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Association of thyroid disorders with diabetes: A cross-sectional study

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[2]Department of Biochemistry, College of Medicine, University of Hail. Hail 55476, Kingdom of Saudi Arabia. Tel./fax.: +96-6551803367, ♥email: shahahid@uoh.edu.sa
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Abstract. *Zafar M, Shahid SMA, Alshammari RF, Kausar MA, Ginawi TAN, Hatim AW, Wadi AM, Ali H, Hamed AA, Al-Zahrani MS, Hussain A, Alduhaim AS, Mohammed A. 2022. Association of thyroid disorders with diabetes: A cross-sectional study. Nusantara Bioscience 14: 135-140.* Two common endocrine disorders that correlate with each other are diabetes mellitus (DM) and thyroid dysfunction (TD). Undiagnosed thyroid disorders (TD) have a high risk for diabetes mellitus (DM) patients. A common complication among these patients is cardiovascular disease. This study aims to assess the association of TD among diabetes patients. It is a cross-sectional study, and 338 patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) were observed through a simple random sampling method from a public sector hospital. The diabetes status of patients was confirmed through clinical and laboratory investigation. Those patients who were under treatment of thyroid were excluded from the study. The chi-square test was used for analysis, and a p-value <0.05 was considered significant. The frequency of TD among diabetic patients was 47.6%. The main type of TD was subclinical hypothyroidism, and its prevalence is 43.8% and 23.5% among patients with T1DM and T2DM, respectively. Subclinical hyperthyroidism prevalences are 12.3% and 24.4% among TIDM and T2DM patients, respectively. The study found a high-frequency rate of TD among DM patients. Therefore, there is a need for regular screening of DM patients for TD and increased awareness regarding TD among DM patients.

Keywords: Diabetes mellitus, hyperthyroidism, hypothyroidism, prevalence, thyroid dysfunction

INTRODUCTION

Diabetes is one of the most common disorders in the human population. There is a link between diabetes and other metabolic disorders (Kalra et al. 2019). The association between these two disorders is recognized. The prevalence of thyroid disorders in the diabetic population varies widely between studies (Gu et al. 2017). The pancreas releases insulin, and the thyroid gland releases T3 and T4, which affect the body's metabolism (Al-Omrani et al. 2018). Thyroid-stimulating hormone (TSH) levels in the blood regulate the T3 and T4 levels in the serum because TSH stimulates the thyroid gland to release the T3 and T4 (Ogbonna et al. 2019). In diabetes, patients have thyroid disorders (TD) symptoms, including hypothyroidism and hyperthyroidism among type 2 diabetes patients. A study conducted in a hospital outpatient medicine department found a high prevalence of TD among type 2 diabetes patients (T2DM) (Rubaye 2019). Diabetes mellitus (DM) has been affected on multiple levels of the thyroid gland through thyroid-stimulating hormone (TSH). Also known as non-communicable, DM is a systemic disease with a high prevalence and mortality rate (Haryta et al. 2021). It increased the serum's T4, T3, and Insulin levels (Gronich et al. 2015; Chuang et al. 2016; Shahid et al. 2020). The first study, which was conducted in 1979 and found that a correlation between TD and diabetes mellitus had been established (Bellastella et al. 2018). The burden of TD among diabetes (DM) patients ranges from 3.2% to 57.6% (Bano et al. 2019). There are different types of TD in diabetes patients, and the most common type is sub-clinical hypothyroidism, specifically in type 2 diabetes patients. This prevalence in diabetes patients is comparatively high in the general population (Luna et al. 2014; Mehran et al. 2014). Various studies found that subclinical hypothyroidism is the common type in diabetes patients (Palma et al. 2013; Hoermann et al. 2021).

Poor glucose control in the serum leads to TD. The reason for this disorder is a high level of TSH in the serum at night which inhibits the thyroid from releasing hormones in the hypothalamus, which leads to a decreased level of T3 and T4 in the serum, which causes hypothyroidism (Hussain et al. 2019). Decreased serum T3 level is observed in diabetes patients. A low T3 level in the serum leads to a low level of T4 due to low conversion from T3 to T4. This mechanism is reversed if glycaemic control is good. The main enzyme present in the liver is thyroxine 5 deiodinase, which is converted from T3 to T4, and when the concentration of this enzyme is low, ultimately, the outcome is hypothyroidism. Insulin also contributes to TD, increased levels of insulin in the serum lead to insulin resistance, thyroid tissue proliferative mechanism has

started, leading to nodule formation in the thyroid, and goiter disease has developed (Hasan et al. 2016).

