Type 2 Diabetes Mellitus Association with Anemia and Thyroid Status in the Southern Region of Saudi Arabia

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ABSTRACT

Objective: In this cross-sectional study we tried to evaluate the prevalence of thyroid dysfunctions and anemia in patients with type 2 diabetes mellitus in a cohort of diabetic patients from the southern region of Saudi Arabia.

Method: This is a retrospective cross-sectional study. Archived clinical data from the different private labs, governmental labs and various specialized clinics following the diabetic patients, from three biggest cities located in the southern region of Saudi Arabia, i.e., Abha, Khamis Mushayt, and Najran. We screened the baseline demographic characteristics, glycosylated hemoglobin (HbA1c), thyroid profile, iron profile, and erythrocytes indices. Data were analyzed by SPSS statistics for the window.

Results: There was a significant difference (p<0.05) in the mean value of FT4, TSH, Hbg, RBC, HCT, MCH, MCHC, serum ferritin and iron, respectively between female and male patients, while MCV and FBS showed no significant difference (p>0.05). Overall, 50.8% anemia was detected in the study population, among which there were 35.74% patients with a thyroid disorder (p=0.000). TSH shows a significantly negative correlation with Hbg, HCT, serum ferritin, iron, and a strong positive correlation with HbA1c.

Conclusion: Our study demonstrated the high incidence of thyroid dysfunctions and anemia in type 2 diabetes mellitus patients and continuous positive correlation of TSH with HbA1c, and negative correlation between TSH and iron profile. Furthermore, HbA1c demonstrated the significantly negative correlation with iron profile.

Keywords: Thyroid Dysfunctions, Hypothyroidism, Anemia, Type 2 diabetes mellitus, HbA1c, Hyperthyroidism

INTRODUCTION

Diabetes mellitus (DM) is one of the most common endocrine disorders, and it is a major cause of the morbidity and mortality throughout the world. According to the International Diabetes Federation (IDF), 537 million adults live with DM and are expected to increase 643 million by 2030 and 783 million by 2045[1]. Furthermore, 1 in 6 adults (73 million) are living with diabetes in the middle east and north Africa (MENA region and this number is expected to reach 95 million by 2030 and 136 million by 2045[1]. Saudi Arabia is one of the 21 countries and territories of the IDF MENA region, with a 17.7% prevalence of diabetes in adults[1]. Saudi Arabia has the second-highest DM rate in the Middle East and is ranked seventh globally[2].

Thyroid disorder is the second most common endocrine disorder in the world[3]. DM and thyroid disorder have been reported to affect each other mutually[4]. The Association between DM and thyroid disorder has been a topic of interest in clinical study worldwide[4,5]. Thyroid disorders are more common in type 2 diabetes mellitus[5,6]. Over time, many diabetic patients develop symptoms of thyroid dysfunction[6,7]. There is evidence that type 2 diabetes mellitus influences thyroid function at various levels, and in the other side the thyroid hormones impact glucose metabolism, pancreatic function, hematological profile, and iron profile[5,8-12]. Hypothyroidism is associated with decreased GIT glucose absorption, prolonged peripheral glucose accumulation, decreased hepatic glucose output, and decreased glucose utilization[13,14]. In subclinical hypothyroidism, insulin resistance is caused by a reduced rate of insulin-stimulated glucose transport rate due to poor expression of glucose transporter type 2 gene (GLUT 2)[5,15]. In addition, because insulin clearance is reduced in hypothyroid conditions, physiological insulin requirements are reduced[5,15]. In hyperthyroidism, increased glucose output from the liver is the primary cause of hyperinsulinemia and glucose tolerance, leading to insulin resistance development[16]. Thus, insulin resistance is the most critical link between thyroid dysfunction and type 2 diabetes mellitus, and it can be found in both hypothyroidism and hyperthyroidism[17].

