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ORIGINAL RESEARCH

Prevalence and Predictors of Thyroid Dysfunction Among Type 2 Diabetic Patients: A Case–Control Study

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Background: Type 2 diabetes mellitus (T2DM) and thyroid disorders are common endocrine disorders. This case–control study aims to determine the prevalence and predictors of thyroid disorders in T2DM patients.

Methods: A total of 998 T2DM patients attending a tertiary hospital were included and underwent investigations for thyroid function: thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3); and glycated hemoglobin (HbA1c). They were compared with 343 non-diabetic subjects as controls.

Results: A total of 1341 participants were included in the study. The mean age ± SD was 60.14 ± 12.21, and 47.9% were females. Among T2DM patients, 140 (14%) were known to have thyroid disorders; and as a direct result of screening, 126 (12.6%) new cases of thyroid disorder were diagnosed. Thus, the overall prevalence of thyroid disorders was found to be 26.7% in T2DM patients which significantly higher than the controls (13.7%), ($p<0.001$). Subclinical hypothyroidism was the most common one. Using logistic regression, after adjusting for age, gender, obesity, smoking, anemia, presence of goiter, disease duration, and poorly controlled, the risk factors for thyroid dysfunction among T2DM patients were an age of ≥50 years with an adjusted OR of 3.895 (95% CI 2.151–7.052, $p<0.001$); female gender (OR 1.757, 95% CI 1.123–2.747, $p=0.013$); goiter (OR 2.904, 95% CI 1.118–7.547, $p=0.029$), and HbA1c>7% (OR 2.553, 95% CI 1.472–4.429, $p=0.001$). However, there were no significant associations between thyroid disorders and complications or duration of diabetes ($p>0.050$).

Conclusion: A high prevalence of thyroid disorders was reported in T2DM patients. Therefore, we suggest that diabetic patients should be routinely screened for thyroid dysfunction. Old age, female gender, goiter, and poorly controlled diabetes found to be risk factors for thyroid dysfunction among T2DM patients. Consequently, appropriate management and control of diabetes may lower the risk of thyroid dysfunction and vice versa.

Keywords: type 2 diabetes mellitus, DM, thyroid dysfunction, thyroid disorders, hypothyroidism, hyperthyroidism, poorly controlled diabetes

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most common chronic endocrine disorders and constitutes a major growing public health problem particularly in developing countries.[1] A previous study has found that the prevalence of diabetes was up to 17.1% in Jordan and is increasing.[2] On the other hand, thyroid dysfunction is commonly reported in the general population. Many studies have shown that the prevalence of hypothyroidism range between 0.2% and 4.8% whereas of hyperthyroidism between

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0.5% and 3.0%.[3–5] The association between diabetes and thyroid dysfunction has been known for decades.[6,7] Most of the researchers have studied the prevalence of thyroid disease among type 1 diabetic patients, due to the autoimmune nature of this disease.[8–10]

On the contrary, the association between type 2 diabetes and thyroid disorders has been understudying. Some studies have shown that the prevalence of thyroid dysfunction is higher in patients with type 2 diabetes than in the general population where exact prevalence varies among studies ranging between (5.4–31.4%).[11–14]

This case–control study aims to determine the prevalence and incidence of thyroid disorders in T2DM patients attending a tertiary referral hospital in the north of Jordan. Besides, evaluating the predictors of thyroid dysfunction in this such population.

Methods

Participants, Study Design, and Data Collection

Jordan is a Middle Eastern country with a population of 11 million. This single-center, case–control study was conducted in King Abdullah University Hospital (KAUH), Jordan between the period from March 2017 to March 2019. KAUH is a tertiary educational hospital that serves a population exceeding 2 million in the North of Jordan. In our hospital, we follow the American Diabetes Association (ADA) criteria for the diagnosis of diabetes which includes: a fasting plasma glucose (FPG) level of 126 mg/dL or higher, or a 2-hour plasma glucose level of 200 mg/dL or higher during a 75-g oral glucose tolerance test, or a random plasma glucose of 200 mg/dL or higher in the presence of classic symptoms of hyperglycemia or hyperglycemic crisis, or a glycated hemoglobin (HbA1c) level of 6.5% or higher.[15] Patients were eligible to be included in the study if they were Jordanians and diagnosed with T2DM based on archived records of a) having the disease for at least 12 months, b) having at least two HbA1c readings ≥6.5, c) diagnosed with an age >25 years, d) without insulin use in the first year after diagnosis, e) without a history of ketosis or ketonuria, and f) C-peptide was normal to high. These strict inclusion criteria were conducted to ensure T2DM diagnosis, and rule out type 1 diabetes and latent autoimmune diabetes in adults (LADA). Patients diagnosed with type 1 diabetes mellitus (T1DM), or LADA or those who refused to participate were excluded from the study.

Out of 5735 diabetic patients attending KAUH, Jordan between the period from March 2017 to March 2019, 998 (17.4%) T2DM patients were included in the study as a case group (Figure 1). On the other hand, a total of 343 subjects were included as an age- and gender-matched control group. This group was: a) neither diabetic nor impaired glucose tolerant as assessed by the history of normal HbA1c readings <5.7 or/and FPG levels of 99 mg/dL or lower, and having at least two documented readings; b) no history of taking anti-diabetic drugs; c) no history of any disease or medication that may affect the thyroid function. The control group was collected from the same hospital.

For both groups, venous blood samples were obtained from each patient to assay thyroid function: thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3), also, to measure HbA1c in T2DM patients. Serum TSH, T4, and T3 were measured by using the enzyme-linked immunosorbent assay (ELISA) method. HbA1c was assayed by using the turbidimetric inhibition immunoassay (TINIA) method. Demographic data, medical history, underlying comorbidities, medications, and laboratory findings were extracted from the electronic medical records. The normal range of values for TSH was 0.27–4.64 mIU/L, free T4 was 12–22 pmol/L, and free T3 was 3.1–6.8 pmol/L. Based on these reference ranges, overt hyperthyroidism was diagnosed when TSH< 0.27 mIU/L and free T4 >22 pmol/L and/or free T3>6.8 pmol/L. Overt hypothyroidism when TSH>4.64 mIU/L and free T4<12 pmol/L and/or free T3<3.1 pmol/L. Subclinical hyperthyroidism when TSH<0.27 mIU/L with normal free T4 and free T3. Subclinical hypothyroidism when TSH>4.64 mIU/L with normal free T4 and free T3. The subject that was found to have any of these thyroid function abnormalities or already diagnosed with thyroid disorder based on the medical records, was considered as a patient with thyroid dysfunction. Serum thyroid peroxidase antibodies (anti-TPO) (normal range <10U/L) was also assayed by ELISA. Among T2DM patients, the goal HbA1c was determined to be 7% according to ADA.[16] Thus, HbA1c >7% was defined as poorly controlled Diabetes Mellitus. Also, the albumin to creatinine ratio in an early morning spot urine sample that equals 3–29 mg/mmol was defined as microalbuminuria and ≥30 mg/mmol as macroalbuminuria.[17] Anemia was typically defined as a hemoglobin (Hb) level of less than 13.5 g/dl in males and as Hb of less than 12.0 g/dl in females.