In diabetes, a common cause is insulin resistance due to multiple factors such as sendatory lifestyle, obesity, smoking, etc. This disease develops for years after a disturbance of hormone regulation (Chen et al. 2019). At the initial stage, the pancreas β cells produce a high insulin level to decrease the glucose level because it increases resistance in the cell and muscular tissues. At the later stage, *β* cells burn out, increase serum glucose levels, and start diabetes. Metabolic syndrome is a cluster of diseases, including diabetes, due to insulin resistance (Evron et al. 2020). It is also comprised of cardiovascular diseases, polycystic ovaries, hypertension, and other endocrine disorders, with additional risk factors, are increased age, smoking, and genetic disorders (Biondi et al. 2019). The TD is part of a metabolic syndrome caused by autoimmunity against thyroid cells. Common TD are hypothyroidism, thyrotoxicosis, and goiter (Hoermann et al. 2021). Previous studies found that the prevalence of TD among diabetes patients is 6-25% in North America and Europe (Giugliano et al. 2020; Groothof et al. 2021).

A previous study was conducted on a sample size of 386 patients with diabetes at the hospital's outpatient department. The results found that hypertension and dyslipidemia are risk factors for TD among diabetes patients. These patients had undiagnosed TD, and the common type of TD was sub-clinical hypothyroidism (Jun et al. 2017a,b). In addition, a previous study was conducted on diabetes patients (T2DM), and the results showed that T3 and T4 levels in the serum were very high in diabetic patients (Vries et al. 2019).

In Middle East countries, the prevalence of diabetes is very high, and limited data is available for TD among diabetes patients. This study determines the actual burden of TD among diabetes patients. Diabetes has been associated with myocardial infarction and other diseases of endocrine disorders, specifically the thyroid gland. This study's results will benefit the community by increasing the awareness level among the general population, and it will also benefit the physician in managing diabetic patients with TD and preventing the complication of diabetic patients. It is, therefore, important to make an early diagnosis of thyroid dysfunction in diabetic patients to prevent further complications, and this practice is carried out in the clinic.

MATERIALS AND METHODS

Study area

This cross-sectional study was conducted in a primary health Centre (Figure 1).

Procedures

The sample size was calculated using world health organization (WHO) software for sample size determination in health studies. To measure sample size by using a prevalence of TD was 17% among DM patients from the previous study (Hall et al. 2020), at a confidence level of 95% and a bound of error of 4%, the estimated sample size came out to be 338. Therefore, taking the largest sample, a minimum of 338 participants were included in the study. The sampling technique employed was a multi-stage cluster sampling, first selecting the cluster, then selecting the strata within the cluster, and then selecting the household through systematic random sampling.