Hypothyroidism can cause hypoplasia of erythroid cells in the bone marrow or proliferation of immature erythroid progenitor cells, while hyperthyroidism can cause hyperplasia of erythroid cells in the bone marrow[9,18,19]. Thyroid dysfunction, in general, can cause a variety of effects on blood cells and anemia of varying severity and type[9,20-23]. The main objective of the present study was to evaluate that association between type 2 diabetes mellitus, thyroid dysfunction and anemia in the southern region of Saudi Arabia

MATERIAL AND METHODS

This study was designed and conducted following the Helsinki Declaration standards[24]. In this retrospective cross-sectional study, the data were collected and screened over one-year period (December 2020 to December 2021) from private labs, governmental labs and the medical clinics serving the diabetic patients located in the three biggest cities of this region: Abha, Khamis Mushayt and Najran. The reports for the patients above 30 years and older with type 2 diabetes mellitus were reviewed and excluded for any incomplete biochemical

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data; and finally, a total of 1494 lab reports were included in this study. The reports from the screened participants were either from customers who visited the labs for a routine health check-up or as a follow-up on chronic health conditions. Various lab results, including blood profile, thyroid profile, glycated hemoglobin (HbA1c) and iron profile, were recorded from the electronic file system.

Definition of Variables: Type 2 diabetes mellitus, as defined by the American Diabetes Association, is characterized by fasting plasma glucose (FBG) level 126 mg/dl or higher and HbA1c (6.5% or higher)[25]. Thyroid-stimulating hormone (TSH) had a normal reference range of 0.35 to 4.94 µIU/mL, while free tetraiodothyronine (FT4) normal range is 0.7 to 1.48 ng/dL[9,26]. Thyroid dysfunction was defined as the presence of thyroid hormones that are abnormally high or low in comparison to the reference range, i.e., TSH level 0.35 - 4.94 µIU/mL and FT4 0.7-1.48 48 ng/dL[9,26]. According to this range, study participants with thyroid dysfunction were classified into four categories[9,26-29]. (a) Primary hypothyroidism: High TSH and low FT4 (b) Primary hyperthyroidism: Low TSH and high FT4. (c) Sub-clinical hyperthyroidism: normal FT4 and low TSH (d) Sub-clinical hypothyroidism: normal FT4 and high TSH. Low hemoglobin (Hbg) (below 12 g/dL in women and 13.5 g/dL in men) is the lab result predictor of anemia, which is further subdivided in our study into microcytic hypochromic (low MCV and MCH) and normocytic normochromic (normal MCV and normal MCH)[8,9,20,30]. Those two types of anemia are the most common and frequent types found in a diabetic patient clinically and biochemically, and the other less common types were not included in our study because of insufficient data.

Statistical Analysis: Statistical analysis was performed by IBM® SPSS, version 24 (SPSS Inc. Chicago, USA). Person Chi-square was used for analyzing categorical variables and expressed as frequency and percentage[8,31-36]. Kolmogorov-Smirnov test or Shapiro-Wilk test was used the assess the normality of data. Independent-samples T-test and Mann-Whitney test were used to analyze the difference between groups based on normally or non-normally distributed data[21,37]. Data were expressed as percentages, mean ± standard error of the mean (SEM) for normally distributed continuous data and median ± interquartile range (IQR) for no-normal continuous data[9,36]. The linear association between TSH, FT4, HbA1c, FBS, selected hematological parameters, iron profile, and correlation of these variables with gender and age was assessed using Spearman's correlation test[37-40]. The level of statistical significance was set at $p < 0.05$.

Ethical Approval: Ethical approval and subject consent waiver were obtained from the research ethics committee at King Khalid University (HAPO-06-B-001) (approval number ECM#2021-4405).