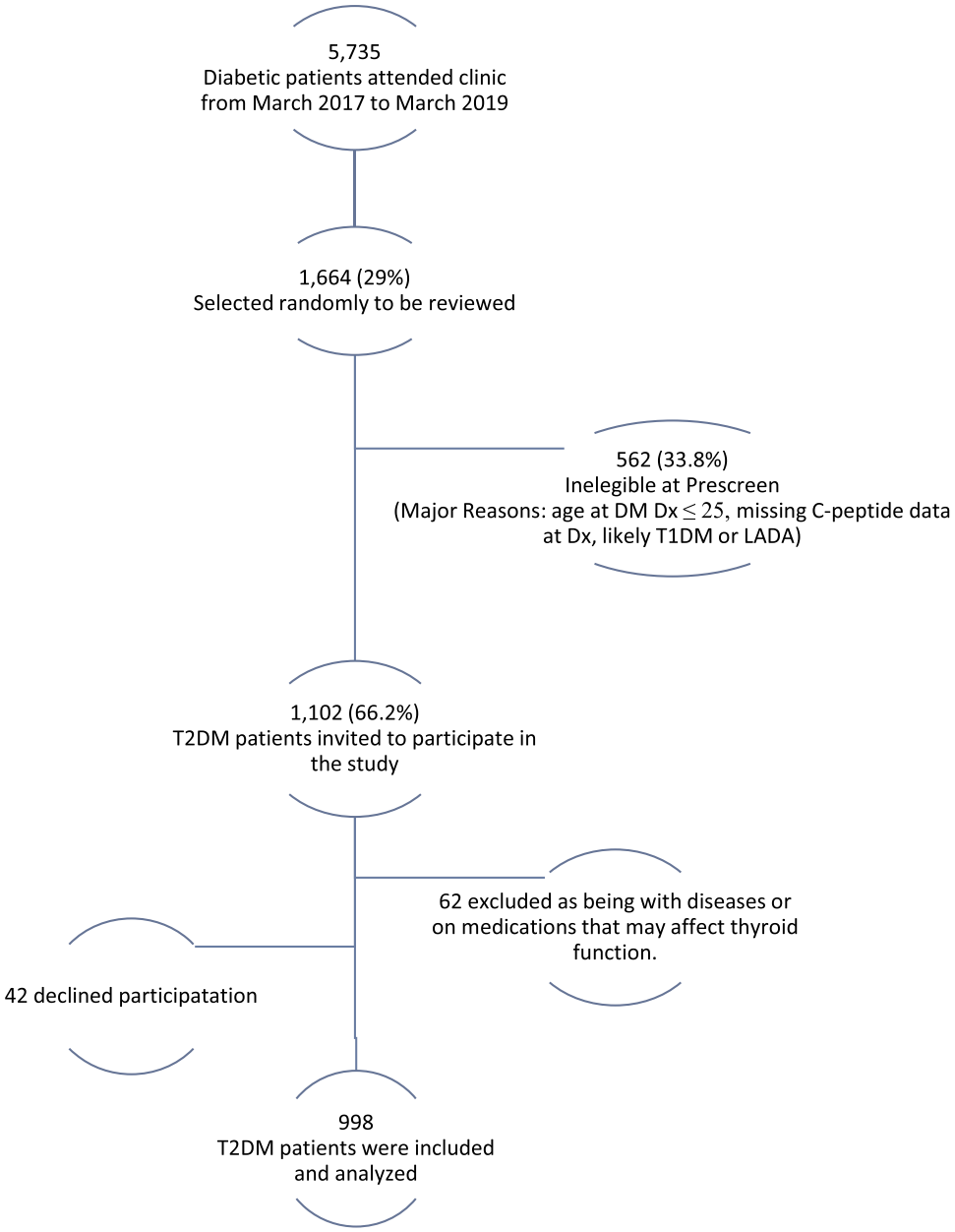

Figure 1 Type 2 diabetes mellitus patients flow chart.

Informed consent was obtained from the recruited participants. This study was approved by the institutional review board (IRB), and the research and ethics committee at Jordan University of Science and Technology and KAUH with an identified number (50/134/2020).

Statistical Analysis

The characteristics of participants were described using frequency and percentage for categorical variables and mean ± standard deviation for continuous variables. A chi-square test or Fisher's exact test was used to assess the association between categorical variables, whereas continuous variables were analyzed by the Student's *t*-test or ANOVA. These tests were used to figure out the differences between the T2DM patients' group and the non-diabetic subjects' group. To investigate factors associated with thyroid dysfunction among T2DM patients, chi-square test or Fisher's exact test, and Student's *t*-test or ANOVA were conducted to compare differences between groups with and without thyroid dysfunction among T2DM patients. A binary logistic regression model was used to assess the risk factors for the development of

thyroid dysfunction among T2DM patients after adjusting for age, gender, obesity, smoking, anemia, goiter, T2DM disease duration, and glycemic control. Odds ratio (OR) and their 95% confidence intervals (95% CI) were reported. A *p*-value of less than 0.05 was considered statistically significant. The IBM Statistical Package for Social Sciences Software (SPSS) for Windows, version 25.0 was used for data processing and analysis.

