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Original Article

Thyroid dysfunction and associated risk factors among type 2 diabetic patients: a cross-sectional study

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Abstract. *Background and aim:* The link between diabetes and thyroid dysfunction has been established. Thus, the current study was carried out to estimate the prevalence of thyroid dysfunction, specifically hypothyroidism, and predictors of thyroid disorders in type 2 diabetes mellitus (T2DM) patients in Jordan. *Research design and methods*: In this cross-sectional observational study, 552 T2DM patients attending the Diabetes Center in Amman were included and underwent investigations for thyroid function. Information on demographics and risk factors for thyroid dysfunction was collected. Weight, height, and waist circumference were measured. All the patient-related biochemical data were extracted from their medical records. Patients were divided into three groups: those with euthyroidism, those with hypothyroidism (both established [old]s and new cases), and those with hyperthyroidism. P <0.05 was considered statistically significant. *Results*: The prevalence of hypothyroidism among T2DM was 21.0%. Hypothyroidism was significantly more common in females (26.1%) than in males (15.1%) (P = 0.002). There is a significantly higher proportion of diabetic patients who have hypothyroidism (38.2%) had a history of hypertension than those with euthyroidism (26.6%) (P = 0.035). Significant risk factors for hypothyroidism were BMI (OR 1.29 with 95% CI (1.056–1.577)), P= 0.013. Furthermore, the BMI cutoff value for predicting hypothyroidism in T2DM patients was more than 32.2 [(AUC) (95% CI (0.523–0.609)), P = 0.034]. Nevertheless, there were no significant associations between hypothyroidism and diabetes duration or HbA1C. *Conclusion*: Hypothyroidism is common among Jordanian diabetic patients. Obesity among the female gender could be an indicator for detecting hypothyroidism in T2DM patients. (www.actabiomedica.it)

Key words: hypothyroidism, predictors, risk factors, cross-sectional study, prevalence, obesity

Introduction

Thyroid dysfunction (TD) is a spectrum of thyroid gland disorders exhibiting either hypothyroidism or hyperthyroidism. It is the second most common condition that affects the endocrine system after diabetes (1), measured by the circulating thyroid-stimulating hormone (TSH) levels. Thyroid gland hormones regulate many organs that regulate glucose homeostasis by controlling pancreatic β-cell development (2). TD influences glycaemic control by increasing β-cell apoptosis, which results in glucose intolerance (3). TD and diabetes mellitus (DM) are closely connected. Thyroid disorders were more common in

poorly controlled T2DM patients (78.2%) than in well-controlled T2DM patients (4). Thyroid hormone fluctuations may predispose prediabetes to develop into T2DM (5). Hypothyroidism increases the risk of developing diabetic nephropathy and diabetic peripheral neuropathy (6). An imbalance in the production of thyroid hormones arises from the thyroid gland; TSH is produced by the pituitary gland and controlled by the hypothalamus. Hypothyroidism among DM patients results when nocturnal TSH is reduced, and TSH response to Thyroid release hormone (TRH) is reduced (7). Among diabetic persons, TD may be undiagnosed because many mutual symptoms are common among both conditions.

The diabetes-thyroid relationship is believed to be bidirectional. Thyroid hormones are crucial in metabolic processes by activities in the brain, skeletal muscle, liver, brown fat, and pancreas. It is expected to see individuals affected by both thyroid diseases and DM. The association between T2DM and TD is complex, with contradicting findings (8,9). It implicates many variables, including insulin resistance, metformin use, autoimmunity, and TSH's circadian rhythm. TD among T2DM worsens the quality of life with macrovascular and microvascular complications (10). Thyroid gland dysfunction is associated with obesity, metabolic syndrome, and insulin resistance (11,12). Risk factors for TD among T2DM patients include the age of more than 55 years, family history, female gender, poorly controlled diabetes,(4,13) duration of diabetes over ten years (14), and obesity (15).

Thyroid dysfunction prevalence was inconsistent with a range of 8.4% to 48%, which predominates among females, individuals over 50, and with poor glycemic control (16). Previous studies showed that the prevalence of thyroid dysfunction is higher among T2DM than the overall population; the prevalence varies between 5.4–31.4% (4).

