets (2010 Microsoft© Corporation). Statistical analyses were made in MedCalc statistical software, version 18.5 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Descriptive statistical analyses were made with the frequency distribution of the categorical variables and measures of central tendency and dispersion of the continuous variables. The normality of the continuous variables was assessed with the Shapiro-Wilk test. Analyses were made with the chi-square and Fisher's exact statistical tests and the Mann-Whitney U test; crude odds ratios were also determined, considering the 5% *P*-value ($p < 0.05$) as the significance level.

Ethical and Legal Aspects

The research was approved by the Human Research Ethics Committee (CEPSH-UFSC), under CAAE (Certificate of Presentation for Ethical Appraisal) no. 79373717.0.0000.0121 (Annex A), to be conducted at the University Hospital, following the guidelines and criteria established by Resolution 466/12 of the National Health Council, and respecting information authenticity and confidentiality.

Results

The research analyzed 145 medical records – 102 (70.30 %) participants were females, and 43 (29.70 %) were males. Most participants were 43 to 52 years old (median: 48.0 years; interquartile range [IQR]: 33.75 – 66.00). Patients diagnosed with hyperthyroidism and its sub classifications were predominantly 32 to 45 years old (median: 38.0 years; IQR = 29.0 – 50.0). Female patients' median age was 38.0 years (IQR: 24.0 – 52.0), while male patients' median age was 40.5 years (IQR: 34.0 – 48.0). Patients diagnosed with hypothyroidism and its sub classifications were predominantly 48 to 59 years old (median: 53.0 years; IQR = 38.0 – 67.0). Female patients' median age was 53.5 years (IQR: 37.5 – 68.5), while male patients' median age was 53.0 years (IQR: 40.0 – 66.0).

ICD-10 diagnosis of 97 study participants was hypothyroidism and its sub classifications and of the other 48 was hyperthyroidism and its sub classifications. Percentage results per sex verified that females comprised 70.1% of hypothyroid and 70.8% of hyperthyroid patients, while males were 29.9% of hypothyroid and 29.2% of hyperthyroid patients. Primary hypothyroidism was the most frequent thyroid disorder, present in 42.0% of females and 60.5% of males.

Regarding hypothyroidism and its sub classifications, most male and female patients in this study had primary hypothyroidism; in this case, the percentage was higher among men. There was only one case of Riedel's thyroiditis, a female participant. As for hyperthyroidism, the following differences in sub classifications stood out: primary hyperthyroidism predominated among females, while Graves' disease predominated among males. Moreover, only

women were diagnosed with subclinical hyperthyroidism in this study.

This research was adjusted to analyze the frequency of anemia. It showed that 55 patients whose medical records reported Hb concentrations (35 females and 20 males) were anemic – corresponding to 41% of the population with Hb data. There was a pregnant woman and a child in the selected group with Hb data, who were classified according to the reference values proposed by WHO.

Of the anemic patients, 76.3% (n = 42) had hypothyroidism and 23.7% (n = 13) had hyperthyroidism. The frequency of anemia was also analyzed among patients diagnosed with hypothyroidism and hyperthyroidism. Patients with hypothyroidism had a greater frequency of anemia, as it was present in 45% (n = 42) of this population. As for those with hyperthyroidism, the frequency was 30.2% (n = 13). In both cases, most anemic patients were females. Among those with hypothyroidism, 93 had one or more hematologic data. Among females, 65 presented RBC, Hb, Hct, MCV, MCH, and MCHC indices; 39 presented RDW. Among males, 27 presented RBC, Hct, MCV, MCH, and MCHC indices; 28 presented Hb concentrations; 16 presented RDW.

Hematologic data of patients with hypothyroidism are shown in Table 1. The median total RBC was $4.22x10^6/mm^3$ in women and $4.31x10^6/mm^3$ in men. Median Hb concentrations and Hct determinations were respectively 12.40 g/dL and 37.20% in women and 12.50 g/dL and 38.00 % in men – these values are below the reference ones for men: Hb > 13.0 g/dL and Hct > 39% (WORLD HEALTH ORGANIZATION, 2011). Median MCV, MCH, and MCHC results were respectively 89.90 fL, 29.70 pg, and 33.30 g/dL in women and 90.00 fL, 30.50 pg, and 33.40 g/dL in men. Median RDW values were 13.90% in men and 13.60% in women.