Results

A total of 1341 participants were included in the study. The mean age ± SD was 60.14 ± 12.21 and ranged from 30 to 93 years old, 642 (47.9%) were females. The T2DM patients' group consisted of 998 (74.4%) patients with a mean age ± SD was 60.13 ± 11.80 and ranged from 30 to 92 years old with 465 (46.6%) were females. T2DM patients were selected randomly, and following inclusion criteria, out of a total of 5735 diabetic patients with a mean age ± SD was 49.41 ± 17.41 and ranged from 2 to 100 years old with 2822 (49.2%) were females. On the other hand, the age- and gender-matched non-diabetics' group consisted of 343 (25.6%) subjects with a mean age ± SD was 60.15 ± 13.34 and ranged from 30 to 91 years old with 177 (51.6%) were females. The BMI of T2DM patients (31.14 ± 6.67 kg/m2) was significantly higher compared with that of control subjects (28.57 ± 5.47 kg/m2) ($p<0.001$). About one-quarter of participants were ex- or current smokers with higher prevalence (9.5%; 16.5%, respectively) among T2DM patients in comparison to control subjects (4.7%; 14.6%, respectively), ($p=0.009$). Comorbidities such as hypertension, dyslipidemia, ischemic heart disease, anemia, chronic kidney disease, and stroke were more prevalent in T2DM patients compared to non-diabetic subjects ($p<0.050$). Diabetic nephropathy and retinopathy were the most common comorbidities and complications in T2DM patients in this study. Serum creatinine and blood urea nitrogen were significantly higher in T2DM patients as compared to non-diabetic subjects ($p=0.001$). On the other hand, hemoglobin, and mean cell volume were significantly lower among T2DM patients as compared to non-diabetic subjects ($p<0.001$). Table 1 summarizes the demographic features, comorbidities, medications, clinical characteristics, and laboratory findings of the whole cohort.

Among the T2DM patients' group, 140 (14%) T2DM patients had a previous thyroid disease; hypothyroidism was identified in 125 patients: 76 (60.8%) with idiopathic hypothyroidism, 26 (20.8%) with Hashimoto thyroiditis, 18 (14.4%) post-thyroidectomy, four with panhypopituitarism, and one with Riedel's thyroiditis. Ten T2DM patients have hyperthyroidism, most of them (six patients) were on Thioamide treatment, two of them were diagnosed as Grave's disease, three were still having active disease post-RAI treatment, and five with idiopathic hyperthyroidism. Five euthyroid T2DM patients: 3 had thyroidectomy for large goiter, and two post-RAI treatment. The prevalence of established thyroid disease was higher in females comprised of 105 (75%) patients than in males with 35 (25%) patients ($p<0.001$). One hundred and twenty-six (12.6%) new cases of thyroid disease were diagnosed in the studied T2DM patients: subclinical hypothyroidism was diagnosed in 76 (7.6%) patients, overt hypothyroidism in 19 (1.9%) patients, subclinical hyperthyroidism in 20 (2%) patients, and overt hyperthyroidism in 11 (1.1%) patients. The overall prevalence of already known and newly discovered thyroid disorders among T2DM patients was 266 (26.7%) with a higher prevalence in females consisted of 166 (62.4%) than in males with 100 (37.6%), ($p<0.001$).

In the age- and gender-matched control group, thyroid disease was already known in 35 (10.2%) subjects, with hypothyroidism was the most common one (31 subjects, 9%), followed by 2 subjects (0.6%) had hyperthyroidism, and two (0.6%) euthyroid subjects; one post-thyroidectomy for large goiter, and one post-RAI treatment. In such a group, a new diagnosis of thyroid disease was made in 12 subjects, with a prevalence of 3.5%; subclinical hypothyroidism was discovered in 7 (2%) subjects, subclinical hyperthyroidism in 4 (1.2%), and overt hyperthyroidism in one (0.3%). No subjects were newly diagnosed with overt hypothyroidism. Among the control group, females were found to have a higher prevalence of thyroid disorders consisted of 33 (70.2%) than males 14 (29.8%), ($p=0.006$).

The univariate logistic analysis showed that thyroid dysfunction was significantly more prevalent in the T2DM patients' group composed of 266 (26.7%) compared to 47 (13.7%) among non-diabetic subjects with unadjusted OR of 2.289 (95% CI = 1.632–3.210, $p<0.001$). There was a lower serum-free T3 level and a higher level of serum-free T4 in T2DM patients as compared to the control group ($p<0.050$). On the other hand, the mean serum TSH levels were comparable between the two groups ($p=0.119$) (Table 2).

Thyroid peroxidase antibodies (Anti-TPO) were available for 90 (9%) T2DM patients and 15 (4.4%) subjects in the control group. Of the 90 T2DM patients, 64 (71.2%) had thyroid dysfunction, and anti-TPO was positive in 31

Table 1 Demographics, Clinical Characteristics, and Laboratory Findings of Cohort and the Differences Between the Two Groups

	All Cohort (n = 1341)	**T2DM Patients (n = 998)**	**Non-Diabetic Subjects (n = 343)**	***p*-value**
Age (years), m±sd	60.14 ± 12.2	60.13 ± 11.80	60.15 ± 13.34	0.978
Females	642 (47.9%)	465 (46.6%)	177 (51.6%)	0.109
BMI (kg/m^2), m±sd	30.66 ± 6.54	31.14 ± 6.67	28.57 ± 5.47	< 0.001
Smoking Status				0.009
Non-smoker	1015 (75.7%)	738 (73.9%)	277 (80.8%)	
Ex-smoker	111 (8.3%)	95 (9.5%)	16 (4.7%)	
Current smoker	215 (16.0%)	165 (16.5%)	50 (14.6%)	
Comorbidities				
Hypertension	910 (67.9%)	744 (74.5%)	166 (48.4%)	< 0.001
Dyslipidemia	371 (27.7%)	315 (31.6%)	56 (16.3%)	< 0.001
IHD	369 (27.5%)	336 (33.7%)	33 (9.6%)	< 0.001
Anemia	471 (35.1%)	402 (40.3%)	69 (20.1%)	< 0.001
CKD	114 (8.5%)	102 (10.2%)	12 (3.5%)	< 0.001
Gout	53 (4%)	35 (3.5%)	18 (5.2%)	0.153
Stroke	105 (7.8%)	92 (9.2%)	13 (3.8%)	0.001
Diabetes Complications				
Nephropathy	–	184 (18.4%)	–	
Retinopathy	–	170 (17%)	–	
PVD	–	58 (5.8%)	–	
Peripheral Neuropathy	–	61 (6.1%)	–	
Medications				
L-Thyroxin	148 (11%)	121 (12.1%)	27 (7.9%)	0.03
ACE inhibitors	267 (19.9%)	233 (23.3%)	34 (9.9%)	< 0.001
ARBs	425 (31.7%)	328 (32.9%)	97 (28.3%)	0.115
Thiazide diuretics	492 (36.7%)	413 (41.4%)	79 (23%)	< 0.001
CCB	371 (27.7%)	302 (30.2%)	69 (20.1%)	< 0.001
Beta-blockers	575 (42.9%)	479 (48%)	96 (28%)	< 0.001
Statins	776 (57.9%)	659 (66%)	117 (34.1%)	< 0.001
Fibrates	67 (5%)	45 (4.5%)	22 (6.4%)	0.162
PPIs	744 (55.5%)	558 (55.9%)	186 (54.2%)	0.588
Aspirin	670 (50%)	557 (55.8%)	113 (32.9%)	< 0.001
Nitrates	105 (7.8%)	96 (9.6%)	9 (2.6%)	< 0.001
Digoxin	21 (1.6%)	17 (1.7%)	4 (1.2%)	0.489
Clopidogrel	154 (11.5%)	136 (13.6%)	18 (5.2%)	< 0.001
Warfarin	28 (2.1%)	20 (2%)	8 (2.3%)	0.714
LMWH	28 (2.1%)	21 (2.1%)	7 (2%)	0.944
Allopurinol	58 (4.3%)	39 (3.9%)	19 (5.5%)	0.200
Colchicine	17 (1.3%)	10 (1%)	7 (2%)	0.138
Oral Hypoglycemic Medications				
Metformin	–	784 (78.6%)	–	–
Sulfonylureas	–	380 (38.1%)	–	–
DPP-4 inhibitors	–	120 (12%)	–	–
TZD	–	5 (0.5%)	–	–
GLP-1 receptor agonists	–	2 (0.2%)	–	–
Insulin	–	546 (54.7%)	–	–
Systolic BP (mmHg), m±sd	133.43 ± 18.31	134.07 ± 18.44	131.34 ± 17.80	0.032
Diastolic BP (mmHg), m±sd	81.38 ± 10.26	81.35 ± 10.39	81.49 ± 9.87	0.842

