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Frequency and characteristics of anemia in hypothyroid patients: A cross-sectional study

Abdullah S. Babaker[1], Reem M. Al-Qahtani[1,2]

Abstract:

BACKGROUND: Hypothyroidism leads to a metabolic slowdown that affects all body systems and significantly impacts the hematopoietic system, resulting in anemia in 20%–60% of patients. This study aims to evaluate the prevalence of anemia in hypothyroid patients and describe the factors associated with anemia in those patients.

MATERIALS AND METHODS: We reviewed the electronic health records (EHRs) of all the patients attending the Outpatient Department of King Abdulaziz University Hospital, Jeddah, Saudi Arabia, during January 1, 2018, to December 31, 2022. All patients aged 18-70 years who had received a diagnosis of hypothyroidism, ICD-10 code E03.9, and had undergone simultaneous blood tests for complete blood count and iron profile along with thyroid function tests were included in the study. Data on demographic characteristics, laboratory test results, and comorbidities was retrieved from EHRs. Anemia was defined according to WHO as Hb levels <12.0 g/dL in women and <13.0 g/dL in men. Data was analyzed using SPSS version 28.0. Categorical variables were presented as frequencies and percentages while continuous variables were described by mean and standard deviation. Multiple logistic regression was applied to determine the risk factors for hypothyroidism.

RESULTS: Study included a total of 413 patients with hypothyroidism; 40% of hypothyroid patients were found to be anemic and most had microcytic normochromic anemia. Logistic regression revealed that males had much lower risk of anemia compared to females (adjusted odds ratio [AOR] = 0.14; 95% confidence interval [CI]: 0.05–0.39), while obesity was associated with a higher risk of anemia (AOR = 1.67; 95% CI: 1.11–2.50).

CONCLUSION: A higher proportion of anemia was seen in patients with hypothyroidism, indicating a significant relationship between anemia, obesity, and gender. This highlights the importance of monitoring anemia in patients with hypothyroidism, especially in females and obese individuals.

Keywords:

Anemia, free thyroxine, free triiodothyronine, hemoglobin, hypothyroidism, Jeddah, Saudi Arabia, thyroid-stimulating hormone

[1]Department of Family Medicine, King Abdulaziz University Hospital, [2]Department of Family Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Address for correspondence:
Dr. Abdullah S. Babaker, Department of Family Medicine, King Abdulaziz University Hospital, Jeddah 22252, Saudi Arabia.
E-mail: abd.babaker@gmail.com

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Introduction

Hypothyroidism is one of the most common diseases characterized by thyroid hormone deficiency, possibly caused by iodine deficiency or autoimmune thyroiditis.[1] It may be overt or subclinical.[2] Overt or clinical hypothyroidism occurs when thyroid-stimulating hormone (TSH) levels are higher than the normal range, and free triiodothyronine (FT3) and free thyroxine (FT4) are less than the reference range. Subclinical hypothyroidism is a condition in which TSH levels are elevated while normal levels of Thyroxine are maintained. The prevalence of hypothyroidism varies across the world.[3] In Europe, the prevalence of overt hypothyroidism in the general population is 0.2%–5.3%; in contrast, the prevalence of undiagnosed hypothyroidism,

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both subclinical and overt, has been estimated at approximately 5% based on a meta-analysis of seven studies. In the United States of America (USA), the prevalence of overt hypothyroidism and subclinical hypothyroidism is estimated at 0.3% and 4.3%, respectively.[2] In Saudi Arabia, the estimated prevalence of subclinical hypothyroidism in primary care settings is 10.3%.[4] A study of 257 adults over 50 years of age attending an outpatient clinic in Jeddah showed that 35% had subclinical hypothyroidism.[5]

Thyroid dysfunction significantly impacts health outcomes, including cardiovascular and metabolic dysfunction and mental and bone health.[6-8] Hypothyroidism results in a metabolic slowdown in various body systems. The hematopoietic system is one of the most affected in patients with hypothyroidism, and anemia has been reported in 20%–60% of cases.[9] Thyroid hormones play a role in hematopoiesis in hypothyroidism and the severity of anemia, which can be determined by the degree of hypothyroidism. Normochromic normocytic anemia is the most frequently encountered type of anemia, the primary cause of which is bone marrow repression caused by thyroid hormone deficiency and the lack of erythropoietin production resulting from reduced oxygen requirements.[10] Pernicious anemia has also been associated with the presence of hypothyroidism, possibly due to hypothyroidism slowing intestinal motility, and impairing Vitamin B12 absorption.[11]

To the best of our knowledge, there is no study on the prevalence of anemia in hypothyroid patients in Jeddah, Saudi Arabia. The dearth of knowledge of this prevalence and association has a negative impact on our understanding of the well-being of the patients. Therefore, the aim of this study was to estimate the prevalence and identify factors affecting anemia in patients at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia, with hypothyroidism, and identify the characteristics of anemia in these patients.