RESULT

The descriptive characteristic of the study population is presented in Table 1, overall, and by the age group and gender. Of the 1494, 65.9% (984) were female and 34.1% (510) were male (p=0.01), and the most representative age group was 51-60 years (n=600, 40.2%). The population mean age (mean±SD) was 55.73±11.59 years (median = 56 years), ranging from 30 to 86 years. There was a significant difference (p=0.006) between the mean age of females (55.83±11.30 years) and males (55.54±12.13 years). The median FT4 value was 1.02 (0.18) ng/dL in the overall population and was 1.30 (0.18) ng/dL and 1.0(0.18) in female and male respectively. The median (IQR) TSH, HbA1c and FBS were 3.21(4.10), 7.5(2.30), and 143 (52.25), respectively. The general characteristics and laboratory data of the study population stratified by gender are presented in Table 2.

The mean±SEM value of FT4, TSH, blood profile, serum ferritin, iron, and HbA1C in cohort with different types of anemia are presented in table 3. We observed a statistically significant difference in hematological profiles between different groups of anemia (p=0.000). The same is observed TSH (p=0.000), serum ferritin (p=0.000), iron (p=0.000) and HbA1c (p=0.046). The RBC count, serum ferritin, iron was significantly lower (p=0.000) in the population with normocytic normochromic anemia.

Table 1: Demographics of the study subject

	Age range				Total
	31-40	41-50	51-60	Above 60	
Female	8% (120)	9.1% (136)	28.3% (423)	20.4% (305)	65.9% (984)
Male	5.5% (82)	5.6% (83)	11.8% (177)	11.2% (168)	34..1% (510)
Total	13.5% (202)	14.7% (219)	40.2% (600)	31.7% (473)	100% (1494)

Table 2: Biochemical and hematological variables in patients with T2DM

	Female			Male			p* value
	Mean±SEM	Median±IQR	95%CI	Mean±SEM	Median±IQR	95%CI	
FT4 ng/dL	1.30±0.038	1.03±0.18	1.23-1.37	1.16±0.044	1.0±0.18	1.07-1.24	0.000 †
TSH µIU/mL	3.70±0.078	3.62±4.20	3.55-3.86	3.12±0.098	2.87±3.75	2.93-3.32	0.000 †
Hbg g/dL	12.89±0.069	12.90±2.70	12.75-13.03	13.98±0.091	14.30±2.80	13.80-14.16	0.000 †
RBC 10^{12} /L	4.73±0.022	4.74±0.87	4.68-4.77	4.91±0.33	5.00±0.82	4.84-4.97	0.000 †
HCT%	39.85±0.186	40.25±7.00	39.49-40.22	41.70±0.23	42.20±6.02	41.23-42.17	0.000 †
MCH Pg	28.67±0.078	28.90±2.88	28.52±28.83	29.01±0.099	29.20±2.60	28.80-29.19	0.017 †
MCHC g/dL	33.83±0.051	33.90±2.20	33.73-33.94	34.25±0.063	34.25±1.63	34.13-34.38	0.000 †
MCV (fL)	84.61±0.213	84.90±6.70	84.19-85.03	84.68±-.264	84.90±6.53	84.16-85.20	0.809 †
Serum ferritin µg/L	58.10±1.81	45.89±69.16	54.54-61.65	75.08±2.80	52.27±92.34	69.57-80.59	0.000 †
Iron µg/dL	48.73±0.93	37.46±5.40	46.90-50.55	61.01±1.15	76.52±48.34	58.73-63.27	0.000 †
HbA1c%	8.04±0.062	7.40±2.50	7.92±8.16	7.97±0.088	7.15±2.70	7.79±-8.14	0.140 †
FBS mg/dl	165.19±1.71	143±49	161.82-168.56	170.62±2.62	144±58.25	165.47-175.78	0.698†

* The level of statistical significance was set at p<0.05; †Mann-Whitney U Test.

At the same time, TSH level and HbA1c value were significantly higher in cohorts with normocytic normochromic anemia.

Across the cohort, the most common comorbid condition includes subclinical hypothyroidism (34.9%), among which there were 26.6% female (n=397) and 8.4% male (n=125). The prevalence of subclinical hypothyroidism was statistically significant among the female and male populations. (p=0.000), and normocytic normochromic anemia (41.2%), with 31.7% female (n=474) and 9.4% male (141). The prevalence of normocytic normochromic anemia stratified by gender was statistically significant (p=0.000). We observed a statistically significant difference in the prevalence of thyroid disorder in the study population with different categories of anemia stratified by gender. These data are presented in table 4. The prevalence of normocytic normochromic anemia was significantly higher in the thyroid disorder group (Figure 1).