In Jordan, the general prevalence of thyroid dysfunction was 11.9%, with about 76% of patients with thyroid dysfunction previously undiagnosed (17). Since the association between T2DM and thyroid dysfunction has been understudied, this study aims to determine the prevalence of thyroid dysfunction among T2DM patients and its associated risk factors.

Patients and methods

Study design and participants

A cross-sectional study was conducted at the Diabetes Center in Amman, Jordan, from the outpatient clinic between January 2022 and December 2022. The inclusion criteria of the subjects were T2DM patients aged >18 years old.

Sample size

The sample size was determined using the most recent T2DM prevalence rate estimate (18). Assuming that the prevalence of T2DM is 16%, 384 patients were estimated to be the minimum sample size required to estimate the prevalence within a margin of error of 5% at a significance level of 5% and power of 80%. The sample size was increased to increase power.

Demographics, medical history, anthropometric and laboratory data assessment

The two primary data collection methods were interviewing and extracting data from the electronic medical record system. Patients were interviewed for demographic information such as age, sex, marital status, educational level, and smoking history. Body mass index (BMI) was calculated as weight (kg) divided by height squared $(m)^2$: normal if BMI 18.5-24.99 kg/m^2, overweight if BMI 25-29.9 kg/m^2, and obese if BMI 30 kg/m^2. Waist circumference (WC) was measured in women and considered normal if less than 88 cm and in men if less than 102 cm (19). Waist-to-height ratio (WHtR) was calculated. A WHtR cutoff of ≥0.5 is commonly used as a universal cutoff for obesity (20). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured, and data on the duration of diabetes and the history of hypertension were collected.

Laboratory assessments

Glycosylated hemoglobin (HbA1c), hemoglobin (Hb), total cholesterol (TC), triglyceride (TG),

high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), serum creatinine (Scr), serum uric acid (SUA), serum vitamin B12, and thyroid stimulating hormone (TSH), were extracted from the electronic medical records. Depending on TSH levels, patients were classified into three categories: hyperthyroidism, hypothyroidism, and euthyroidism.

The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation. Where eGFR is expressed as mL/min/1.73 m^2 of body surface area and serum creatinine (Scr) is expressed in mol/L (21), the most commonly prescribed analysis in medical laboratories to estimate the glomerular filtration rate.

Ethics

As the study was approved by the Hashemite University Institutional Review Board (IRB) Committee (Approval Reference Number: 12/01/2021/2022) and the hospital where the study was conducted (approval reference number: 2275), all patients signed an informed consent form to participate in the study following the Helsinki Declaration.

Statistical analysis

The IBM SPSS Statistics program was used to analyze the data. (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp) and MedCalc Statistical Software version 19.5.1 (MedCalc Software bv, Ostend,

Belgium. Chi-square was used to analyze categorical variables. For continuous variables, one-way ANOVA was used. Receiver operative characteristic (ROC) curve and 95% confidence interval (CI) analyses were used to compare the predictive power of different anthropometric and biochemical parameters with hypothyroidism. The area under the curve (AUC) was used to compare the predictive power of different anthropometric and biochemical parameters for hypothyroidism. Receiver Operator Characteristic (ROC) was used to evaluate the accuracy of the anthropometric and biochemical parameters in discriminating hypothyroidism. The area under the ROC curve (AUC) measures these parameters' ability to discriminate. AUC between 0.90 and 1.00 has excellent discrimination ability; AUC from 0.80 to 0.90, 0.70 to 0.80, 0.60 to 0.70, and 0.50 to 0.60 indicates good, fair, poor, and fail discrimination ability (22). The risk factors for hypothyroidism were investigated using multivariate logistic regression, and the OR value and 95% CI were calculated. *P* value of less than 0.05 was considered significant.

Results

This study enrolled 587 T2DM patients. Table 1 displays the baseline characteristics of the study subjects. The study population was 55.9% male and 44.1% female, with a mean age of 59.5 years. Obesity indices such as BMI, WC, and WHtR revealed that 57.7%, 73.8%, and 96.0% of the subjects were obese, respectively. The prevalence of euthyroidism, hypothyroidism (both established [old] and new cases), and hyperthyroidism in the study population was 79.0%, 19.9%, and 1.1%, respectively, as shown in Figure 1.