Materials and Methods

This was a cross-sectional study of the electronic health records (EHRs) of patients attending the Outpatient Department (OPD) of KAUH, Jeddah, Saudi Arabia, between January 1, 2018, and December 31, 2022. Ethical approval was obtained from the Institutional Review Board vide Letter No. 134-22 dated 09/03/2022, with a waiver of informed consent since there was no direct relation with human subjects in this study.

Inclusion criteria consisted of male or nonpregnant females, aged 18–70 years, who had a labeled diagnosis of hypothyroidism through ICD-10 code E03.9, and had blood tests for complete blood count and iron profile (ferritin and serum iron) in the same encounter of the blood sample taken for the thyroid function tests (TSH, FT3, and FT4). The inclusion criteria were extended to all patients, irrespective of nationality, sex, or presence of chronic diseases.

Individuals with conditions such as hemolytic anemia, peptic ulcers, hemorrhoids, any apparent bleeding disorders, suppressed bone marrow function, or those who had received blood transfusion in the previous 3 months were excluded; all EHRs that fulfilled the inclusion criteria within the specified period were included.

The information on the diagnosis was obtained through EHRs, using ICD 10 code E03.9. Hence, patients labeled with this code were included as per the inclusion and exclusion criteria.

Furthermore, demographic data including age, sex, weight, height, body mass index (BMI), and nationality were collected. Regarding laboratory values, we included TSH, FT3, FT4, hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and iron profile if available (ferritin and serum iron).

Information on comorbidities such as hypertension (HTN), diabetes mellitus, atherosclerotic cardiovascular disease, renal insufficiency, autoimmune diseases (e.g., rheumatoid arthritis or systemic lupus erythematosus, thyroid cancer, or other malignancies), and iron supplements intake were all obtained.

Patients were classified into anemic and nonanemic according to the World Health Organization; anemia was defined as Hb levels <12.0 g/dL in women and <13.0 g/dL in men.[12] Regarding the normal ranges of TSH, FT3, and FT4, we depended on our study on the ranges of the local laboratory of the hospital.

The data were analyzed using the Statistical Package for the Social Sciences software version 28 (SPSS, IBM Corporation, Armonk, NY: USA). Categorical variables were presented as frequencies and percentages. While the continuous variables were described by mean with standard deviation, the Chi-square test or Fischer's exact test was used to test the association between the categorical variables. In contrast, an independent *t*-test was used to test the mean difference between groups. Pearson's product-moment correlation coefficient was used to assess the correlation between continuous variables; the correlation was classified as small (0.10–0.29), medium (0.30–0.49), and large (0.50). A multivariable logistic regression model was developed with nonanemic cases as the reference level for examining

factors associated with anemia. For all statistical analyses, statistical significance was set at $P < 0.05$.

Results

All demographic characteristics of the patients with confirmed hypothyroidism attending the outpatient clinic are presented in Table 1. There was a total of 413 participants, most of whom were female (90.1%), with a mean age of 41.8 ± 12.3 years of age. Nineteen percent of the study population had chronic diseases, with a significantly higher proportion of females in the anemic group compared to the nonanemic group (97.6% vs. 85%, respectively, $P < 0.001$). Furthermore, there was a higher percentage of the obese population in the anemic population compared to the nonanemic group (55.4% vs. 42.5%, $P = 0.02$). However, there were no statistically significant differences in age or nationality between groups. The distribution of chronic diseases was comparable between patients with anemia and those with no anemia. As regards comorbid conditions, the anemic cohort had numerically higher rates of HTN (14% vs. 8.5%, $P = 0.08$) and diabetes (13.3% vs. 11.3%, $P = 0.5$), although the difference was not statistically significant. Other chronic diseases were generally comparable between the groups.

The prevalence of anemia in patients with confirmed hypothyroidism was 40% (166 of 413 patients). Only 9% of the participants took iron supplements.

Table 2 also details mean values for TSH level, FT3, FT4, Hb, serum iron, MCH, and MCV, highlighting significant differences ($P < 0.001$) in serum Hb, serum iron, MCH, and MCV between anemic and nonanemic subjects. The key findings included the predominance of subclinical hypothyroidism in both groups (63% in anemic and 61% in nonanemic participants) followed by overt hypothyroidism (25% in anemic and 30% in nonanemic participants); the distribution of the thyroid disorders was comparable between both groups [Figure 1].