Hematologic data	Females			Males		
	N	Median	Interquartile Range	N	Median	Interquartile Range
RBC ($10^6/mm^3$)	65	4.22	3.830 - 4.467	27	4.31	3.685 - 4.480
Hemoglobin (g/dL)	65	12.4	11.275 - 13.225	28	12.5	11.500 - 13.950
Hct (%)	65	37.2	33.625 - 40.325	27	38	34.725 - 41.425
MCV (fL)	65	89.9	86.125 - 90.450	27	90	89.000 - 92.675
MCH (pg)	65	29.7	28.575 - 30.425	27	30.5	29.300 - 31.375
MCHC (g/dL)	65	33.3	32.700 - 33.925	27	33.4	32.625 - 34.225
RDW (%)	39	13.6	12.625 - 14.100	16	13.9	13.300 - 15.900

Table 1: Results presented as the median of the hematologic data of male and female research participants diagnosed with hypothyroidism.
RBC – red blood cell count, Hct – hematocrit, MCV - mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, RDW – red blood cell distribution width.
Source: The authors (2018).

Regarding hematologic results in patients with hyperthyroidism (n = 43), 28 females presented RBC, Hct, MCV, MCH, and MCHC values; 29 presented Hb concentrations; and 20 presented RDW data. Among males, 13 presented RBC, Hct, MCV, MCH, and MCHC values; 14 presented Hb concentrations; and eight presented RDW data. These values are shown in Table 2. The median total RBC was $4.31x10^6/mm^3$ in women and $4.62x10^6/mm^3$ in men. Median Hb concentrations and Hct determinations were respectively 12.40 g/dL and 37.85% in women and 13.50 g/dL and 40.70% in men. Median MCV, MCH, and MCHC results were respectively 86.90 fL, 28.60 pg, and 33.25 g/dL in women and 87.20 fL, 29.90 pg, and 34.50 g/dL in men. No statistical difference was found in RDW values between men (median of 13.20%) and women (median of 14.10 %).

Hematologic data	Females			Males		
	N	Median	Interquartile Range	N	Median	Interquartile Range
RBC ($10^6/mm^3$)	28	4.31	3.910 - 4.605	13	4.62	4.187 - 5.128
Hemoglobin (g/dL)	29	12.4	11.275 - 13.325	14	13.5	12.700 - 15.100

Hct (%)	28	37.85	33.300 - 40.000	13	40.7	37.450 - 44.275
MCV (fL)	28	86.9	81.750 - 90.050	13	87.2	85.275 - 90.000
MCH (pg)	28	28.6	26.950 - 30.250	13	29.9	29.000 - 31.025
MCHC (g/dL)	28	33.25	32.720 - 34.000	13	34.5	33.125 - 35.025
RDW (%)	20	14.1	12.900 - 15.350	8	13.2	12.600 - 14.450

Table 2: Results presented as the median of the hematologic data of male and female research participants diagnosed with hyperthyroidism.
RBC – red blood cell count, Hct – hematocrit, MCV - mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, RDW – red blood cell distribution width.
Source: The authors (2018).

Hematologic data were compared between patients with hypothyroidism and hyperthyroidism per sex. In female patients, only MCV (p = 0.0459) had a statistically significant difference (Table 3). Among males, there were statistically significant differences in RBC (p = 0.0141), Hb (p = 0.0203), Hct (p = 0.0403), MCV (p = 0.0250), and MCHC (p = 0.0463).