The anthropometric and biochemical parameters of diabetic patients in euthyroid, hypothyroid, and hyperthyroid groups are given in Table 2. A significantly increased BMI and vitamin B12 were found in diabetic subjects with hypothyroidism (*P*=0.018, 0.017, respectively). In diabetic patients with hyperthyroidism, HbA1C, hemoglobin in females, and total cholesterol levels were significantly higher (P=0.011, 0.039, and 0.01, respectively). A significantly higher proportion of diabetic patients with hypothyroidism (38.2%) had a history of hypertension than those with euthyroidism (26.6%) (P = 0.035).

Area under the curve (AUC) and ROC cutoff levels that are used to determine the cutoff levels of anthropometric and biochemical parameters for predicting hypothyroidism are shown in Table 3 and Figure 2, a and b. The cutoff value of BMI was >32.2, with a corresponding specificity of 58.9% and sensitivity of 55.1% and area under the ROC curve [(AUC) (95% CI (0.523–0.609)), P = 0.034]. The cutoff value of HbA1C was ≤6.9%, with a corresponding

Table 1. Socio-demography and clinical characteristics of the study subjects.

Characteristics	Total	Euthyroid (n=436)	Hypothyroid (n=110)	Hyperthyroid (n=6)	*P*-values
Age [a] (years)	59.53 ± 10.9	59.35±10.8	59.97±11.4	64.5±9.6	0.464
Gender [b]					
Males	307(55.6%)	258(84.4%)	46(15.0%)	2 (0.7%)	**0.002**
Females	245 (44.4%)	177(72.2%)	64 (26.1%)	4 (1.6%)	
Marital Status [b]					
Single	14 (3.1%)	13(92.9)	1 (7.1%)	0 (0.0%)	0.919
Married	426 (92.6%)	339(79.6%)	84 (19.7%)	3 (0.7%)	
Widowed/Divorced	20 (3.1%)	15 (75.0%)	5 (25.0%)	0 (0.0%)	
Educational level [b]					
Primary	40 (9.0%)	32 (9.1%)	8(9.1%)	0 (0.0%)	0.306
Secondary	277 (62.4.3%)	214(60.6%)	61(69.3%)	2(66.7%)	
Post degree	127 (28.6%)	107(30.3%)	19(21.6%)	17(33.3%)	
Smoking History [b]					
Non-smoker	269(59.0%)	204(56.2%)	63(70.0%)	2(66.7%)	**0.056**
Smoker	187 (41.0%)	159 (43.8%)	27 (30.0%)	1 (33.3%)	
Diabetes Duration [b]					
< 10 years	350(76.8%)	281(77.6%)	67(73.6%)	2(66.7%)	0.662
>10 years	106 (23.2%)	81 (22.4%)	24 (26.4%)	1 (33.3%)	
Hypertension history [b]					
No	326(70.9%)	270(73.4%)	55(61.8%)	1 (33.3%)	**0.035**
Yes	134 (29.1%)	98 (26.6%)	34 (38.2%)	2(66.7%)	
BMI [a] (kg/m^2)					
Normal	56(10.3%)	46 (10.7%)	9 (8.4%)	1 (16.7%)	0.601
Overweight	181 (33.3%)	146(33.9%)	32(29.9%)	3(50.0%)	
Obese	307 (56.4%)	239(55.5%)	66 (61.7%)	2(33.3%)	
WC*					
Normal	138(26.4%)	118(28.2%)	19(19.2%)	1(20.0%)	0.176
Abnormal	384 (73.6%)	300 (71.8%)	80 (80.8%)	4 (80.0%)	
WHtR [†]					
Normal	22(4.2%)	18(4.3%)	3(3.0%)	1(20.0%)	0.180
Abnormal	499 (95.8%)	399(95.7%)	96 (97.0%)	4 (80.0%)	

Abbreviations: *Abnormal waist circumference: >102 cm male; >88 cm female. [†]Abnormal WHtR: ≥0.5. [a] Mean ± SD; [b] Frequency (n, %)

specificity of 80.3% and sensitivity of 36.3% and area under the ROC curve [(AUC) (95% CI (0.549–0.634)), P = 0.003]. Furthermore, significant AUC was seen in hemoglobin for the female gender and total cholesterol.