TSH levels in anemic individuals were slightly lower (12.4 ± 17.3 μU/mL) compared to nonanemic individuals (14.1 ± 21.2 μU/mL), suggesting a variation

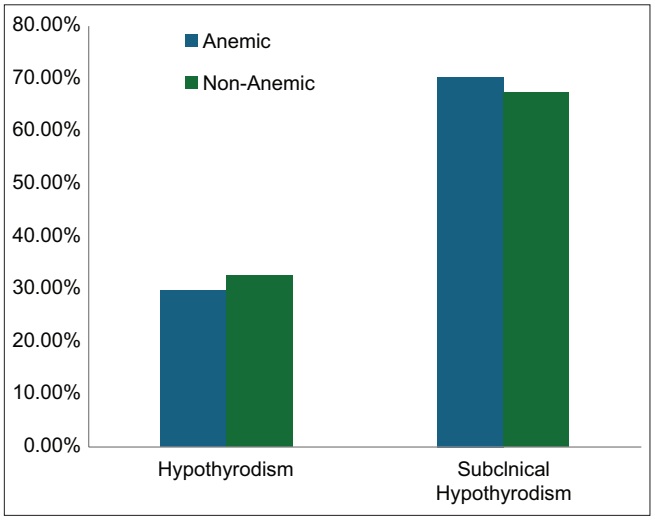

Figure 1: The distribution of anemia in patients with hypothyroidism at King Abdulaziz University Hospital, Jeddah, Saudi Arabia

Table 1: Demographic and health-related characteristics of hypothyroidism patients attending the Outpatient Department at King Abdulaziz University Hospital, Jeddah, Saudi Arabia (*n*=413)

Characteristics	Anemia		Total (*n*=413) *N* (%)	*P-value*
	Yes (*n*=166) *N* (%)	No (*n*=247) *N* (%)		
Gender				
Males	37 (22.3)	4 (1.6)	41 (9.9)	<0.001*
Females	162 (97.6)	210 (85)	372 (90.1)	
Age (years)	42.2±11.9	42±12.7	41.8±12.3	0.86
Nationality				
Saudi	107 (64.0)	156 (63.0)	263 (64.0)	0.8
Non-Saudi	59 (36.0)	91 (37.0)	150 (36.0)	
BMI	29.6±6.6	30.8±6.6	30.1±6.63	0.07
Obesity (BMI ≥30)	92 (55.4)	195 (42.5)	197 (47.6)	0.02*
Presence of chronic diseases	33 (20.0)	46 (19.0)	79 (19.0)	0.08
Comorbidities				
DM	22 (13.3)	28 (11.3)	50 (12.1)	0.5
HTN	23 (14)	21 (8.5)	44 (11.0)	0.08
ASCVD	2 (1.2)	6 (2.4)	8 (1.9)	0.5
Others†	8 (4.8)	11 (4.5)	19 (4.6)	0.8
History of thyroid cancer	1 (2.4)	1 (0.3)	2 (0.5)	0.2
Using iron supplements	15 (9.0)	11 (4.5)	26 (6.3)	0.06

*P<0.05 was significant, †Other diseases include heart failure, RA, SLE. Data are expressed as the *n* (%), and the *P*-value was calculated using a Chi-square test or Fisher's exact test. BMI=Body mass index, ASCVD=Atherosclerotic cardiovascular disease, HTN=Hypertension, DM=Diabetes mellitus, RA=Rheumatoid arthritis, SLE=Systemic lupus erythematosus

Table 2: Results of thyroid profile, complete blood count, and type of anemia for the patients diagnosed with hypothyroidism at King Abdulaziz University Hospital, Jeddah, Saudi Arabia (*n*=413)

Laboratory tests	Anemia		Total (*n*=413) *N* (%)	*P-value*
	Yes (*n*=166) *N* (%)	No (*n*=247) *N* (%)		
TSH status				
Within normal range	19 (11.0)	21 (8.5)	40 (9.7)	0.4
Subclinical hypothyroidism	105 (63.0)	151 (61.0)	256 (62.0)	
Overt hypothyroidism	42 (25.0)	75 (30.0)	117 (28.3)	
TSH level (μU/mL)	12.4±17.3	14.1±21.2	13.4±19.5	0.3
FT3 (ng/dL)	3.9±0.9	4.0±0.9	3.9±0.9	0.07
FT4 (ng/dL)	12.8±3.1	12.8±3.2	12.8±3.2	0.8
Hb	10.7±1.2	13.2±1.0	12.2±1.6	<0.001*
Iron	7.2±4.4	12.3±4.9	10.4±5.3	<0.001*
Ferritin	33.2±53.4	50.1±66.6	42.5±61.3	0.1
MCH	31.7±1.4	33.1±1.2	32.5±1.4	<0.001*
MCV	80±9	85±5	83±7.5	<0.001*
Using iron supplements	15 (9.0)	11 (4.5)	26 (6.3)	0.06
Anemia (n=166)				
MCV classification				
Microcytic	101 (60.8)			
Normocytic	63 (38.0)			
Macrocytic	2 (1.2)			
MCH classification				
Normochromic	97 (58.4)			
Hyperchromic	69 (41.9)			