Table 5 represents Spearman's correlation between the hematological, serum ferritin, iron, HbA1c, FBS with FT4 and TSH. It is observed that there is a strongly positive (r=0.916) and statistically significant (p=0.001) correlation between HbA1c and TSH. Furthermore, a strongly negative (r=-.635) and statistically significant (p=0.000) correlation was observed between iron profile and TSH. HbA1c demonstrated the significant (p=0.016) negative (r=-0.62) but strong correlation with iron profile. Similarly, a strong but significant negative correlation was observed between serum ferritin and TSH (r=-0.558, p=0.000); however, a weak but significant negative correlation was observed between serum ferritin and FT4 (Table 5).

DISCUSSION

Diabetes is one of the foremost causes of mortality and morbidity worldwide. The prevalence of type 2 diabetes mellitus continues to rise daily throughout the world, posing a significant threat to public health. Also, in the general population, thyroid disorders are pervasive endocrine disorders. Hence, having thyroid disorder and type 2 diabetes mellitus is not uncommon. Thyroid disorders significantly impacts normal physiology, and most of them need medical management. Many

Table 3: Biochemical and hematological variables (mean±SEM) in cohort with T2DM according to the presence of anemia

				p-value *
	Normocytic	**Microcytic**	**Non-Anemic**	
FT4 ng/dL	1.13±0.03	1.28±0.08	1.37±0.05	0.640†
TSH µIU/mL	4.50±0.09	3.83±0.17	2.54±0.07	0.000†
Hbg g/dL	11.79±0.06	11.23±0.11	15.10±0.04	0.000†
RBC 10^{12} /L	4.51±0.02	4.60±0.07	5.09±0.02	0.000†
HCT%	38.81±0.21	36.10±0.40	43.12±0.18	0.000†
MCH **Pg**	27.04±0.06	28.02±0.27	29.29±0.07	0.000†
MCHC g/dL	33.66±0.06	33.16±0.14	34.47±0.05	0.000†
MCV **(fL)**	81.27±0.15	77.83±0.87	84.99±0.20	0.000†
Serum ferritin µg/L	49.41±2.44	56.12±4.36	78.77±2.09	0.000†
Iron µg/dL	41.24±1.15	47.42±2.13	64.71±0.90	0.000†
HbA1c%	8.09±0.07	7.90±0.13	7.97±0.079	0.046†
FBS mg/dl	169.17±2.2	169.69±3.99	164.47±1.44	0.055†

* The level of statistical significance was set at p<0.05; †Analyzed by Kruskal-Wallis test

Table 4: Prevalence of thyroid disorder in cohort with T2DM according to anemia

Thyroid disorder	**Female**			**Male**			p-value
	Normocytic	**Microcytic**	**Non-anemic**	**Normocytic**	**Microcytic**	**Non-anemic**	
Subclinical hypothyroidism	28.8% (283)	7.1% (70)	4.5% (44)	12.4% (63)	2.4% (12)	9.8% (50)	0.000
Subclinical hyperthyroidism	2.3% (23)	0.8% (8)	4.1% (40)	1.2% (6)	1% (5)	6.5% (33)	0.071
Primary hypothyroidism	1.8% (18)	0.4% (4)	0.5%)5)	2.5% (13)	0.4% (2)	0.2% (1)	0.492
Primary hyperthyroidism	1.4% (14)	0.4% (4)	4.3% (42)	0.8% (4)	1% (5)	2% (10)	0.061
Euthyroidisim	13.8% (136)	4.9% (48)	24.9% (245)	10.8% (55)	5.1% (26)	44.1% (225)	0.000

Table 5: Results of correlation analysis using Spearman's test for the hematological indices, iron parameter HbA1c and FBS with TSH and FT4 level in all study participants