Table 4 shows the factors associated with hypothyroidism among patients with T2DM in multivariate analysis. Obese subjects were approximately 1.29 times more likely to have hypothyroidism than those with euthyroidism (OR=1.29, 95% CI: 1.056– 1.557, *P*=0.013).

Discussion

Thyroid dysfunction is a common health problem in T2DM patients. It has gained attention in endocrinology. Many studies with different designs and objectives have been conducted to determine the prevalence and risk factors associated with thyroid dysfunction in T2DM patients (4,23,24).

This study has found that the proportion of hypothyroidism and hyperthyroidism in T2DM was 112 subjects (19.9%) with hypothyroidism and six subjects

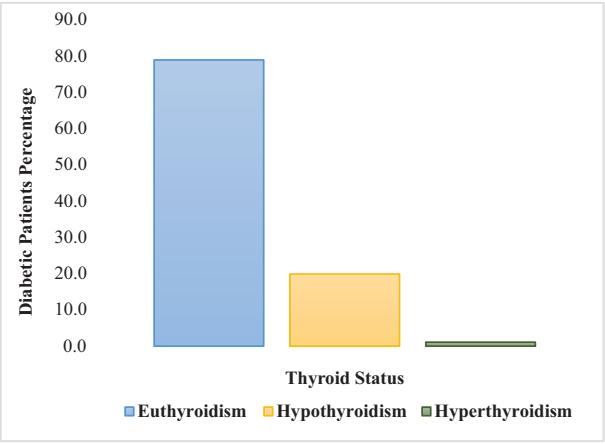

Figure 1. Distribution of diabetic patients according to thyroid status.

(1.1%) with hyperthyroidism. The proportion of thyroid dysfunction in this cross-sectional study was 21.0%. Our findings on the prevalence of thyroid dysfunction are consistent with previous studies on T2DM patients in Jordan and other countries. Two studies in Jordan found that the prevalence of thyroid dysfunction was (26.7% and 12.5%) (4,25). Four studies from India's various regions were reported (9.83%, 20.16%, 23.0%, and 28.0%) (13,24,26,27). In Saudi Arabia, two studies found that the prevalence was (23.0% and 28.5%) (14,28). A study in Egypt found 25.0 % of people had thyroid dysfunction (29). Thyroid diseases and T2DM are inseparably linked. Thyroid disorders can exacerbate T2DM, and diabetes can worsen thyroid dysfunction. Insulin resistance has been found to play a

Table 2. Comparison of clinical and biochemical parameters between euthyroid, hypothyroid, and hyperthyroid patients.

	Euthyroid (n=444) mean±SD	**Hypothyroid (n=112) mean±SD**	**Hyperthyroid (n=6) mean±SD**	***P*-values**
BMI (kg/m^2)	31.38 ±5.8	33.12 ±6.8	29.5 ±5.6	**0.018**
WC (cm)	107.0 ±15.1	108.0 ±15.9	93.6 ±22.6	0.120
WHtR	0.65 ± 0.09	0.66 ±0.10	0.57 ±0.12	**0.055**
SBP (mmHg)	138.5± 20.9	136.4±21.2	137.7± 16.0	0.680
DBP (mmHg)	80.5± 12.1	79.4± 12.3	87.0± 5.3	0.290
HbA1C (%)	8.50 ±1.7	8.01 ±1.8	9.5 ±3.2	**0.011**
Hemoglobin (g/dL) Males Females	 14.4±2.0 12.9±1	 14.2±1.2 12.6±1.5	 15.0±0.42 14.3±1.4	 0.722 **0.039**
Triglycerides (mg/dL)	186.5±114.9	199.7±151.8	201.9±72.9	0.650
Total cholesterol (mg/dL)	179.5±44.8	193.8±49.7	215.7±67.9	**0.010**
LDL-cholesterol (mg/dL)	119.9±50.4	112.9±36.3	115.2±65.6	0.540
HDL-cholesterol (mg/dL)	40.4±12.8	40.4±11.3	45.8±10.3	0.688
25-OH-vitamin D (ng/mL)	23.3±11.8	23.1±9.1	23.1±14.4	0.997
Creatinine (µmol/L)	92.8±54.8	100.0±67.9	70.1±18.3	0.300
eGFR (mL/min/1.73 m^2)	82.9±36.5	81.7±39.2	112.8±55.2	0.139
Vitamin B12 (pg/mL)	299.4±165.8	376.6±281.6	181.3±67.9	**0.017**
TSH (mU/L)	1.83±0.94	3.32±2.79	0.775±1.38	**<0.001**
Uric Acid (µmol/L)	345.9±112.2	348.5±98.8	433.5±34.2	0.385