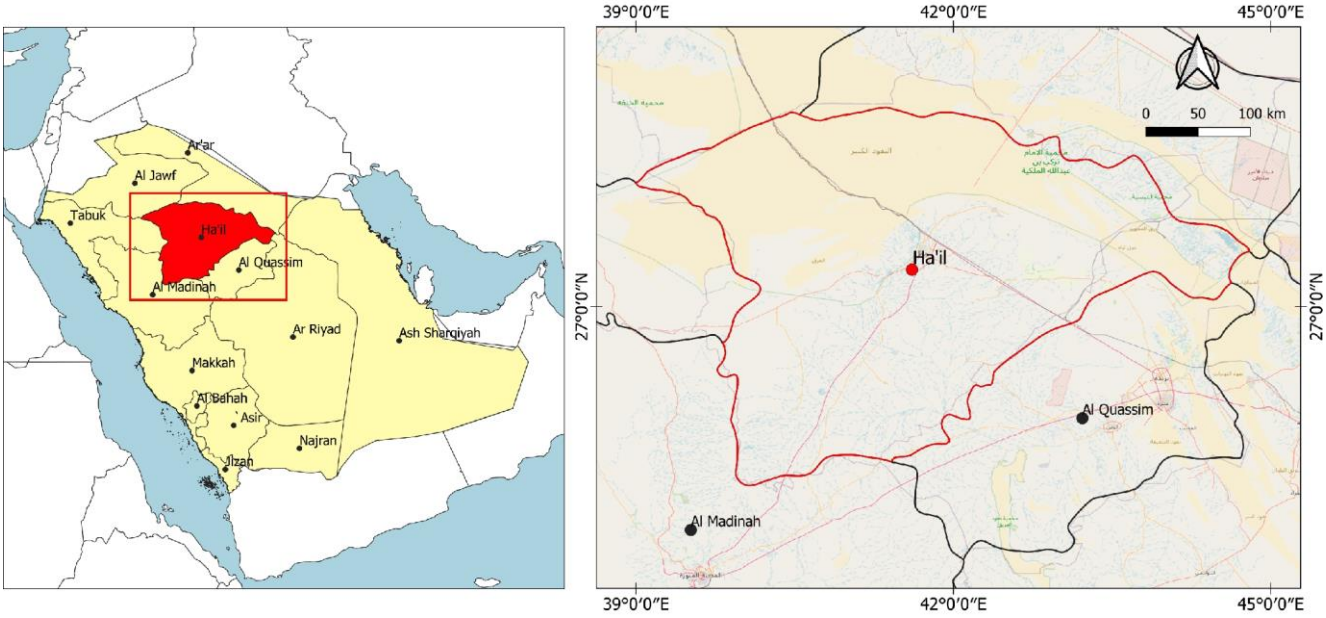

Figure 1. Location of Hail, Kingdom of Saudi Arabia

Instrument and data collection

All persons aged 18 to 60 years were included in the study. The study instrument was a validated questionnaire (Chang et al. 2017) comprising three sections. Part 1 relates to the socio-demographic characteristics, and part 2 relates to the study participants' clinical characteristics.

First, check the reliability and validity of the questionnaire and translate it into Arabic. To check reliability and validity, we collected data from other cities in the northern region and improved the quality of the questionnaire. There is sampling bias in the study because it is a cross-section study and this bias minimize through the blinding of study participants. Participants with diabetes and those patients above 60 years and below 18 years were excluded from the study. Study variables are age, gender, smoking status, type of diabetes, and status of TD.

Data collection procedure

The inclusion criteria of study participants were 6 months duration of DM among T2DM and one year for T1DM. T2DM patients are diagnosed at an age ≥30 years, without using insulin in the first year after diagnosis, and without a history of ketosis or ketonuria. The T1DM patients were diagnosed with clinical presentation, weight loss, polydipsia, polyphagia, polyuria, and the need to use insulin continuously since the diagnosis without discontinuation and at least one year medical follow-up. Written informed consent for the study was obtained from all patients aged 18 years or older or from the parents or guardians of patients younger than 18. Exclusion criteria for study participants were those unable to understand and sign the informed consent, pregnant women, and past medical history of hospitalization for less than 6 months. There are standard classification of TD, which is classified as Subclinical hyperthyroidism (SC-Hyper) if TSH < 0.27 μUI/mL, Sub-clinical hypothyroidism (SC-Hypo) if TSH > 4.20, Clinical hyperthyroidism(C-Hyper) if TSH < 0.27, clinical hypothyroidism (C-Hypo) if TSH > 4.20 μUI/mL, FT4 in the normal range (0.93 and 1.7 ng/dL), FT4 < 0.93 ng/dL; μUI/mL and FT4 ranged from 0.93 to 1.7 ng/dL.

Data analysis

Epi Data Entry software version 1.3 was used for data entry; data were entered twice and cleaned for any missing variables. Data were analyzed using software SPSS version 23. Descriptive statistics analysis was done for categorical variables and is present as frequency (percentage) and mean ±standard deviation. Student T was used for differences between the two groups. The Chi-square test was used for categorical variables to compare two or more groups. The p-value was statistically significant when it was less than or equal to 0.05.