		Hbg	**RBC count**	**HCT**	**MCH**	**MCHC**	**MCV**	**Serum Ferritin**	**Iron**	**HbA1c**	**FBS**
FT4	r value	.003	.13	.350	.000	-.010	.000	-.087	.045	-.042	-.045
	p value	.910	.029	.047	.990	.698	.988	.001	.029	.106	.009
TSH	r value	-.330	-.22	-.39	-.026	-.058	.026	-.558	-.635	.916	.078
	p value	.000	.038	.013	.323	.026	.321	.000	.000	.001	.002
Iron	r value	.36	0.25	.034	.019	.027	.037	.014	-	-.62	.015
	p value	.007	.011	.191	.455	.298	.151	.588	-	.016	.558

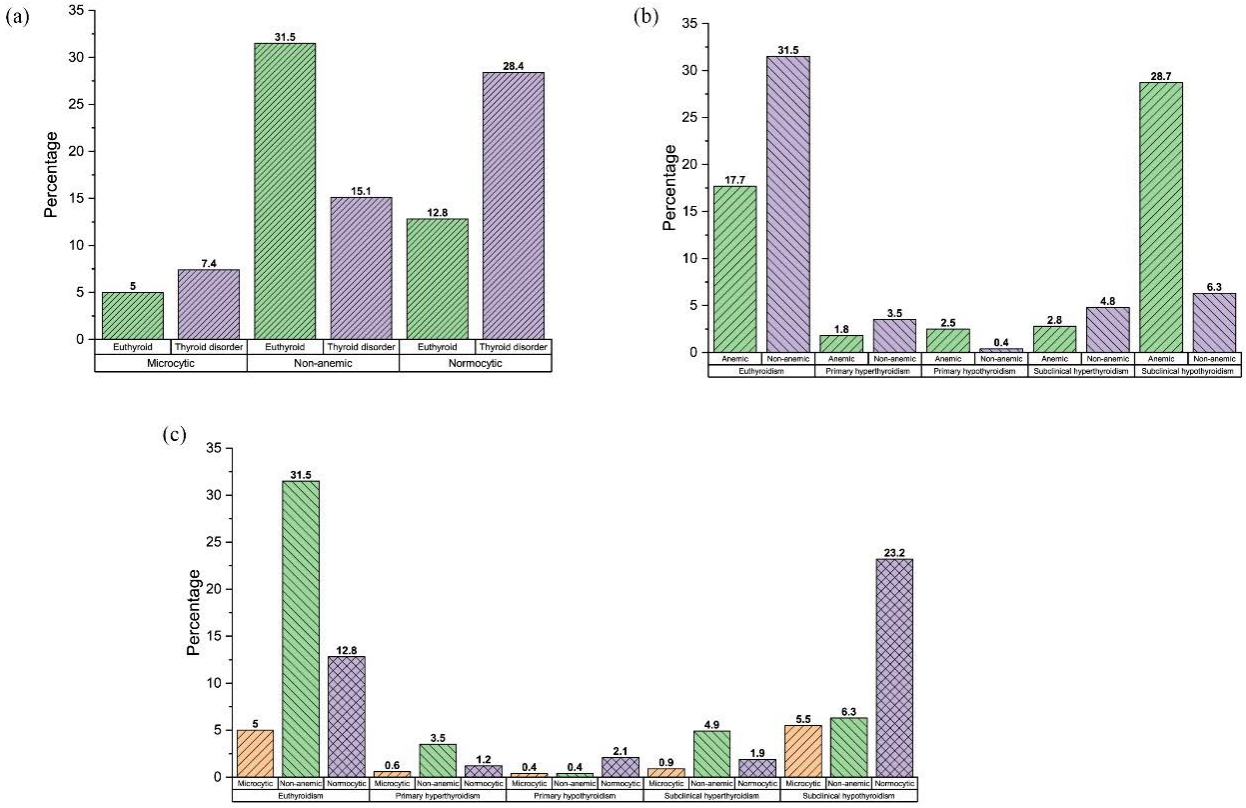

Figure 1: (a) Percentage and types of anemia according to a thyroid disorder (b) Percentage of anemia according to types of thyroid disorder (c) Percentage and types of anemia according to the type of thyroid disorder