(*Continued*)

Table 1 (Continued).

	All Cohort (n = 1341)	T2DM Patients (n = 998)	Non-Diabetic Subjects (n = 343)	*p*-value
FPG (mg/dL), m±sd	158.67 ± 85.43	181.70 ± 87.26	89.86 ± 6.19	< 0.001
HbA1c (%), m±sd	7.51 ± 2.16	8.18 ± 2.00	5.19 ± 0.29	< 0.001
HbA1c <7%		322 (32.3%)		
HbA1c 7–8%		210 (21.0%)		
HbA1c >8%		466 (46.7%)		
Poorly controlled Diabetes	–	676 (67.7%)	–	–
Diabetes duration (years), m±sd	–	11.50 ± 8.57	–	–
Hb (g/dl), m±sd (total n. = 1277)	13.14 ± 1.87	12.91 ± 1.88	13.77 ± 1.71	< 0.001
Hb ≤ 13, n./total n.	590/1277 (46.2%)	481/937 (51.3%)	109/340 (32.1%)	< 0.001
MCV, m±sd	83.45 ± 7.83	82.71 ± 8.13	85.52 ± 6.55	< 0.001
S.Cr, m±sd	93.39 ± 73.33	97.68 ± 81.93	80.86 ± 35.81	< 0.001
BUN, m±sd	6.59 ± 6.01	6.97 ± 6.02	5.67 ± 5.90	0.001
Albumin: creatinine ratio in a urine sample (total n. = 385)				
Microalbuminuria, n./total n.	–	139/385 (36.1%)	–	–
Macroalbuminuria, n./total n.	–	52/385 (13.5%)	–	–

Abbreviations: T2DM, type 2 diabetes mellitus; BMI, body mass index; IHD, ischemic heart disease; CKD, chronic kidney disease; PVD, peripheral vascular disease; ACE inhibitors, angiotensin-converting enzyme (ACE) inhibitors; ARBs, angiotensin II receptor blockers; CCB, calcium channel blocker; PPIs, proton pump inhibitors; LMWH, low-molecular-weight heparin; TZD, thiazolidinediones; GLP-1 receptor agonists, glucagon-like peptide 1 receptor agonists; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; BP, blood pressure; FPG, fasting plasma glucose; S.Cr, serum creatinine; BUN, blood urea nitrogen.

(34.4%); 16 had subclinical hypothyroidism, 13 had overt hypothyroidism, and 2 had overt hyperthyroidism. Of the 15 subjects in the control group, 10 (66.7%) had thyroid dysfunction, and anti-TPO was positive in 8 (53.3%); 6 with subclinical hypothyroidism, and 2 with overt hypothyroidism. No subclinical hyperthyroidism cases were found in both groups with positive anti-TPO.

Table 3 shows the associations between the presence of thyroid dysfunction and different variables among T2DM patients. The majority of thyroid dysfunction patients were females (62.4%) with unadjusted OR of 2.4 (95% CI = 1.801–3.208, $p<0.001$). Approximately half of the T2DM patients with thyroid dysfunction (47%) found to have anemia in comparison to 37.8%

Table 2 Thyroid Disorders and Function in the Whole Cohort, T2DM Patients, and Non-Diabetic Subjects

	All Cohort (n = 1341)	T2DM Patients (n = 998)	Non-Diabetic Subjects (n = 343)	*p*-value
Thyroid Dysfunction	313 (23.3%)	266 (26.7%)	47 (13.7%)	< 0.001
Thyroid Disorders				< 0.001
Subclinical Hypothyroidism	152 (11.3%)	125 (12.5%)	27 (7.9%)	
Overt Hypothyroidism	106 (7.9%)	95 (9.5%)	11 (3.2%)	
Subclinical Hyperthyroidism	28 (2.1%)	23 (2.3%)	5 (1.5%)	
Overt Hyperthyroidism	27 (2%)	23 (2.3%)	4 (1.2%)	
Thyroid Function Test				
TSH (μUI/mL), m±sd	2.79 ± 3.2	2.87 ± 3.21	2.56 ± 3.17	0.119
FT4 (μUI/mL), m±sd	15.84 ± 3.04	15.95 ± 3.10	15.55 ± 2.83	0.034
FT3 (μUI/mL), m±sd	4.53 ± 0.94	4.46 ± 0.95	4.73 ± 0.86	< 0.001
+ve Anti-TPO test, n./total n.	39/105 (37.1%)	31/90 (34.4%)	8/15 (53.3%)	0.161
Presence of goiter	34 (2.5%)	27 (2.7%)	7 (2%)	0.499

Abbreviations: TSH, thyroid-stimulating hormone; FT4, Free thyroxine; FT3, free tri-iodothyronine; Anti-TPO, Thyroid peroxidase antibody.