RESULTS AND DISCUSSION

The mean age of patients was 33.51±1.51SD. Mostly (52.1%) are male patients and 219(64.8%) with T1DM, and 119(35.2%) with T2DM. The frequency of TD in diabetes mellitus patients is 47.6% (Table 1).

The prevalence of SC-Hypothyroidism was 43.8% in T1DM and 23.5% in T2DM. The prevalence of C-Hypothyroidism was 3.56% and 1.7% among TIDM and T2DM, respectively. The prevalence of SC-hyperthyroidism was 12.3% and 24.4% in T1DM and T2DM, respectively. C-hyperthyroidism prevalence was 3.8% and 0.7% among TIDM and T2DM, respectively. (Table 2).

The prevalence of SC-Hypothyroidism in females is 59.9% and 15.3% in male patients (Figure 2).

Discussion

The study found that 47.6% prevalence of TD among diabetic patients. Among thyroid diseases, Subclinical hypothyroidism was the top type of TD, found at 43.8%, which is consistent with the other studies (Journy et al. 2017; Mehran et al. 2017). Another study found that 16% prevalence of thyroid among T2DM (Journy et al. 2017). The basic cause of TD among people with diabetes is that Thyroid hormones and insulin antagonize each other, and both affect the biochemistry of human body cells (Ogbonna et al. 2019). The prevalence of TD among the general population is 7.6% (Bano et al. 2019).

Table 1. Clinical and demographic characteristics of study participants (n= 338)

Characteristics	Frequency (%)
Age (Years) (Mean ±SD)	33.51±1.51
18-40	187(55.3)
41-60	151(44.7)
Gender	
Male	176(52.1)
Female	162(49.9)
Smoking	
Ever	122(36.1)
Never	216(63.9)
Type of Diabetes Mellitus	
Type 1(T1DM)	219(64.8)
Type 2(T2DM)	119(35.2)
Thyroid Dysfunction(TD)	
Yes	166(47.6)
No	177(52.4)

Table 2. The frequencies of thyroid dysfunction among T1DM and T2DM patients

Thyroid function	TIDM (219) (%)	T2DM (119) (%)
Euthyroidism	37.16	49.7
SC-Hypothyroidism	43.8	23.5
C-Hypothyroidism	3.56	1.7
SC-Hyperthyroidism	12.3	24.4
C-Hyperthyroidism	3.8	0.7

Note: SC: subclinical, C: clinical

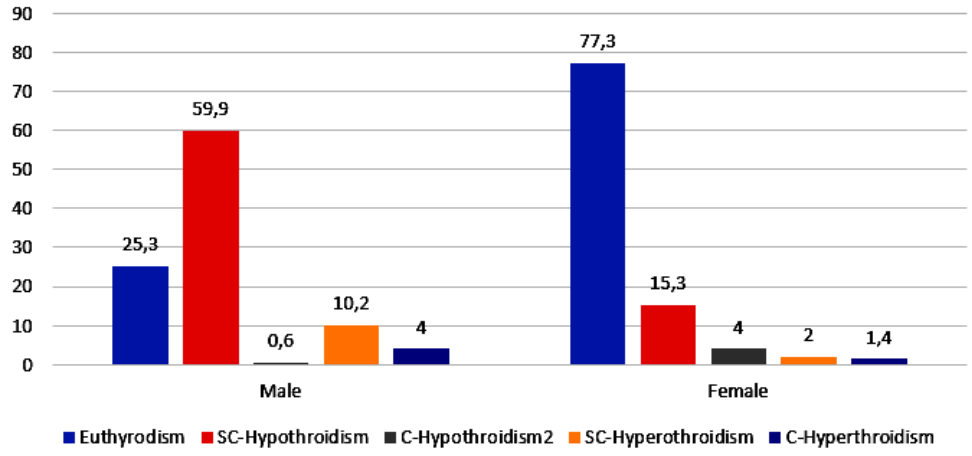

Figure 2. Gender distribution of thyroid function among diabetic patients

This study found that the prevalence of hyperthyroidism among T2DM was higher by 24.4% compared to T1DM. However, another study showed that TD among T2DM (Ittermann et al. 2018) found 31.4%, and SC-hyperthyroidism was the highest-burden among TD in these patients, followed by C-hyperthyroidism (24.2%), similar to our study results. The reason for this difference is that TSH is linked with insulin resistance and endothelial function, which leads to the increased serum level of TSH and dyslipidemia and disturbs the endothelial function of cells (Zhao et al. 2016).