*One one-way ANOVA test was applied

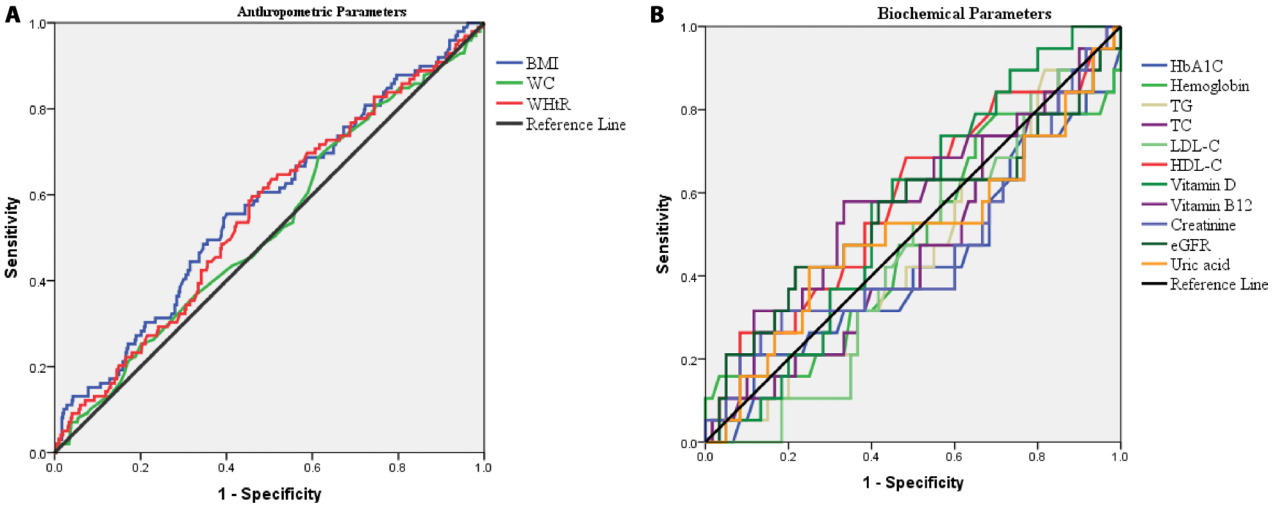

Figure 2. a: ROC curves that compare various anthropometric parameters as discriminators of hypothyroidism in T2D patents. BMI: body mass index; WC: waist circumference; WHtR: Waist-to-height ratio. b: ROC curves that compare various biochemical parameters as discriminators of hypothyroidism in T2DM patients. HbA1C: Glycosylated hemoglobin; Hemoglobin; TG: Triglycerides; TC: Total cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol; Vitamin D; Vitamin B12; Creatinine; eGFR: estimated Glomerular Filtration Rate; Uric Acid.

Table 3. Area under ROC curve (AUC), optimal cutoff values, sensitivities, specificities, and Youden index of anthropometric and biochemical parameters in predicting hypothyroidism in T2DM patients.

