

Thyroid Dysfunction among Saudi Patients with Type 1 and Type 2 Diabetes Mellitus

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Abstract

Background and Objective: Diabetes Mellitus (DM) and thyroid dysfunctions (TD) are common endocrine problems encountered globally. Therefore, the aim of this study was to evaluate the prevalence of TD in patients with type 1 (T1DM) and type 2 (T2DM) Diabetes Mellitus in the western region of the Kingdom of Saudi Arabia (KSA).

Design: A “cross-sectional study” was conducted in the Diabetes centre at King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia from January 2018 to March 2019. Patients with T1DM and T2DM were included and diagnosed on the basis of American Diabetes Association criteria. Patients enrolled into the study were older than 12 years old. Thyroid stimulating hormone (TSH), free thyroxin (FT4) and HbA1c were measured. Hypothyroidism was defined as a clinical syndrome of hypothyroidism associated with elevated TSH > 4.2 mIU/l and decreased serum levels of FT4. Subclinical hypothyroidism was defined as elevated TSH > 4.2 mIU/l and normal circulating FT4. Hyperthyroidism was defined as TSH < 0.22 mIU/l with elevated FT4. Subclinical hyperthyroidism was defined as TSH < .22 mIU/l and normal circulating FT4. TD was diagnosed if any types of hypothyroidism or hyperthyroidism were found.

Results: A total of 158 patients (48.9%) with T1DM and 165 patients (51.1%) with T2DM were included in this study. There was a statistically significant higher prevalence of TD among T2DM in comparison to T1DM (26.7% vs. 17.1%) ($p = 0.04$). TD was found in 27 patients (38%) with T1DM and 44 patients (62%) with T2DM. Mean age of patients with T1DM were statistically significant younger compared to patients with T2DM (16.6 ± 2.1 and 24.8 ± 2.7 respectively, $p < 0.0001$). There was statistically significant more frequent of males compared to females in patients with T1DM (55.6% vs. 44.4%) and more frequent of females compared to males in patients with T2DM (84.1% vs. 15.9% respectively, $p = 0.001$). Mean HbA1c was statistically non-significant different between T1DM and T2DM patients (7.6 ± 2.7 vs. 7.3 ± 2.6 , respectively, $p = 0.8$). Patients with T1DM compared to patients with T2DM have statistically non-significant higher prevalence of hypothyroidism and lower prevalence of hyperthyroidism (92.5% vs. 90.9%) and (7.4% vs. 9.0%) respectively, $p = 0.9$. In addition, compared patients of T1DM with T2DM, there was higher prevalence of clinical (44.4% vs. 34.1%) and lower prevalence of subclinical (48.1% vs. 56.8%) hypothyroidism and clinical (3.7% vs. 4.5%) and subclinical hyperthyroidism (3.7% vs. 4.5%), $p = 0.9$. We found that age, gender, HbA1c and type of diabetes were statistically non-significant to be independent predictors of patients with TD.

Conclusion: Our results showed that TD occurred more frequently in patients with T2DM, in particular, females. Therefore, regular screening of thyroid function may be considered in all T2DM patients.

Keywords: Thyroid Dysfunction; Type 1 and Type 2 Diabetes

Introduction

The World health organization estimated that Diabetes Mellitus (DM) prevalence was 2.8% in 2000 and will be 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030 [1]. Saudi Arabia is the seventh of the top ten countries in terms of the prevalence of DM among the adult population [2]. DM and thyroid dysfunctions (TD) are common endocrine problems encountered by physicians globally [3]. In this regard, TD comprises hypothyroidism and hyperthyroidism. They have been shown to influence each other and associations between both conditions have been reported [4-6]. These findings are consistent from the studies of many researchers done globally. In general population, about 6% of people have some forms of TD [7]. However, the prevalence of TD increased to over 10% or more in people with DM. This was commoner in women as most women with type 1 diabetes mellitus (T1DM) have a 30% chance of developing autoimmune thyroid disease (AITD) [7]. Although type 2 diabetes mellitus (T2DM) is not an autoimmune problem, there have been reports of a higher occurrence of thyroid disease, especially hyperthyroidism among people with T2DM [7].