Hematologic data	Hypothyroidism			Hyperthyroidism			P [a]
	N	Median	Interquartile Range	N	Median	Interquartile Range	
RBC (10^6/mm^3)	26	3.72	3.430 - 4.020	9	3.75	3.103 - 3.905	0.473
Hemoglobin (g/dL)	26	10.85	9.500 - 11.400	9	10.6	8.575 - 11.025	0.439
Hct (%)	26	32.6	29.900 - 34.700	9	31.3	25.975 - 33.050	0.234
MCV (fL)	26	89.15	85.800 - 90.000	9	82.1	78.075 - 90.025	0.29
MCH (pg)	26	28.95	27.600 - 29.800	9	27	26.008 - 30.100	0.473
MCHC (g/dL)	26	32.95	32.400 - 33.600	9	33.1	32.350 - 33.400	0.91
RDW (%)	16	13.75	13.050 - 14.650	6	15	14.400 - 15.600	0.051

Table 3: Comparison of hematologic data between female patients with hypothyroidism and hyperthyroidism, classified with anemia.
RBC – red blood cell count, Hct – hematocrit, MCV - mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, RDW – red blood cell distribution width.
[a] P-value based on the Mann-Whitney test to compare medians per thyroid disorder.
Source: The authors (2018).

In the assessment of anemic patients' hematologic data, each index was compared between patients with hypothyroidism and hyperthyroidism per sex. Among females, no statistical difference was found in patients with either hypothyroidism (n = 26) or hyperthyroidism (n = 9), as shown in Table 4. RBC values in women, as well as the other data, were characteristic of anemic individuals, with medians in patients with hypothyroidism and hyperthyroidism respectively of $3.72x10^6$/mm^3 and $3.75x10^6$/mm^3. Median Hb concentrations and HCT determinations were respectively 10.85 g/dL and 32.60% in women with hypothyroidism and 10.60 g/dL and 31.30% in those with hyperthyroidism. Median MCV, MCH, and MCHC results were respectively 89.15 fL, 28.95 pg, and 32.95 g/dL in patients with hypothyroidism and 82.10 fL, 27.00 pg, and 33.10 g/dL in those with hyperthyroidism. Median RDW values were 13.75% in women with hypothyroidism and 15.00% in those with hyperthyroidism. Male patients were also compared, and likewise, no statistically significant differences were found between patients with hypothyroidism and hyperthyroidism.

These patients' values are compatible with anemic patients. Median RBC in men with hypothyroidism and hyperthyroidism were respectively $3.85x10^6$/mm^3 and $4.09x10^6$/mm^3. Median Hb concentrations and Hct determinations were respectively 11.65 g/dL and 34.80 % in patients with hypothyroidism and 12.15 g/dL and 36.07% in those with hyperthyroidism. Median MCV, MCH, and MCHC results were respectively 89.10 fL, 29.50 pg, and 33.10 g/dL in patients with hypothyroidism and 88.27 fL, 29.37 pg, and 33.33 g/dL in those with hyperthyroidism. Median RDW values were 14.20 % in patients with hypothyroidism and 11.20 % in those with hyperthyroidism.

Hematologic data	Hypothyroidism			Hyperthyroidism			P [a]
	N	Median	Interquartile Range	N	Median	Interquartile Range	
RBC (10^6/mm^3)	15	3.85	2.873 - 4.287	3	4.09	3.935 - 4.258	0.407
Hemoglobin (g/dL)	16	11.65	8.850 - 12.400	4	12.15	11.700 -12.600	0.298
Hct (%)	15	34.8	26.750 - 37.573	3	36.07	35.425 - 36.625	0.515
MCV (fL)	15	89.1	87.550 - 90.375	3	88.27	86.100 - 90.000	0.859
MCH (pg)	15	29.5	28.300 - 30.600	3	29.37	29.000 - 29.750	0.767
MCHC (g/dL)	15	33.1	32.450 - 33.850	3	33.33	32.450 - 34.250	0.953
RDW (%)	11	14.2	13.525 - 16.150	1	11.2	11.200 -11.200	0.111

Table 4: Comparison of hematologic data between male patients with hypothyroidism and hyperthyroidism, classified with anemia.

RBC – red blood cell count, Hct – hematocrit, MCV - mean corpuscular volume, MCH – mean corpuscular hemoglobin, MCHC – mean corpuscular hemoglobin concentration, RDW – red blood cell distribution width.