of the symptoms that patients with thyroid disorders experience result from either an excess or a deficiency of thyroid hormones. The presence of thyroid dysfunction may have an impact on diabetes management. It is frequently associated with deteriorating glycemic control and an upsurge in insulin demands. Underlying factors include increased hepatic gluconeogenesis, rapid gastrointestinal glucose absorption, and possibly increased insulin resistance. Furthermore, Patients with type 2 diabetes mellitus are twice as likely as those without diabetes to develop anemia[41]. Bosman et al. reported that anemia is a risk factor for CVS and end-stage renal disease in type 2 diabetes mellitus[42]. Keane and Lyle demonstrated that diabetes patients with low Hbg levels are more likely to be hospitalized and may undergo premature death[43]. Anemia has a significant negative impact on quality of life in diabetics and is associated with disease progression and the development of comorbidities such as obesity and dyslipidemia, which are strongly associated with the diabetic framework and significantly contribute to the risk of CVS disease[44,45]. Our current report demonstrated the prevalence of thyroid disorders as well as anemia in diabetic group of population in the southern region of Saudi Arabia.

This study investigated the prevalence of thyroid disorder, anemia and the associations of TSH, FT4, erythrocytes indices, iron profile with type 2 diabetes mellitus in this area. The present study demonstrated thyroid disorder in 50.8% of the study population, and the most common thyroid abnormalities were subclinical hypothyroidism (34.9%) followed by subclinical hyperthyroidism (7.7%). This agrees with Aljabri et al., who reported 27% thyroid dysfunction in the type 2 diabetes mellitus study subject[11]. Aljabri et al. studied the prevalence of hypothyroidism in a Saudi community-based hospital in Jeddah and reported 29.1% cases with hypothyroidism[12]. Perros et al. reported the prevalence of 13.4% thyroid disorder in patients with diabetes[46]. Similarly, Radaideh et al. reported the prevalence of 12.5% thyroid disorder with type 2 diabetes mellitus[47]. Recently, Khassawneh et al. reported the prevalence of 26.7% thyroid disorder with type 2 diabetes mellitus[48]. In another study, Telwani et al. demonstrated that subclinical hypothyroidism was more prevalent (16%) in diabetic patients[49]. Furthermore, they also reported that primary hyperthyroidism and subclinical hyperthyroidism were more prevalent in the diabetic group[49]. The NHANES III study found a higher prevalence of thyroid disorder in diabetic patients compared to non-diabetics in the United States[50]. Our results are in agreement with the above finding.

The FT4 with fasting blood sugar shows significant correlation (r=-.045, p=0.09); however, TSH demonstrated the significant positive correlation (r=0.078, p=0.002). This agrees with the findings of Rong et al[46]. They demonstrated that high TSH levels and low FT4 were related to a higher risk of type 2 diabetes mellitus[46]. Also, Dimitriades and Ahren, in two different studies, reported that TSH shows an insignificant positive correlation and FT4 shows a significant negative correlation with blood sugar[47,48].

In this study, high prevalence of anemia was observed in diabetic patients. This altered pathophysiological process is due to the significantly high production of internal inflammatory markers and systemic inflammation, reduced production and release of erythropoietin and altered iron metabolism in chronic disease, this subsequently impairs the synthesis of red blood cells[46,54,55]. Thomas et al. observed in their study that anemia is a frequent co-morbid condition associated with diabetes[56]. Another investigation in Pakistan demonstrated that about 63% of the diabetic patients were suffering from anemia[57]. In our study, a significantly high prevalence of anemia was observed in female diabetic patients, and it was associated with

reduced RBC count, Hbg, HCT, MCH, and MCV. Furthermore, serum ferritin and iron concentration were significantly low in an anemic group compared with the non-anemic group of patients. Also, in our study, normocytic normochromic and microcytic hypochromic anemia were detected in the study population. The prevalence of both types was significantly high in females compared to males. Furthermore, Iron profile shows a significantly positive correlation with Hbg and RBC count and a strongly negative correlation with HbA1c. Also, TSH shows a significantly negative correlation with Hbg, HCT, serum ferritin, iron, and a strongly positive correlation with HbA1c. FT4 correlated significantly positively with Hbg. RBC, HCT, and weakly but significantly with serum ferritin and iron.