There was a large variability between studies in the general population, concerning the prevalence of overt or subclinical hypothyroidism ranging from 2 - 4% to 4 - 20%, respectively [8-11]. Subclinical hypothyroidism is the most common endocrinopathy among the different studies [9-13]. In contrast, the prevalence of overt or subclinical hyperthyroidism was much lower 0.3% and 1%, respectively [8-11]. The Wickham survey revealed that the prevalence of TD in male adults in England was 6.6% [14]. According to the National Health and Nutrition Examination Survey, hypothyroidism and hyperthyroidism were reported to have prevalence of 4.6% and 1.3% of the total participants, respectively [8]. A prevalence of 12.3% for TD in T2DM patients was reported in Greece and 16% in Saudi Arabia [3]. The frequency of TD was higher with advancing age. Reports have it that the prevalence of TD in diabetic population was reported to be 13.4% with higher prevalence (13.4%) in female T1DM as compared to 6.9% in male T2DM [15]. Sanchez-Lugo reported a total of 78 patients who had T1DM and were confirmed to have TD [16]. Radaideh, *et al.* conducted an investigation into the prevalence of TD in T2DM in Jordan and recruited students over a 6 month period. 5.9% of the DM patients had TD [17].

The Kingdom of Saudi Arabia (KSA), which is the largest country in the Middle East that houses approximately four-fifths of the Arabian Peninsula, supports a population of more than 33 million people [18]. Studies indicated, in the recent decades, a significant increase in prevalence and incidence rates of T1DM and T2DM in KSA [19-21]. Thus, it becomes imperative to study interrelationship between the two entities [22]. However, a few studies have evaluated the prevalence and characteristics of TD occurring with T1DM and T2DM in KSA. Therefore, the aim of this study was to evaluate the prevalence of TD in patients with T1DM and T2DM in the western region of KSA.

Methods

This cross-sectional study was performed in Jeddah, KSA between January 2018 to March 2019. Patients with T1DM and T2DM were included and diagnosed on the basis of American Diabetes Association criteria [23]. Patients enrolled into the study were older than 12 years old and had a health profile in King Fahad Armed Forces Hospital with regular attending to the Diabetes centre. We excluded individuals with history of recent or acute illness and history of taking drugs affecting thyroid function. Thyroid stimulating hormone (TSH) was measured with a chemiluminescent immunoassay method (CMIA) (Architect i2000 system, Abbott, USA). Serum free thyroxine (FT4) was estimated by radioimmunoassay. The assays have intra- assay precision of 4.3%. TSH levels between 0.22 - 4.2 mIU/L and Free T4 12.0 - 22.0 pmol/L were regarded normal [24]. Hypothyroidism was defined as a clinical syndrome of hypothyroidism associated with elevated TSH > 4.2 mIU/l and decreased serum levels of FT4. Subclinical hypothyroidism was defined as elevated TSH > 4.2 mIU/l and normal circulating FT4. Hyperthyroidism was defined as TSH < 0.22 mIU/l with elevated FT4. Subclinical hyperthyroidism was defined as TSH < .22 mIU/l and normal circulating FT4 [25]. TD was diagnosed if any types of hypothyroidism or hyperthyroidism were found. HbA1c was measured with high performance liquid chromatography and expressed as percentage. The study was approved by the ethical board of King Fahad Armed Forces Hospital.

Statistical analysis

Data are presented as means \pm standard deviation (SD) or numbers (%). Quantitative variables were compared between two groups by using the Student's test. Differences in categorical variables were analyzed using the chi-square test. Differences between TD types were tested with ANOVA. Logistic regression analysis was carried out to identify the independent predictors of TD considering age, gender, HbA1c and types of diabetes as risk factors and to estimate odds ratio (OR) and 95% CI. P value $<$ 0.05 indicates significance. The statistical analysis was conducted with SPSS version 23.0 for Windows.

Results

A total of 158 patients (48.9%) with T1DM and 165 patients (51.1%) with T2DM were included in this study. Average age of patients with of T1DM were statistically significant younger compared to patients with T2DM (Table 1). There was statistically significant more frequent of males compared to females in patients with T1DM and more frequent of females compared to males in patients with T2DM ($p <$ 0.0001). Mean HbA1c was statistically significant higher in patients with T1DM compared to patients with T2DM ($p <$ 0.0001). There was a statistically significant higher prevalence of TD among T2DM in comparison to T1DM (26.7% vs. 17.1%) ($p =$ 0.04).

Parameters		Type 1 diabetes	Type 2 diabetes	P value
Numbers		158 (48.9)	165 (51.1)	
Age (years)		16.1 \pm 2.1	24.4 \pm 2.6	$<$ 0.0001
Gender	Male	88 (55.7)	42 (25.5)	$<$ 0.0001
	Female	70 (44.3)	123 (74.5)	
HbA1c (%)		9.1 \pm 2.7	7.5 \pm 2.4	$<$ 0.0001
TSH (mIU/l)		4.0 \pm 13.0	3.8 \pm 6.6	0.8
FT4 (pmol/l)		13.5 \pm 2.9	13.8 \pm 4.3	0.5
Thyroid dysfunction		27 (17.1)	44 (26.7)	0.04

Table 1: Demographic characteristics of patients with type 1 and type 2 diabetes [mean \pm standard deviation or number (%)].