[a] *P-value based on the Mann-Whitney test to compare medians per thyroid disorder.*

Source: The authors (2018).

Of the 136 patients who had hematologic data, 24 had information on cytomorphological erythrocyte changes – 18 were diagnosed with hypothyroidism, and six with hyperthyroidism. The main changes found were poikilocytosis (15 cases); polychromasia (10 cases); ovalocytes (10 cases); anisocytosis with microcytes and macrocytes (7 cases); hypochromia (5 cases); acanthocytes (4 cases); teardrop-shaped and target-shaped red blood cells (3 cases). Three patients were characterized with hypochromia in the analysis according to CHCM values (< 31.0 g/dL) (OMS, 2011), two of whom were anemic.

Only some patients had biochemical and hormonal dose results in their medical records. Data were analyzed only with parameters that interfered at some moment with the thyroid function or determination of some type of anemia. The doses selected for statistical analysis were Fe (n = 18), ferritin (n = 17), TSH (n = 125), and FT_4 (n = 99).

In patients with hypothyroidism, median Fe values were 71.67 µg/dL in females and 72.50 µg/dL in males, while median ferritin was 199.80 ng/mL in females and 460.15 ng/mL in males. Median TSH was 13.24 µUI/mL in females and 8.05 µUI/mL in males, whereas median FT_4 was 0.98 ng/dL in females and 1.00 ng/dL in males. In patients with hyperthyroidism, median Fe was 90.50 µg/dL in females and 117.0 µg/dL in males (only one patient had Fe values), while median ferritin was 194.00 ng/mL in females and 336.00 ng/mL in males (only one patient had ferritin values). Median TSH was 0.01 µUI/mL in both sexes, whereas median FT_4 was 1.83 ng/dL in females and 1.58 ng/dL in males.

Of the patients with hypothyroidism, 62.0% (n = 49) had high TSH at the first moment (> 4.5 µUI/mL), while 82.6% (n = 38) of those with hyperthyroidism had low TSH (< 0.4 µUI/mL). Percentage analysis was made with these subjects to find how many anemic patients had high TSH and how many had low TSH, considering not only anemia and TSH concentrations but also their sex. It found that 19.40% of anemic males had high TSH and 11.10% had low TSH; also, 17.50% of anemic females had high TSH and 11.30% had low TSH. This demonstrates that the effect of TSH was relatively more perceptible in anemic patients with high TSH.

The comorbidities that most stood out in the study (Table 5) were systemic arterial hypertension, in 33.80% of the study population (n = 49); diabetes, in 23.40% (n = 34); obesity, in 8.30% (n = 12); and cardiovascular diseases, in 6.90% (n = 10). The statistical analysis revealed an association between hypothyroidism diagnosis and some comorbidities, such as hypertension (p = 0.0026), diabetes (p = 0.0030), and cardiovascular diseases (p = 0.0307). No significant results were found regarding the other comorbidities. The odds ratio was calculated for comorbidities with statistical differences, showing greater odds of the population with hypothyroidism having hypertension (3.6 times), diabetes (4.9 times) and cardiovascular diseases (11.64 times) than those with hyperthyroidism.