*P<0.05, was significant. Data are expressed as mean±SD or the n (%) where appropriate, and the P-value was calculated using independent t-test, Chi-square test, or Fisher's exact test. TSH=Thyroid-stimulating hormone, FT3=Free triiodothyronine, FT4=Free thyroxine, Hb=Hemoglobin, MCV=Mean corpuscular volume, MCH=Mean corpuscular hemoglobin, SD=Standard deviation

in thyroid function in both groups, but the difference was not statistically significant (P = 0.3). Similarly, FT3 and FT4 levels, representing thyroid hormones, showed minimal differences between the anemic (FT3: 3.9 ± 0.9 pg/mL and FT4: 12.8 ± 3.1 ng/dL) and non-anemic (FT3: 4.0 ± 0.9 pg/mL and FT4: 12.8 ± 3.2) groups, with P values of 0.07 and 0.8, respectively, indicating no significant variation in thyroid hormone levels between these groups. Other continuous variables such as serum Hb, serum iron, MCH, and MCV were significantly lower in anemic individuals (P < 0.001); only the mean serum ferritin did not differ significantly between both groups; 60% of the anemic patients had microcytic anemia, while 58.4% had normochromic anemia.

Key findings included the predominance of subclinical hypothyroidism in both groups (63% in anemic and 61% in nonanemic participants) and notable differences in Hb, serum iron, MCH, and MCV, all of which were significantly lower in anemic individuals than in nonanemic individuals (P < 0.001).

Pearson correlation identified a weak positive correlation between the mean Hb and the FT3 (r = 0.1, P = 0.03); however, there was no significant correlation between serum FT4 and TSH levels with the serum iron (P > 0.05).

Table 3 displays the results from a multivariable logistic regression model examining the associations between selected factors and anemia risk in the 413 clinical cohort patients. After adjustment for confounders, male sex and low BMI were significantly associated with lower odds of anemia, whereas age, TSH level, and chronic disease status were not associated with the occurrence of anemia.

Males had 86.4% lower risk of anemia than females (adjusted odds ratio [AOR] = 0.14; 95% confidence interval [CI]: 0.05–0.39), while obesity defined by a BMI of 30 or higher was associated with 67% rise in anemia risk (AOR = 1.67; 95% CI: 1.11–2.50). However, age, TSH level, and chronic disease were not significantly associated with anemia in patients with hypothyroidism.

In summary, after adjustment for confounders, the analysis highlights male sex and lower BMI as protective factors against anemia in hypothyroidism patients. At the same time, no significant associations were observed for age, thyroid function, or chronic disease status in our study participants.

Discussion

The aim of our study was to investigate the prevalence of anemia in patients labeled with hypothyroidism

Table 3: Multiple logistic regression analysis: Risk factor for anemia in patients with hypothyroidism at King Abdulaziz University Hospital, Jeddah, Saudi Arabia (*n*=413)

Variables	β	SE	AOR	95% CI	*P-value*
Gender (male)	−2.00	0.54	0.14	0.05–0.39	<0.001*
Age	−0.01	0.01	1.00	0.98–1.01	0.57
Obesity	0.51	0.21	1.67	1.11–2.50	0.014*
TSH	−0.01	0.01	1.00	0.98–1.01	0.39
Chronic disease (yes)	−0.21	0.29	0.81	0.46–1.44	0.48

*P<0.05, a BMI of 30 or higher is considered obesity. SE=Standard error, AOR=Adjusted odds ratio, 95% CI=95% confidence interval, BMI=Body mass index, TSH=Thyroid-stimulating hormone

based on ICD-10 code E03.9. Owing to the nature of the study, we did not specifically target patients with new diagnosis or patients with impaired TSH, but rather relied on the ICD-10 code to retrieve targeted data from EHRs for the study, regardless of the duration of diagnosis, thyroid replacement therapy, or control status. 413 participants, predominantly females from Jeddah, Saudi Arabia, were included in the study. Most of the participants had subclinical hypothyroidism as per laboratory results. The study revealed a high prevalence of anemia in hypothyroid patients, with a statistically significant relationship between BMI and serum iron levels, as well as sex and Hb and ferritin levels. The results showed that most patients with anemia were microcytic normochromic. This study is the first in Saudi Arabia to address the prevalence of anemia and identify the factors affecting it.