Table 2 showed the Clinical and biochemical characteristics of patients with type 1 and type 2 diabetes associated with thyroid dysfunction. TD was found in 27 patients (38%) with T1DM and 44 patients (62%) with T2DM. Mean age of patients with of T1DM were statistically significant younger compared to patients with T2DM ($p <$ 0.0001). There was statistically significant more frequent of males compared to females in patients with T1DM (55.6% vs. 44.4%) and more frequent of females compared to males in patients with T2DM (84.1% vs. 15.9% respectively, $p =$ 0.001).

Parameters		Type 1 diabetes with thyroid dysfunction	Type 2 diabetes with thyroid dysfunction	P value
Numbers		27 (38)	44 (62)	
Age (years)		16.6 \pm 2.1	24.8 \pm 2.7	$<$ 0.0001
Gender	Male	15 (55.6)	7 (15.9)	0.001
	Female	12 (44.4)	37 (84.1)	
HbA1c (%)		7.6 \pm 2.7	7.3 \pm 2.6	0.8
TSH (mIU/l)		14.4 \pm 29.6	8.8 \pm 11.3	0.3
FT4 (pmol/l)		13.6 \pm 4.2	14.9 \pm 6.9	0.4

Table 2: Clinical and biochemical characteristics of patients with type 1 and type 2 diabetes with thyroid dysfunction [mean \pm standard deviation or number (%)].

Table 3 showed the distribution of types of thyroid dysfunction in patients with T1DM and T2DM. Patients with T1DM compared to patients with T2DM have statistically non-significant higher prevalence of hypothyroidism and lower prevalence of hyperthyroidism (92.5% vs. 90.9%) and (7.4% vs. 9.0%) respectively, $p = 0.9$. In addition, compared patients of T1DM with T2DM, there was higher prevalence of clinical (44.4% vs. 34.1%) and lower prevalence of subclinical (48.1% vs. 56.8%) hypothyroidism and clinical (3.7% vs. 4.5%) and sub-clinical hyperthyroidism (3.7% vs. 4.5%), $p = 0.9$.

Parameters	Type 1 diabetes		Type 2 diabetes		P value
	No.	%	No.	%	
Clinical hypothyroidism	12	44.4	15	34.1	0.9
Subclinical hypothyroidism	13	48.1	25	56.8	
Total	25	92.5	40	90.9	
Clinical hyperthyroidism	1	3.7	2	4.5	
Subclinical hyperthyroidism	1	3.7	2	4.5	
Total	2	7.4	4	9.0	
Total	27	100.0	44	100.0	

Table 3: Distribution of types of thyroid dysfunction in patients with type 1 and type 2 diabetes.

In order to identify the independent factors affecting patients with TD, a multivariate regression model was constructed using patients with TD as the dependent factor. The constructed model is shown in table 4. Age, gender, HbA1c and types of diabetes were the independent predictors of patients with TD. In the constructed model, we found that age, gender, HbA1c and type of diabetes were statistically non-significant to be independent predictors of patients with TD; age (OR: 0.969, 95% CI: 0.799 - 1.176, $P = 0.8$), female gender (OR: 2.179, 95% CI: 0.886 - 5.359, $P = 0.09$), HbA1c (OR: 1.1, 95% CI: 0.911 - 1.33, $P = 0.3$) and being T2DM (OR: 1.634, 95% CI: 0.278 - 9.592, $P = 0.6$).

Parameters	Coefficients	Standard error	Expo (B)	95% CI	P value
Age (years)	-0.031	0.099	0.969	0.799 - 1.176	0.8
Female gender	0.779	0.459	2.179	0.886 - 5.359	0.09
HbA1c (%)	0.096	0.097	1.100	0.911 - 1.330	0.3
Type 2 diabetes	0.491	0.903	1.634	0.278 - 9.592	0.6

Table 4: Regression analysis using thyroid dysfunction as the dependent variable.

Discussion

We found a higher prevalence of TD among T2DM in comparison to T1DM (26.7% vs. 17.1%) ($p = 0.04$). The association between DM and thyroid disease has long been recognized, although the reported prevalence of TD in patients with DM varied widely between studies [3-5,15,22,26-34]. Sanchez-Lugo reported a total of 78 patients who had T1DM and were confirmed to have TD while more than 75% were females [16]. Radaideh, *et al.* conducted an investigation into the prevalence of TD in T2DM in Jordan. 5.9% of the T2DM patients had TD [17]. However, this study was able to diagnose 6.7% new cases of TD among patients with T2DM. Thus, the total prevalence of TD was 12.5%, with subclinical hypothyroidism being the most common presentation. Cardoso, *et al.* carried out a study on the 8.3% of patients had subclinical hypothyroidism in T2DM, while 21% had subclinical hypothyroidism [35]. Akbar, *et al.* investigated the observation between TD in T2DM patients of Saudi origin. They concluded that TD was found in 16% of patients with T2DM [3]. Similarly, Ghawil, *et al.* defined the prevalence of AITD among the patients with T1DM in Libya. They found that the major thyroid pathology was subclinical hypothyroidism (2.3%) [36].