Variables (Comorbidities)	Total		Hypothyroidism		Hyperthyroidism		P* (Hypo X Hyper)
	Absolute frequency (n)	Relative frequency (%)	Absolute frequency (n)	Relative frequency (%)	Absolute frequency (n)	Relative frequency (%)	
Preexisting anemia							
Yes	3	2.10%	2	2.10%	1	2.10%	P = 1.0000
No	142	97.90%	95	97.90%	47	97.90%	
Asthma							
Yes	2	1.40%	1	1.00%	1	2.10%	P = 1.0000
No	143	98.60%	96	99.00%	47	97.90%	
Thyroid cancer							
Yes	1	0.70%	1	1.00%	0	0.00%	P = 1.0000
No	144	99.30%	96	99.00%	48	100.00%	
Depression							
Yes	9	6.20%	7	7.20%	2	4.20%	P = 0.7180
No	136	93.80%	90	92.80%	46	95.80%	
Diabetes							
Yes	34	23.40%	30	30.90%	4	8.30%	P = 0.0030
No	111	76.60%	67	69.10%	44	91.70%	
Dyslipidemia							
Yes	7	4.80%	7	7.20%	0	0.00%	P = 0.0956
No	138	95.20%	90	92.80%	48	100.00%	
Cardiovascular diseases							
Yes	10	6.90%	10	10.30%	0	0.00%	P = 0.0307
No	135	93.10%	87	89.70%	48	100.00%	
Chronic obstructive pulmonary disease							
Yes	3	2.10%	3	3.10%	0	0.00%	P = 0.5509
No	142	97.90%	94	96.90%	48	100.00%	
Chronic kidney disease							
Yes	4	2.80%	4	4.10%	0	0.00%	P = 0.3021
No	141	97.20%	93	95.90%	48	100.00%	
Hepatic steatosis							
Yes	5	3.40%	5	5.20%	0	0.00%	P = 0.1706
No	140	96.60%	92	94.80%	48	100.00%	
Gout							
Yes	2	1.40%	2	2.10%	0	0.00%	P = 0.5540
No	143	98.60%	95	97.90%	48	100.00%	

Systemic arterial hypertension							
Yes	49	33.80%	41	42.30%	8	16.70%	P = 0.0026
No	96	66.20%	56	57.70%	40	83.30%	
HIV-seropositive							
Yes	1	0.70%	1	1.00%	0	0.00%	P = 1.0000
No	144	99.30%	96	99.00%	48	100.00%	
Systemic lupus erythematosus							
Yes	5	3.40%	4	4.10%	1	2.10%	P = 1.0000
No	140	96.60%	93	95.90%	47	97.90%	
Myasthenia gravis							
Yes	2	1.40%	1	1.00%	1	2.10%	P = 1.0000
No	143	98.60%	96	99.00%	47	97.90%	
Obesity							
Yes	12	8.30%	8	91.80%	4	8.30%	P = 1.0000
No	133	91.70%	89	8.20%	44	91.70%	
Other types of cancer							
Yes	2	1.40%	1	1.00%	1	2.10%	P = 1.0000
No	143	98.60%	96	99.00%	47	97.90%	
Smoking							
Yes	7	4.80%	4	4.10%	3	6.30%	P = 0.6850
No	138	95.20%	93	95.90%	45	93.70%	
Transplanted							
Yes	1	0.70%	0	0.00%	1	2.10%	P = 0.3310
No	144	99.30%	97	100.00%	47	97.90%	
*** Fisher's exact test**							

Table 5: Comorbidities found in the study population and their association with hypothyroidism and hyperthyroidism. Source: The authors (2018).

Discussion

Thyroid disorders are associated with hematologic changes, of which anemia is the most prevalent. However, few studies point out the correlation between anemia and thyroid disorders, and the ones that do usually report conflicting results regarding anemia presentation in patients with hypothyroidism or hyperthyroidism [12,13]. Hematologic, biochemical, and hormonal data were difficult to collect in this study, which decreased the number of research participants whose data were analyzed. Many medical records lacked essential information for the study- the data in some of them referred only to hospitalization, lacking or having incomplete hormonal and biochemical doses, hematologic data, and cytomorphological change results, which are essential to correlate thyroid function with anemia assessment.