Table 3 Univariate Analysis of Factors Associated with Thyroid Dysfunction in T2DM Patients

	T2DM Patients without Thyroid Dysfunction (n = 732)	**T2DM Patients with Thyroid Dysfunction (n = 266)**	***p*-value**
Age (years), m±sd	60.11 ± 11.43	60.17 ± 12.78	0.945
Females	299 (40.8%)	166 (62.4%)	< 0.001
Obesity (BMI ≥ 30 kg/m^2)	201 (27.5%)	77 (28.9%)	0.643
Smoking Status			0.744
Non-smoker	538 (73.5%)	200 (75.2%)	
Ex-smoker	69 (9.4%)	26 (9.8%)	
Current smoker	125 (17.1%)	40 (15.0%)	
Comorbidities			
Hypertension	553 (75.5%)	191 (71.8%)	0.230
Dyslipidemia	239 (32.7%)	76 (28.6%)	0.220
IHD	248 (33.9%)	88 (33.1%)	0.814
Anemia	277 (37.8%)	125 (47%)	0.009
CKD	68 (9.3%)	34 (12.8%)	0.107
Gout	26 (3.6%)	9 (3.4%)	0.898
Stroke	62 (8.5%)	30 (11.3%)	0.175
Presence of goiter	14 (1.9%)	13 (4.9%)	0.010
Diabetes Complications			
Nephropathy	131 (17.9%)	53 (19.9%)	0.465
Retinopathy	135 (18.4%)	35 (13.2%)	0.062
PVD	46 (6.3%)	12 (4.5%)	0.290
Peripheral Neuropathy	41 (5.6%)	20 (7.5%)	0.263
Oral Hypoglycemic Medications			
Metformin	582 (79.5%)	202 (75.9%)	0.225
Sulfonylureas	288 (39.3%)	92 (34.6%)	0.171
DPP-4 inhibitors	80 (10.9%)	40 (15%)	0.078
TZD	3 (0.4%)	2 (0.8%)	0.499
GLP-1 agonists	2 (0.3%)	0	0.393
Insulin	393 (53.7%)	153 (57.5%)	0.282
HbA1c result categories:			< 0.001
HbA1c <7%	264 (36.1%)	58 (21.8%)	
HbA1c 7–8%	118 (16.1%)	92 (34.6%)	
HbA1c >8%	350 (47.8%)	116 (43.6%)	
Poorly controlled Diabetes	468 (63.9%)	208 (78.2%)	< 0.001
Diabetes duration (years), m±sd	11.65 ± 8.77	11.10 ± 7.98	0.544
Hb (g/dl), m±sd (total n. = 1277)	13.08 ± 1.88	12.47 ± 1.80	< 0.001
Low Hb, n./total n.	319 (46.4%)	162 (65.1%)	< 0.001
Albumin: creatinine ratio in a urine sample (total n. = 385)			0.770
Microalbuminuria, n./total n.	105/284 (37%)	34/101 (33.7%)	
Macroalbuminuria, n./total n.	39/284 (13.7%)	13/101 (12.9%)	

anemic T2DM patients with normal thyroid function (p=0.009). 4.9% of T2DM patients with thyroid dysfunction had a presence of goiter compared with 1.9% of T2DM patients with normal thyroid function (p=0.010). A significant association between the presence of thyroid dysfunction and glycemic control is noted. Poorly controlled T2DM patients had a significantly higher prevalence of thyroid disorders (78.2%) compared with those controlled T2DM patients (21.8%), (p<0.001). There were no significant associations between the presence of thyroid dysfunction and the complications or duration of diabetes (p>0.050).

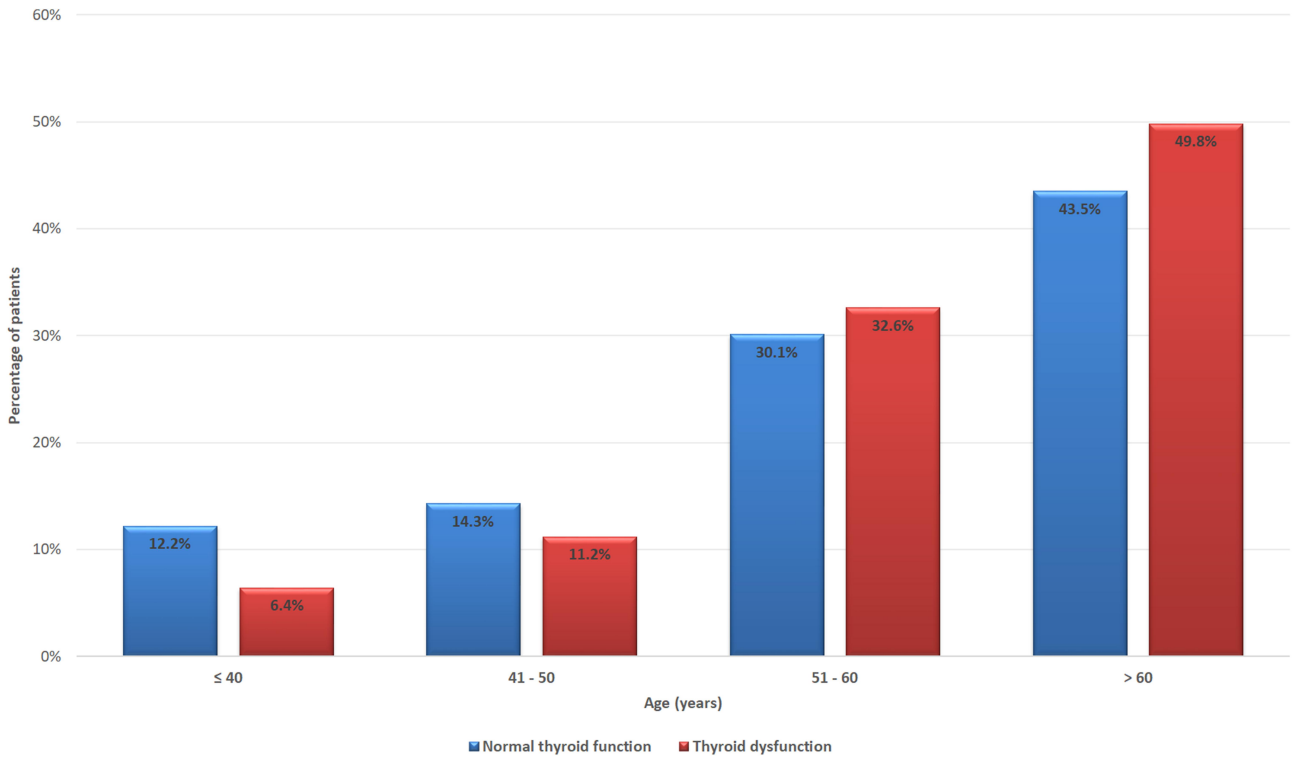

Figure 2 Age-specific prevalence of thyroid dysfunction in the whole cohort (p=0.008).