Variables	AUC (95% CIs)	Cutoff	Sensitivity (95% CIs)	Specificity (95% CIs)	*P*-value
BMI (kg/m^2)	0.566 (0.523-0.609)	>32.2	55.14	58.93	**0.034**
WC (cm)	0.520 (0.476-0.564	>101	68.69	38.52	0.527
WHtR	0.556 (0.512-0.599)	>0.65	59.60	53.72	0.083
HbA1C (%)	0.592 (0.549-0.634)	≤6.9	36.36	80.37	**0.003**
Hemoglobin (g/dL)	0.590 (0.564-0.633)	≤13.9	69.81	48.04	**0.003**
Triglycerides (mg/dL)	0.522 (0.474-0.570)	>175.4	48.31	57.82	0.517
Total cholesterol (mg/dL)	0.579 (0.530-0.626)	>228.3	25.00	89.05	**0.024**
LDL-cholesterol (mg/dL)	0.527 (0.472-0.581)	≤142.2	83.56	25.67	0.466
HDL-cholesterol (mg/dL)	0.509 (0.457-0.561)	>34.9	68.42	39.19	0.800
25-OH-vitamin D (ng/mL)	0.515 (0.457-0.572)	>11.9	92.75	19.33	0.680
Vitamin B12 (pg/mL)	0.571 (0.504-0.637)	>326	44.26	71.60	0.113
Creatinine (µmol/L)	0.519 (0.475-0.563)	>93.3	42.59	67.80	0.563
eGFR (mL/min/1.73 m^2)	0.520 (0.475-0.564)	≤54.1	33.33	79.57	0.541
Uric Acid (µmol/L)	0.525 (0.474-0.575)	>386.6	35.90	72.90	0.492

crucial role in both T2DM and thyroid dysfunction (8). T2DM also lowers thyroid-stimulating hormone levels and impairs peripheral tissue conversion of thyroxine (T4) to triiodothyronine (T3) (30).

One of the aims of this study is to assess factors associated with thyroid dysfunctions, particularly hypothyroidism, the most common disorder among T2DM patients. Many studies have found that age, female gender, obesity, diabetes duration, and glycemic control are all independent predictors of thyroid dysfunction in T2DM patients (14,31,32).

Table 4. Factors associated with hypothyroidism among patients with T2DM in multivariate analysis.

	B	OR (95 CI)	*P*-value
Gender			
Male		1	0.500
Female	0.804	2.23 (0.216-23.1)	
Smoking history			
Non-smoker		1	0.160
Smoker	-1.208	0.299 (0.056-1.61)	
Diabetes Duration			
< 10 years		1	0.315
>10 years	0.829	2.29 (0.455-11.54)	
Hypertension history			
No		1	0.069
Yes	1.491	4.44 (0.892-22.09)	
BMI	0.255	1.29 (1.056-1.577)	**0.013**
Waist circumference	-0.029	0.972 (0.846-1.116)	0.684
WHtR	0.562	1.75 (0.00-2.59)	0.966
HbA1C	-0.809	0.445 (0.233-0.850)	**0.014**
Hemoglobin	-0.056	0.946 (0.595-0.1.505)	0.815
TG	-0.008	0.992 (0.983-1.002)	0.123
TC	0.014	1.014 (0.998-1.031)	0.082
Vitamin D	0.036	1.037 (0.974-1.104)	0.252
Vitamin B12	-0.001	0.999 (0.992-1.006)	0.732
Creatinine	-0.005	0.995(0.971-1.020)	0.694
eGFR	-0.028	0.972(0.939-1.007)	0.115
Uric acid	0.002	1.002 (0.995-1.010)	0.513

This study found that hypothyroidism was significantly higher in women than men (26.1 vs.15.1 %, *P*=0.002). These findings are consistent with the previous studies. A case-control study in Jordan indicated that the female gender is a risk factor for developing thyroid dysfunction in T2DM patients (OR = 1.757, 95% CI: 1.123-2.747, *P*=0.013) (4). In China, Song et al. found that hypothyroidism was higher in hospitalized T2DM women than in men (10.8 % vs.3.4%); additionally, females were 2.02 times more likely to have hypothyroidism (OR = 2.02, 95% CI: 1.05-3.87) (33). According to one study conducted in South Africa, the prevalence of primary hypothyroidism in T2DM patients (34). Ogbonna and Ezeani found a significant association between thyroid dysfunction and female gender in Nigerian T2DM patients using binary logistic regression (OR = 3.8, *P* = 0.002) (31).