Frequency data regarding sex and age in the present study are in line with those found in the literature – except for the median of 48.0 years of age, different from the study by M'Rabet-bensalah et al. (2016), in which the mean age was 59.4 years in patients with thyroid disorders. Most participants in this study (70.30%) were women, which agree with what is found in the literature, as it reports that thyroid disorders affect mostly females [6]. Frequency results in this study regarding sex and age help us clarify the correlation between anemia and thyroid disorders, enabling us to exclude anemia of unknown origin in older adults. Previous studies, such as the ones by Nascimento

MLF, et al. [14], show low Hb concentrations, RBC, and Hct values, increasing the prevalence of anemia in "older" older adults – which suggests that the physiopathology of the disease is somehow associated with aging. Moreover, the frequency of females in thyroid disorders also corroborates the literature, which has a predominance of female patients [15]. Hence, such a low frequency of male patients dismisses other mechanisms relating erythropoiesis to the endocrine function. As men grow older, androgen concentrations decrease, which reflects in a decline in erythropoiesis stimulation and seemingly influences the onset of anemia. Older adults have slight increases in TSH, but it is not known whether this change influences the development of anemia, even though hypothyroidism is known to cause anemia [16].

Results in the present study show a predominance of participants with hypothyroidism and its sub classifications. Such data is also found in the literature, which reports a greater frequency of diagnoses of the various forms of hypothyroidism. A large North American prevalence study, named National Health and Nutrition Examination Survey (NHANES III), researched 13,344 participants of the American population and found that 4.6% of them had hypothyroidism, while 1.3% had hyperthyroidism [17]. This tendency of more patients with hypothyroidism results from treatment because hyperthyroidism and thyrotoxic crises are difficult to control, oftentimes requiring surgical interventions (thyroidectomy) and/or radioactive iodine (^{131}I), which induce hypothyroidism [18]. The most prevalent thyroid disorder is normally primary hypothyroidism [19]. Accordingly, it was the most frequent one in this study – considering all patients in the analysis, 60.50% of male patients and 42.00% of female patients had a medical diagnosis of this sub classification of hypothyroidism.

Anemia is characterized by a decrease in Hct, Hb concentration in the blood, or the number of circulating red blood cells. Hb values below 13g/dL in men or 12g/dL in women characterize the person as having anemia. These values do not vary with race or advanced age [20]. Hb values, the main parameter to characterize anemia, were present in 95.9% of hypothyroid patients and 89.6% of hyperthyroid patients. It was also found in this study that the frequency of anemia in thyroid disorders was 41.0%, indicating higher indices than the few data in the literature. The largest cohort study conducted in the last years by M'Rabet-bensalah K, et al. [21], with 8,791 participants, found that 5.0% of them were diagnosed with thyroid disorders, and 30.6% of these were diagnosed with anemia.

The medical records of only two patients in the present research reported preexisting anemia, suggesting the association between anemia and thyroid disorders. Values found in anemic patients corroborate the literature, which reports that Hb values in these patients are hardly below 8.00 to 9.00 g/Dl [4].

When the analysis by M'Rabet-bensalah K, et al. [21] divided cases between hypothyroidism and sub classifications and hyperthyroidism and sub classifications, 17.9% of them had hyperthyroidism with anemia and 12.7% had hypothyroidism with anemia. These results disagree with the present study, which found 45.0% of patients with hypothyroidism and anemia and 30.2% with hyperthyroidism and anemia. Another study, by Omar S, et al. [13] in patients at a Tunisian hospital, found results that agree with the present study – 40.9% of patients with hyperthyroidism had anemia, and 57.1% of patients with hypothyroidism had anemia. Hematologic data in anemic patients corroborate what has already been demonstrated, that anemia in them is normocytic and normochromic. It is important to highlight that the median MCV in research participants did not reach the limits of microcytosis (MCV < 80 fL) or macrocytosis (MCV > 100 fL) in any of the thyroid disorders. On the other hand, the median MCV in female participants with hyperthyroidism and anemia was 82.10 fL (IQR: 78.075 – 90.025), relatively close to what has already been found in the literature. For instance, the New Zealander study by Omar S, et al. [13] found with MCV values that 87.7% of patients with hyperthyroidism and without anemia had microcytosis. The total red blood cell count indicates a statistical difference only in males between patients with hypothyroidism and hyperthyroidism. These data are also similar to the ones in the study by Omar S, et al. [13].