Among the whole cohort, participants' age was divided into four groups of ≤40 years, 41–50 years, 51–60 years, and >60 years. Prevalence of thyroid disorders was found to be significantly increased as the age increased with the lowest prevalence (6.4%) in the young age group and highest prevalence in patients older than 60 years old (49.8%), (p=0.008) (Figure 2). Among T2DM patients, the duration of diabetes was divided into 4 groups based on the quartiles as: ≤5 years, 6–10 years, 11–16 years, and ≥17 years. Diabetic patients with or without thyroid dysfunction did not differ regarding the duration of diabetes (p=0.141) (Figure 3).

Using binary logistic regression while adjusting for confounding factors including: age ≥50 years, gender, obesity (BMI ≥ 30 kg/m^2), active smoking, anemia, presence of goiter, disease duration, and poorly controlled diabetes mellitus among T2DM patients. The risk factors for developing thyroid dysfunction among T2DM patients were the age of 50 years or older with adjusted OR of 3.895 (95% CI 2.151–7.052, p<0.001); female gender with adjusted OR of 1.757 (95% CI 1.123–2.747, p=0.013); the presence of goiter with adjusted OR of 2.904 (95% CI 1.118–7.547, p=0.029), and poorly controlled diabetes with adjusted OR of 2.553 (95% CI 1.472–4.429, p=0.001) (Table 4).

Discussion

This case–control study shows a significantly higher prevalence of thyroid disorders among T2DM patients (26.7%) as compared to non-diabetic subjects (13.7%), with subclinical hypothyroidism was the most common one followed by overt hypothyroidism and hyperthyroidism. Besides, this study revealed that thyroid disorders were underdiagnosed in this population with 126 (12.6%) thyroid disorder cases were newly diagnosed during the conduction of this study. Old age, female gender, presence of goiter, and poorly controlled diabetes were found to be predictors of thyroid dysfunction among T2DM patients.

Previously, it has been observed that there were variations in prevalence rates of thyroid disorders among T2DM patients[12,13,18–26] (Table 5). Zhu et al[27] have reported a high prevalence of thyroid disorders in T2DM patients which is consistent with the findings of this study. On the contrary, Smithson[12] has reported lower prevalence rates for thyroid disorders in T2DM patients. The high prevalence of thyroid disorders in this study shows that there is a need for focusing on thyroid disorders screening in this target population. However, in the present study, the prevalence of thyroid disorders among T2DM patients was higher than the occurrence rates in healthy elderly populations,[28,29] and in the general population.[3–5]

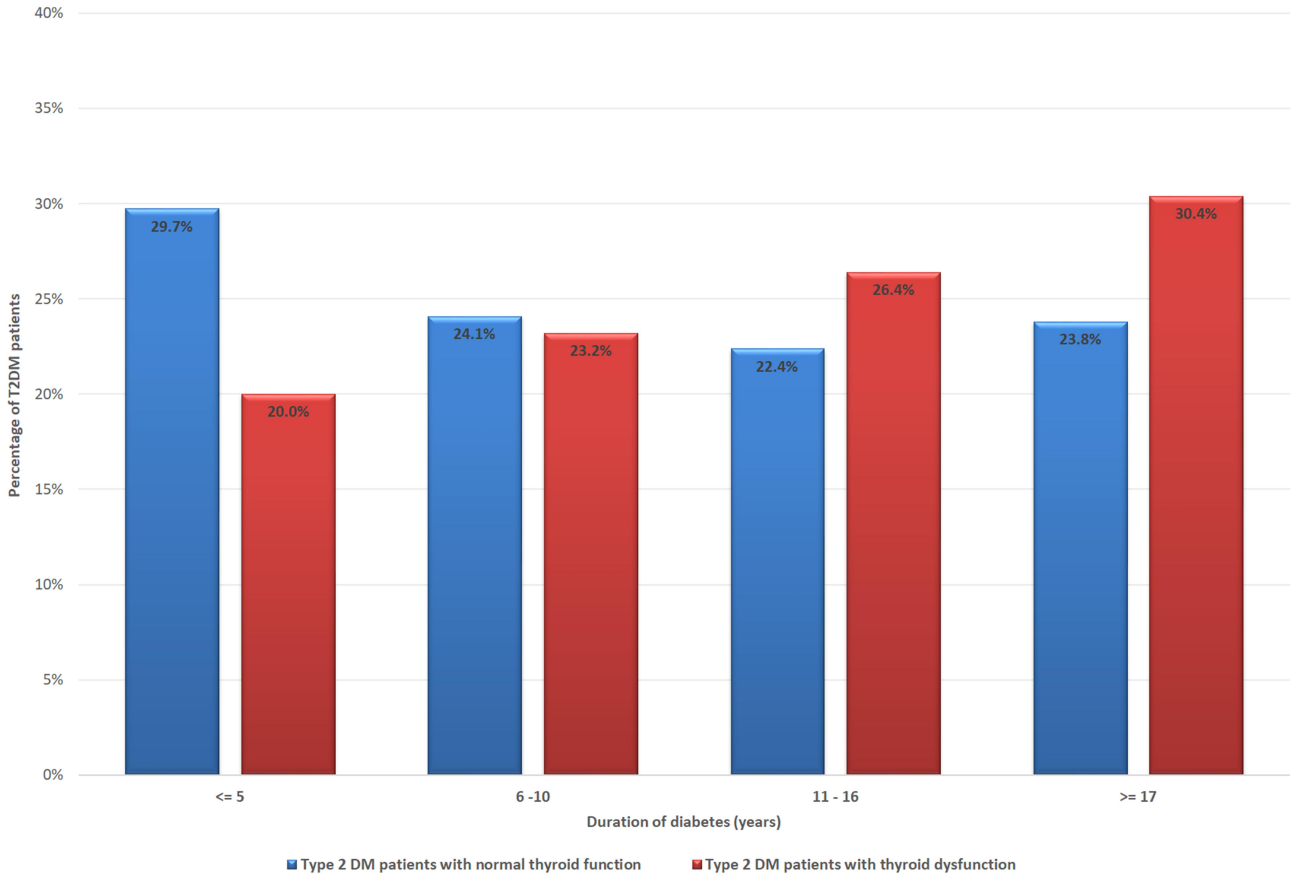

Figure 3 Prevalence of thyroid dysfunction according to duration of T2DM in quartiles (p=0.141).