Our research findings agree with those of Wopereis *et al*., who explored the link between thyroid function and anemia and discovered a significant association between hypothyroidism and anemia. Their comprehensive analysis, involving 23,235 participants in 12 cohort studies, indicated that lower serum FT4 levels and elevated TSH levels were significantly correlated with a higher risk of anemia.[13] Similarly, our observations on the prevalence of anemia in hypothyroid individuals in our study are in accord with the findings presented by Erdogan *et al*., which reported anemia rates of 43% in overt hypothyroid and 39% in subclinical hypothyroid groups.[9] Furthermore, a study by Patel RP (2017) highlighted an anemia prevalence of 75% in hypothyroid patients.[14]

The current study also examined the association of sex, age, obesity, and the presence of chronic diseases with anemia and thyroid function, a unique contribution to previous studies. A meta-analysis by Yang *et al*., found that maternal thyroid dysfunction is associated with an increased risk of gestational anemia. However, that study only focused on pregnant women but did not examine the impact of other factors, such as gender and BMI, on anemia.[15] The present study adds to the literature by investigating the relationship between obesity and anemia in patients with hypothyroidism. A review by Szczepanek-Parulska *et al*., emphasizes the vital role of thyroid hormones in developing red blood cell precursors and elucidates the way in which these hormones not only directly promote the growth of these cells but also enhance the production of erythropoietin, which is essential for erythropoiesis. Conversely, the presence of iron-deficiency anemia can adversely affect the status of thyroid hormones.[16] It also found (consistent with the present study's findings) that anemia was more common among women.[13] This concurrence points to the broader relevance of sex in understanding the epidemiology of anemia, especially in thyroid dysfunction.

Our study contradicts the review of Szczepanek-Parulska *et al*., which revealed that normocytic anemia is the most frequently observed type in individuals with thyroid issues, but revealed that 60% of patients with anemia have microcytic anemia. The same review stated that thyroid hormones play a crucial role in the growth of red blood cell precursors by directly stimulating their proliferation and increasing erythropoietin production. Hyperthyroidism and hypothyroidism were associated with significantly lower mean MCH, mean Hb, mean MCV, and hematocrit levels.[16]

Our findings indicate a mild positive association between Hb levels and FT3 levels, together with an absence of a significant correlation between serum iron levels and serum TSH, FT3, and FT4 levels. This is in contrast with the research conducted by Yilmaz *et al*., who found a noteworthy positive correlation between FT3 levels and serum iron levels in addition to a negative correlation between TSH levels and serum iron levels.[17] The observed discrepancies in our study, particularly the lack of significant correlation between serum iron levels and thyroid hormone levels, might be attributed to the incomplete iron profile assessments of our participants. Not all individuals included in our analysis had undergone comprehensive iron profiling, which could have influenced the detection and strength of the potential correlations between iron status and thyroid function.

Our study has several limitations that impact outcomes and interpretations. First, the study was limited by its cross-sectional design, which precludes the establishment of causality. This design identifies associations but not the direction or causality of these relationships. Second, the small sample size may not accurately reflect the true prevalence rates and could have masked the true associations between serum Hb levels and thyroid hormone levels (TSH, FT3, and FT4). In addition, owing to the nature of the study, we could not obtain information about patients' intake or compliance with thyroid replacement therapy. There is a possibility

that some patients had already been diagnosed with hypothyroidism and on thyroid replacement therapy at the time of their first visit to OPD at KAUH, which might have affected the results.

These limitations raise concerns regarding the findings' robustness and applicability on a larger scale. In addition, the incomplete collection of iron profiles in the EHRs of all participants may have concealed significant associations with the thyroid profile.

Finally, the study included only patients from a single hospital in Jeddah, Saudi Arabia, which may thus limit the generalizability of the findings to other populations. Further research is needed to confirm these findings and examine the prevalence of anemia in patients with hypothyroidism.

Conclusion

This study found a high prevalence of anemia in patients with hypothyroidism, most participants with subclinical hypothyroidism. The results suggest a significant relationship between obesity, sex, and anemia. This study highlights the importance of monitoring anemia and thyroid function in patients with hypothyroidism, especially in obese individuals and females.

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Conflicts of interest
There are no conflicts of interest.

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