The mechanisms and causes of anemia in patients with hypothyroidism result mainly from failures in erythropoietic stimulation due to thyroid hormones. Anemia etiopathogenesis in hypothyroidism is complex, and clinical studies conducted in the last decade demonstrate that erythroid cellularity decreases in thyroid disorders [13,21]. This is probably due to a decrease in erythropoietic activation in the bone marrow, as thyroid hormones promote mitotic division and proliferation of erythroblasts by inducing the transcription of growth factors of pluripotent stem cells and stimulating kidney production of erythropoietin on the adrenergic system [22].

Anemia in hyperthyroidism is little reported in the literature. Erythrocyte changes in hyperthyroidism, in its turn, include erythropoietic stimulation by thyroid hormones, causing bone marrow hyperplasia, decreasing MCV, reducing erythrocyte lifespan, and using iron ineffectively [23]. Studies have aimed to correlate anemia with thyroid disorders. For instance, the analysis by Hambsch K, et al. [24] found that 38 out of the 100 patients with hyperthyroidism reported normo-hypochromic anemia; normocytic and normochromic anemia was also found among these patients. Another study,

conducted by Nightingale S, et al. [25], reports that in a series of 239 patients with thyrotoxicosis, 46 (19.2%) were identified with coexisting anemia.

Fe cytomorphological changes were found in the medical records; the most frequent ones were related to polychromasia, anisocytosis (seven of them with reported microcytes and macrocytes), and poikilocytosis. The two most recurrent erythrocyte shape changes were ovalocytes and acanthocytes. The literature reports acanthocytes in patients with hypothyroidism Silva PHA, et al. [4], which is normally related to problems such as cholesterol deficiency between the lipidic bilayers of red blood cells, hepatic issues, or even malabsorption syndromes. Thyroid hormone deficiency is known to act directly on lipidic metabolism, which may be one of its causes – along with the association of autoimmune hypothyroidism (Hashimoto's Thyroiditis) with other autoimmune diseases (e.g., celiac disease, which directly interferes with nutrient absorption) [26]. However, the presence of ovalocytes had not yet been reported in the literature. Polychromasia, found in 10 cases, may be a response to bone marrow erythrocyte series and anemia in these patients, indicating compensatory erythrocytosis.

Few cohort studies have been found in the literature, despite the increasing interest in investigating anemia in thyroid disorders, and available data have conflicting results [27]. A recently published New Zealander study aimed to assess the prevalence of anemia in patients with thyrotoxicosis (hyperthyroidism); they verified that most investigated patients had preexisting anemia or another underlying cause of anemia and that in most cases the etiology of anemia must be detected with complete clinical assessments and rigorous follow-up. Such clinical assessments dismiss other possible causes of anemia [28]. A study in 600 women with thyroid disorders in Saudi Arabia showed that all hematologic parameters returned to normal when euthyroidism was normalized. The types of anemia detected in the study were hypochromic and microcytic, and normochromic and normocytic, most of them in hypothyroidism. It was also found that thyroid hormones regulate transferrin gene expression and iron metabolism [12].

Iron has an important role in the thyroids, as it is an important component of heme, and thyroid peroxidase in the thyroid membrane belongs to the class of heme-dependent enzymes. Hence, iron deficiency can change the function of this enzyme [29]. A study in Spanish adults demonstrated that a decrease in serum concentrations of ferritin decreases FT_3 and FT_4 [30]. Nonetheless, the results did not directly associate thyroid deficiency with iron or ferritin. Moreover, determining the iron status is essential to confirm whether anemia in participants with thyroid disorders could be related to iron-deficiency anemia. It did not seem to be the case in this study; despite the few doses, it did not find any decrease in serum iron concentrations or depletion in its stocks in macrophages. On the other hand, there was an increase in ferritin and normal serum iron concentrations. Increased serum ferritin is present in chronic disease anemia. This study found five patients with systemic lupus erythematosus, one patient with HIV, three with cancer, and one transplanted. These diseases are related to chronic disease anemia, which can be related to thyroid disorders. An analysis of the literature has demonstrated that chronic disease anemia is the most common type of anemia in patients with hypothyroidism [31]. However, even in the absence of chronic inflammatory diseases, serum and tissue concentrations of post-inflammatory cytokines, such as interleukin 6 (IL-6), increase with age and in diabetes and other comorbidities [32]. Erythropoietin inhibition and hepcidin induction are mechanisms that can contribute to the presence of anemia in thyroid disorders [33].