Perros, *et al.* in their study involving type 1 DM and T2DM patients found that the incidence of TD was high in diabetic but highest in female T1DM patients and lowest in type 2 DM male patients [15]. Papazinfropoulou, *et al.* carried out a similar study to determine the prevalence of TD among T2DM patients attending out-patient clinics [10]. The prevalence was 12.3% with an excess of female patients taking the lead in comparison with normal groups ($p < 0.001$). Also, Diezz, *et al.* found that diabetic patient with TD in their study had a prevalence of 9.7% (95CI, 6.5 - 13.0%) [37]. The NHANESS study in the US population reported an increased frequency of TD in diabetic subjects when compared to individuals without diabetes (25,27) [8]. Finally, Demitrost, *et al.* reported that out the 202 type 2 DM patients for the study of which 16.3% have subclinical hypothyroidism, 11.4% have hypothyroidism, 2% have subclinical hyperthyroidism and 1.5% are hyperthyroidism cases [38].

The high prevalence of subclinical hypothyroidism in T1DM and T2DM patients found in our study was expected. In contrary, the interrelationship between T2DM and hypothyroidism was not yet well defined. Few studies described a common genetic origin among the diseases based on a polymorphism in the gene of type 2 deiodinase [39]. As discussed by Celani, *et al.* subclinical hypothyroidism has the highest prevalence among DM2 patients, followed by overt hypothyroidism as was seen with our report [40]. In the study of Udiong, *et al.* hypothyroidism is the commonest disease in T2DM patients [41]. This is an important finding of this study because in patients with T2DM the etiology of hypothyroidism is not well known. The heterogeneity in the reported prevalence of TD in these studies could be due to the variable population characteristics including age and ethnicity of patients, the differences in study design including the cut-off levels and classification of the disease with different definitions including autoimmune, subclinical, and clinical hypothyroidism [42-45].

The presence of both raised and low levels of thyroid hormones in diabetic might be due to modified thyrotropin releasing hormone (TRH) synthesis and release [41]. The hyperglycaemia was seen in patients with T2DM is known to have negative effect on thyroid function precisely blunting the pituitary TSH response to stimulation by hypothalamic TRH. This might be due to possible alteration of post translational glycosylation of TRH hence affecting its biological activity [46]. T2DM is associated with increased insulin level and C-peptide level. In addition, insulin is an anabolic hormone known to enhance TSH turnover, which is protein in nature. Recently, C-peptide has been shown to enhance Na^+/K^+ -ATPase activity, an action that may also increase protein synthesis. Such an action would induce increased turnover of TSH, a protein hormone [47,48]. Reduced glucose absorption from gastrointestinal tract accompanied by prolonged peripheral glucose accumulation, gluconeogenesis, diminished hepatic glucose output and reduced disposal of glucose are hallmarks of hypothyroidism [49]. In overt or subclinical hypothyroidism, insulin resistance leads to glucose-stimulated insulin secretion [42]. In subclinical hypothyroidism, diminished rate of insulin stimulated glucose transport rate caused by perturbed expression of glucose transporter type 2 gene translocation may lead to insulin resistance. Most of the T2DM patients were obese who might have increased level of leptin. This increased level of leptin develops leptin resistance centrally that causes decreased formation of thyroid hormones and increase TSH secretion by feedback mechanism in T2DM [50].

We aimed to identify the prevalence of TD in patients with T1DM and T2DM in Saudi patients in hospital-based health care setting. In our study, the observed population reflects a selected yet comprehensive group of patients rather than the general population. This study had limitations stemming from its small sample size and cross-sectional study design and therefore may underestimate the true prevalence of TD in patients with T1DM and T2DM. Prospective longitudinal studies with more patients would be needed to characterize the prevalence of TD in patients with DM. The American Diabetes Association, International Society for Pediatric and Adolescent Diabetes and several authors recommend annual screening for thyroid disease in all T1DM subjects with TSH measurement [51-53].

Conclusion

In conclusion, our results showed that TD occurred more frequently in patients with T2DM, in particular, females. Therefore, regular screening of thyroid function may be considered in all T2DM patients. In the absence of registry data, larger cooperative studies involving diverse population samples from multiple centers could help to provide further information on the true relation nationally.

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Funds for Study

Nil.

Conflict of Interest

None.

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