Thyroid disorders affect women more than men. The gender disparity can be explained in part by nodular thyroid growth, which occurs frequently in both premenopausal and postmenopausal women (35), and the mean age of the hypothyroidism patients in this study was 59 years.

Several studies have found a high prevalence of thyroid disorders in hypertensive patients (36,37). The current study's findings revealed that a significantly higher proportion of diabetic patients who have hypothyroidism (38.2%) had a history of hypertension than those with euthyroidism (26.6%) (*P* = 0.035). No significant association was obtained between hypothyroidism and hypertension in a descriptive-analytical study that included 41 hypertensive patients (38).

Obesity and central obesity are other risk factors that have received much attention due to their

association with hypothyroidism in T2DM patients (8,15,39). This study found that a large proportion of the patients (90.0%) were overweight or obese; additionally, approximately 74.0% and 96.0% had central obesity defined by abnormal WC and WHtR, respectively.

In three statistical tests, in a one-way ANOVA test, hypothyroid patients had significantly higher BMI (P=0.018) than euthyroid and hyperthyroid patients. Moreover, the cutoff value of BMI at >32.2 [AUC:(CI 95 %), 0.566 (0.523–0.609; P = 0.034)] was obtained to differentiate hypothyroid patients from euthyroid patients. Finally, multivariate analysis revealed that obese patients were 1.29 times more likely to have hypothyroidism (OR = 1.29, 95% CI: 1.056–1.577; P = 0.013). The findings of this study are consistent with those of previous studies. Nair et al. found that BMI was significantly higher in patients with clinical hypothyroidism than those with euthyroidism (28.2 vs. 26.5, P<0.001), and logistic regression analysis revealed that overweight/obese patients were 2.07 times more likely to have hypothyroidism (24). On the contrary, they documented that abdominal obesity showed no difference among subjects with hypothyroidism compared to euthyroid subjects. The findings contradict those of a previous study conducted in Jordan, which found that obesity is not a risk factor for hypothyroidism (4).

Ogbonna and Ezeani found a significant association between thyroid dysfunction and central obesity in Nigerian T2DM patients using binary logistic regression (OR = 2.5, 95%CI = 1.5–5.2, P = 0.001) (31).

The link between obesity and leptin could partly explain this. Leptin controls energy homeostasis and neuroendocrine, increasing TRH (40,41).

In our study, most T2DM patients had a duration of diabetes of less than ten years; no relationship was found between the duration of diabetes and thyroid dysfunction (Table 4). Similar studies found no significant link between diabetes duration and thyroid dysfunction (4,42). Conversely, some studies found a significant link between diabetes duration and thyroid dysfunction (14,31).

The present study has, however, a few limitations. Because the study was cross-sectional, establishing causality between the variables studied was difficult. Another limitation is that only a limited number of patients in a single center were involved.

Conclusions

Hypothyroidism was 21.0% among T2DM inpatients, and most had obesity, associated with higher odds of hypothyroidism in T2DM patients. Because thyroid dysfunction is so common among Jordanian T2DM patients, routine screening for thyroid dysfunction is highly recommended.

Acknowledgment: We want to thank every patient who took part in the study.

Ethics: As the study was approved by the Hashemite University Institutional Review Board (IRB) Committee (Approval Reference Number: 12/01/2021/2022) and the hospital where the study was conducted (approval reference number: 2275), all patients signed an informed consent form to participate in the study following the Helsinki Declaration.

Conflict of Interest: Each author declares that he or she has no commercial associations such as consultancies, stock ownership, equity interest, or patent/licensing arrangement that might pose a conflict of interest in connection with the submitted article.

Author Contributions: Conceptualization: All Authors; Data curation and analysis: JA, IA, D H Writing original draft preparation: AAL, HAL; Reviewed the manuscript for important intellectual content and editing: MA, MAl, AA. All authors have read and approved the final version of the manuscript.

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