No abnormal hormone doses were found in hypothyroid patients; 62.0% of them had TSH values above the reference, which is characteristic of uncontrolled hypothyroidism; and 38.0% had euthyroid values (TSH values between 0.4 – 4.5 μUI/mL), which is the main goal of the treatment with different doses of Levothyroxine. Among patients with hyperthyroidism, 82.6% had low TSH values – i.e., below the reference value for euthyroidism. The treatment to control hyperthyroidism involves various aspects, and many clinicians would rather induce hypothyroidism with thyroidectomy or radioactive iodine, which can cause hypothyroidism. According to the consensus of the Brazilian Society of Endocrinology and Metabolism, there are three types of clinical management of hyperthyroidism – first, antithyroid drugs, such as methimazole and propylthiouracil; second, treatment with ^{131}I; and third, the most definite one, total thyroidectomy [34].

Another important point to discuss in this study is the presence of comorbidities in the study population. There were relevant percentages of chronic diseases such as diabetes, hypertension, cardiac dysfunction, and smoking. A prediction model was made to associate any thyroid disorder with these comorbidities; the statistical analysis found that patients with hypothyroidism are about 11 times as likely to have cardiovascular diseases, 5 times to have diabetes, and about 4 times to have hypertension as patients with hyperthyroidism.

The literature reports the action of thyroid hormones in the myocardium, stimulating myocardial protein synthesis. The absence of this hormone, as in hypothyroidism, may lead to bradycardia and decreased cardiac output. The effect on arterial hypertension has also been studied, hypothesizing

the increase in peripheral vascular resistance in hypothyroid patients [35,36]. A European study group surveyed patients with major depressive disorder (MDD), comparing those with and without hypothyroidism – it found that 32.2% of MDD patients had both hypertension and hypothyroidism, whereas 16.6% of MDD patients had hypertension but not hypothyroidisiar.

Hypothyroidism is associated with an increased risk of atherosclerosis and cardiovascular events due to lipid and hemodynamic changes, such as, for example, changes in myocardial function and hypertension [37]. Small concentrations of circulating hormones can adversely affect the cardiovascular system, given that the receptors of the thyroid hormone are present in the myocardial and vascular endothelium of tissues, thus impairing contractility, increased heart rate, systolic hypertension, increased left ventricular mass and diastolic dysfunction [38].

Hyperthyroidism has been related to disturbances in bone metabolism, such as early epiphyseal maturation in children and bone loss, by stimulation of osteoclasts in adults, panic disorders, changes in fasting glucose and cardiovascular dysfunction. It is estimated that atrial fibrillation is found in 10 to 15% of patients with hyperthyroidism. In addition to atrial fibrillation, the heart can suffer hemodynamic changes, ventricular hypertrophy, and increase in blood volume, stroke volume, cardiac output and ejection fraction. Therefore, hyperthyroidism is associated with cardiopathies such as heart failure, cardiomegaly and pulmonary hypertension [39].

Conclusion

Considering the variations in anemia frequency results in thyroid disorders reported in the literature, data corroborate the characteristics of anemia in these patients, especially regarding MCV and Hb. There was a large percentage of anemics among patients with hypothyroidism and hyperthyroidism, indicating that erythropoiesis is a complex process regulated by various factors. Also, thyroid hormones have a critical role in regulating both erythropoiesis and erythropoietin concentrations.

Anemia in the study patients was normocytic and normochromic, which confuses many clinicians regarding its origin. Data collection revealed many reports of clinicians trying to discover the origin of the anemia, which was so far unexplained. Besides the hematologic, hormonal, and biochemical results, the frequency of some comorbidities, especially in hypothyroidism, reveals that thyroid disorders directly affect metabolism, changing the function of other systems, which in turn can somehow interfere with erythropoiesis.

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