It has been observed that the extent of T2DM patients who were incidentally diagnosed with thyroid disease during the conduction of this study was relatively high (12.6%) and approximate the prevalence of T2DM patients who were already known to have thyroid disorder before this study (14%). This finding was also consistent with a previous study on the Jordanian population.[19] The majority of the cases were already diagnosed with thyroid disorders because of the evident symptoms of their thyroid disorders, and additional frequent medical reviews with a physician. On the contrary, the lower diagnosis extent for subclinical hypothyroidism might be because of its asymptomatic nature and with non-certain complaints, which make patients inadequate for identifying subclinical hypothyroidism with the absence of routine thyroid dysfunction screening. However, the incidence of thyroid disorders among T2DM patients during the conduction of this study was relatively high (12.6%) with subclinical hypothyroidism was the most common one (7.6%) and revealed that thyroid disorders were underdiagnosed in this population. Therefore, we recommend regular monitoring among T2DM patients for thyroid function that might be significant to enhance health consequences as well as the quality of life in elderly patients with T2DM.[24,30–32]

Table 4 Predictors of Thyroid Dysfunction in T2DM Patients Using Binary Logistic Regression Test

Variables	Odds Ratio (95% C.I.)	*p*-value
Age ≥ 50 years old	3.895 (2.151–7.052)	< 0.001
Female gender	1.757 (1.123–2.747)	0.013
Obesity (BMI ≥ 30 kg/m^2)	1.241 (0.783–1.967)	0.359
Current smoker	1.019 (0.550–1.887)	0.953
Anemia	1.245 (0.797–1.947)	0.335
Presence of goiter	2.904 (1.118–7.547)	0.029
Duration of diabetes	1.006 (0.976–1.037)	0.708
Poorly controlled diabetes	2.553 (1.472–4.429)	0.001

In our study, we found a lower level of serum-free T3 and a higher level of serum-free T4 in T2DM patients as compared to the control group. This finding could be attributed to the effects of long-term hyperglycemia on

Table 5 Comparison of the Present Study Findings with Other Studies from Different Countries on Thyroid Disorders Among T2DM Patients

First Author	Area of the Study	T2DM Patients Sample Size	Age (m ± SD)	Female Gender	Prevalence of Thyroid Disorders	Subclinical Hypothyroidism	Overt Hypothyroidism	Subclinical Hyperthyroidism	Overt Hyperthyroidism
Present study	North of Jordan	998	60.13 ± 11.80	465 (46.6%)	266 (26.7%)	125 (12.5%)	95 (9.5%)	23 (2.3%)	23 (2.3%)
Jali et al[18]	India	713	–	296 (41.51%)	116 (16.2%)	–	100 (14%)	–	16 (2.2%)
Radaideh et al[19]	Amman-Jordan	908	50.8 ± 9.8	480 (52.9%)	113 (12.5%)	37 (4%)	56 (6.2%)	11 (1.2%)	4 (0.4%)
Demitrost et al[20]	India	202	–	141 (69.8%)	33 (16.3%)	23 (11.4%)	4 (2%)	3 (1.5%)	–
Papazafiropoulou et al[21]	Greece	1092	66.35 ± 11.94	568 (52%)	134 (12.3%)	–	–	–	–
Al-Geffari et al[13]	Saudi Arabia	411	59.0 ± 10.8	215 (52.3%)	117 (28.5%)	15.3%, 9.5%, and 0.5% were clinical, subclinical, and overt hypothyroidism, respectively.		11 (2.7%)	2 (0.5%)
Chubb et al[22]	Australia	382	64.0 ± 12.5	382 (100%)	40 (10.4%)	33 (8.6%)	–	7 (1.8%)	–
Díez et al[23]	Spain	1112	66.7 ± 12	647 (58%)	204 (18.3%)	94 (8.5%)	110 (9.9%)	–	–
Perros et al[24]	Scotland	904	53.8 ± 16.3	542 (60%)	161 (17.8%)	71 (7.9%)	61 (6.7%)	9 (1%)	19 (2.1%)
Smithson[12]	UK	184	64.7 ± 14.5	-	10 (5.4%)	4 (2.2%)	4 (2.2%)	1 (0.5%)	1 (0.5%)
Elgazar et al[25]	Egypt	200	54.15 ± 4.6	126 (63%)	58 (29%)	26 (13%)	14 (7%)	12 (6%)	6 (3%)
Palma et al[26]	Spain	304	60.7 ± 10.6	204 (67%)	44 (14.5%)	38 (12.5%)	2 (0.7%)	3 (1%)	1 (0.3%)

Note: Thyroid disorders were diagnosed according to the local reference ranges of each study.

the peripheral conversion of T4 to T3 and on the nocturnal peak of TRH secretion in T2DM patients.[33–36] Besides, insulin as an anabolic hormone, it boosts the levels of FT4 while it suppresses the levels of T3 by inhibiting the hepatic conversion of T4–T3.[37] On the other hand, the serum TSH level was not significantly different in T2DM patients and non-diabetic subjects which is consistent with Uppal et al findings.[38] However, elderly persons have more often elevated TSH Levels without illness value.[39]

T2DM patients in this study had a high mean (± SD) of HbA1c = 8.18 (±2.00). This reflects the poor glycemic status of most diabetic patients in our environment as more than half of the T2DM patients in this study did not achieve the glycemic goal, which is concordant with the pattern in earlier studies.[40–42] Poor drug adherence and financial constraints may be the major contributing factors.