Also, the prevalence of normocytic normochromic anemia was significantly higher in the female with subclinical hypothyroidism. The findings of the present study agree with the previous report by Refaat et al. 2015[29] and Alqahtani et al. 2021[9]. Anemia is the most common hematological disorder associated with thyroid dysfunction, and it is characterized by low Hb concentration, low MCV, low MCH, and decreased RBC count[20,58-60]. Females suffer from anemia at a higher rate than males due to higher physiological requirements, less emphasis and priority on a balanced diet, and a delayed approach to healthcare facilities, which are exacerbated by early marriages and repeated pregnancies.

This study found that FT4 and TSH levels are significantly related to erythrocyte indices and iron parameters, implying that thyroid hormones may play a role in regulating erythropoiesis and iron metabolism[61-63]. In earlier research, thyroid dysfunction has been linked to abnormal red blood cell indices, and this study builds on these findings[23,64,65]. Thyroid hormones may directly affect bone marrow by influencing erythroid precursor proliferation[18,21], indirectly by inducing gene expression, and influencing erythropoietin secretion from the kidney[22,23,66]. Thyroid dysfunction in human hematopoiesis has been studied clinically by Kawa et al[19]. According to their findings, level of thyroid hormones influences the expression of its receptor on human hematopoietic cells[19]. Furthermore, Thyroid status also has an effect on clonogenicity and promotes apoptosis in CD34C-enriched hematopoietic progenitor cells[19].

Although anemia has been reported with various thyroid disorders, it is more common in hypothyroidism than in hyperthyroidism[9,20,29,67]. Our study supports the earlier report as it demonstrates the significant increase in the prevalence of anemia in the subclinical hypothyroidism group compared to the euthyroid group. Our results suggest that thyroid disorder is common in patients with type 2 diabetes mellitus, accompanied by normocytic normochromic and microcytic hypochromic anemia, respectively, in the southern region of Saudi Arabia.

Our study has some limitations, such as the absence of weight and body mass index. Additionally, because this is a cross-sectional study, no distinction between cause and effect can be made. Furthermore, no follow-up patients were included in this study. Another limitation is that the results cannot be generalized to other populations because they are specific to the region studied in this study. Because the data were obtained from the records, potential confounders such as a family history of thyroid disorders and type 2 diabetes mellitus and diet history were not controlled for in this study.

CONCLUSION

Within the confines of the current investigation, this study demonstrated the high prevalence of thyroid dysfunctions and anemia in patients with type 2 diabetes mellitus, and a continuous positive correlation of TSH with HbA1c and negative correlation between TSH and iron profile was also observed. As a result, we conclude that screening for thyroid dysfunction and anemia with iron profile in patients with diabetes mellitus should be performed regularly to detect and manage these dysfunctions early. This will improve the overall quality of life while lowering their morbidity rate. As a result, proper management and control of thyroid dysfunction may reduce the risk of developing type 2 diabetes mellitus and vice versa. Future studies with a larger sample size from different centers are needed to confirm these findings, and more investigation is required to understand the key mechanism.

Authorship Contribution: All authors have participated sufficiently in the work and take responsibility for the content, including conceptualization, writing, editing or revision of the manuscript. Saif Aboud M Alqahtani: Study design, data collection and analysis and finalizing the manuscript. Adil Hassan Alshehri: Writing draft and data interpretation, finalizing the manuscript.

Potential Conflict of Interest: None

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