Among T2DM patients, anemia was associated with thyroid disorders which is concordant with the previous knowledge that thyroid disorders such as hypothyroidism and anemia can occur simultaneously as thyroid hormones are responsible for the proliferation of erythrocyte precursors both directly and via stimulating erythropoietin production and iron-deficient anemia negatively influences thyroid hormone status. Thus, different forms of anemia might develop during thyroid dysfunction, and adding iron to thyroxine therapy improves both conditions compared to thyroxine therapy alone.[43–45]

In the present study, the high prevalence of diabetes complications such as nephropathy and retinopathy can be attributed to the advanced age of the study participants. The average age of the enrolled T2DM patients was 60 years old with 74.5% cases having hypertension and 31.7% having hyperlipidemia. Therefore, the occurrence of diabetes complications were high. However, in the present study, there were no associations between diabetes complications and thyroid disorders. Previously, the occurrence of diabetes comorbidities has been evaluated in several studies in patients with thyroid disorders.[46–49]

The association between aging and thyroid dysfunction has been already known for decades.[50–52] In this study, we found that the prevalence of thyroid disorders was significantly increased as the age increased independent of type 2 diabetes, and old age was a significant predictor for thyroid dysfunction among T2DM which is concordant with the findings of previous studies.[18,20] This can be explained by that elderly patients might have had undetected diabetes for a longer time. However, we did not find any significant association between thyroid dysfunction and the duration of diabetes. Al-Geffari et al 2013[13] found that the duration of diabetes >10 year is a risk factor for developing hypothyroidism in diabetic patients, in comparison to Diez et al, 2011[53] and Jali et al[18] that found no association between thyroid disorders and duration of diabetes which is concordant with our findings.

As shown in many other studies,[13,18,19,54] our study found that T2DM patients with thyroid dysfunction had a significant predominance of females with two times were more affected by thyroid disorders than males. Our study found that poorly controlled diabetes was associated with thyroid dysfunction among T2DM patients without establishing a causality relationship, as it was a cross-sectional study, which is consistent with the findings by previous studies.[14,18,55] Jain et al found that most diabetic patients who had thyroid disorder (81.25%) had HbA1c ≥7 in compared with 18.75% had HbA1c <7.[55] Also, Celani et al reported a high frequency of thyroid dysfunctions in acute hospital admissions of patients with poorly controlled diabetes.[14] Also, thyroid dysfunctions improved with the correction of plasma glucose levels in most of these patients.[14] Bagchi et al showed that the thyroid gland secretory response to large doses of TSH is decreased with poorly controlled diabetes among T2DM patients and strict glycemic control improves the response.[56] Several studies showed an inverse relationship between serum FT3 and HbA1c, and a positive relationship between TSH and HbA1c in the T2DM patients that could be attributed to the effect of prolonged hyperglycemia on the peripheral deiodination of T4 to T3.[33,34,57] These studies indicate that blood glucose, particularly HbA1c, can affect thyroid hormones. Thus, strict glycemic control can improve thyroid function and even correct thyroid hormone abnormalities without the need for thyroid dysfunction treatment. Besides, multiple antidiabetic drugs can affect thyroid function and impact the hypothalamic-pituitary axis by several mechanisms.[58]

On the other hand, several studies suggest that thyroid hormones can affect blood glucose. A large case–control study was conducted by Ardekani et al found that HbA1c was significantly higher in T2DM patients with thyroid disorder as compared to euthyroid patients (8.9 ± 1.99 vs 7.1 ± 1.02).[59] TSH may affect metabolic parameters and cause hyperglycemia by multiple mechanisms, including: stimulating leptin secretion,[60,61] increasing hepatic glucose production,[62] reducing insulin production and secretion from pancreatic β cells.[63] In a longitudinal study conducted by Jun et al[64] including a 6-year follow-up of a large sample of euthyroid subjects without diabetes (n = 17,061), to assess the association between the incidence of T2DM and the consecutive changes in serum TSH showed that the risk of incidence of T2DM was significantly increased with each 1 mIU/L

serum TSH increment. Thus, the relationship between thyroid hormones and blood glucose is complex as each one can affect the other. This present study also demonstrated the presence of goiter as a risk factor for thyroid dysfunction in T2DM patients which has been well known as a risk factor in diabetic patients,[53] as well as non-diabetics.[65]

This study had several strengths. The prospective nature of thyroid function and HbA1c tests were conducted in this study. The risk of selection bias was reduced by including a random sample of diabetic cases and compared with non-diabetic controls. The control group was included to see the viability of thyroid dysfunction in the studied population. All subjects were submitted to the same study protocol. We used a convenience sample of T2DM patients (n = 998). However, the studied T2DM patients were older than the whole cohort of diabetic patients. This could be explained by the inclusion criteria which include the age of diabetes diagnosis should be 26 years old or more in try to exclude T1DM patients. On the contrary, there were several limitations to this study. First, this study did not include individual changes over time and did not include follow-up of patients. Second, a lot of patients' information was obtained from electronic hospital records. Thereby, potential confounders were not adjusted in this study as a family history of thyroid disorders and dietary iodine. Third, we did not measure Glutamic Acid Decarboxylase (GAD) or islet cell autoantibodies. However, we rely on the age, insulin history, and C-peptide test result at the time of diabetes diagnosis to exclude the probability of T1DM, and LADA among our patients. Fourth, some types of selection bias may have occurred because the subjects of this study were attending a tertiary referral hospital and already under medical care. Fifth, the representativeness of our sample may be limited, since this was a local, hospital-based study in one center and conducted on the Jordanian population. Hence, our findings may not be applicable to diabetic patients receiving care in the primary care community and populations other than Jordanian. Sixth, the average age of the enrolled patients was 60.14 which may cause oversampling of older people.

Conclusion

A high prevalence of thyroid disorders was reported in patients with type 2 diabetes. Therefore, it was concluded that screening should be routinely performed for thyroid disorders among this such population to identify these disorders initially. This will reduce the morbidity among them and enhance their quality of life. Old age, female gender, presence of goiter, and poorly controlled diabetes found to be the risk factors for developing thyroid dysfunction among T2DM patients. Consequently, appropriate management and control of diabetes may lower the risk of developing thyroid disorders, and vice versa. Future studies with a larger sample size from different centers should be obtained for confirming these findings and more studies are needed to identify the underlying mechanism.

Data Sharing Statement

The datasets generated and analyzed during the current study are available with the corresponding author.

Compliance with Ethical Standards

All procedures performed in this study involving human participants were reviewed and ethically approved by the Institutional Review Board (IRB) of Jordan University of Science and Technology and King Abdullah University Hospital with an identified number (50/134/2020). This study was conducted following the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Disclosure

The authors declare that they have no competing interests for this work.

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