Different literature also found that the correlation between diabetes and TD might be bidirectional. T2DM patients may have increased thyroid tissue hyperplasia, which leads to goiter and multinodular goiter (Tang et al. 2017; Chen et al. 2019). It also affects the serum level of glucose due to insulin resistance. It also found that SC-Hypothyroidism will increase with age. Another factor is obesity, which is also correlated with hypothyroidism (Song et al. 2017; Song et al. 2019).

Among the type of thyroiditis, postpartum thyroiditis is common in diabetes patients due to autoimmune among women in the postpartum stage. The symptoms include a hyperthyroid state to a hypothyroid state, which leads to mental disorders in women (Moleti et al. 2020). Postpartum thyroiditis prevalence is from 20% to 30% (Jun et al. 2017a,b; Tang et al. 2017; Zhang et al. 2019).

Diabetic patients with TD have an increased risk of retinopathy and cardiovascular disease, and limited studies are available regarding TD impairment in diabetic patients. A previous study showed that TD prevalence among female and male diabetic patients was 23.7% and 79%, respectively (Giugliano et al. 2020). Insulin resistance is the main cause of disturbing the TD, such as T3 and T4 levels in the serum blood. A previous study found 15% TD in female diabetic patients compared to male diabetic patients (Ryödi et al. 2018).

Diabetic patients with TD affect the metabolic disorders on glucose utilization in hypothyroidism. In the liver, glucose metabolism is also affected, decreasing gluconeogenesis and glucose utilization in tissue. In addition, it affects the glucose level in the serum (Ralli et al. 2020). Hypoglycemia was common among children and adults with an increased TSH level and decreased T3 and T4 (Song et al. 2019).

A previous study found that TD among poorly controlled diabetes patients this dysfunction was subclinical and was reversed after a normal level of glucose. Therefore, the treatment of TD is also affected due to diabetic conditions and may increase the dose of T3 to control thyroid function (Sert et al. 2020).

A recent study found that TD patients among elderly diabetic patients correlated with thyroid hormone levels, and this association are not associated with other non-communicable diseases (Zhou et al. 2019).

There are different types of hypothyroidism; subclinical hypothyroidism is the most common type among diabetic patients; in these patients, a high level of TSH is in the serum with a normal level of T3 and T4. SC-hypothyroidism prevalence among diabetic patients was 6%. Specifically, its prevalence among female diabetic patients is around 7%. A previous study was conducted on adult diabetic patients and found that the prevalence rate is 6.5%. A highly significant finding in healthy papulation regarding TSH level in the serum. In diabetic patients, TSH levels increased as the disease progressed toward chronic disease (Tang et al. 2017).

There is no consistent finding on the screening of TD in diabetic patients, and the basic difference was a type of TD test to find the thyroid function test. Also, there are different opinions about the timing of the test, either routine or specific time to conduct the test. There are different guidelines regarding screening tests for TD, endorsing one guideline that routine screening for TSH levels among diabetic patients is contradictory to other guidelines. Some guidelines say only T1DM patients need to screen their TSH level, but others recommend that T2DM patients screen their TSH level. Without the standard guideline, there is a dependence on the physician's experience and knowledge to follow the TSH level process (Sawin et al. 1994).

In T2DM patients, it recommends periodic screening of TSH levels at the period of every three months. In T1DM patients, randomly screened T3 and T4 levels were every

six months. Testing the level of thyroid antibodies and serum TSH is a strong predictor of TD (Shahid et al. 2020).

A previous study found that serum concentration of TSH above 3mU/L was correlated with hypothyroidism and another study found that serum concentration of TSH above 4mU/L was associated with hypothyroidism. A cross-sectional study found that serum concentration of TSH above 1.90mU/L was associated with hypothyroidism (Ralli et al. 2020).

Among diabetic pregnant women, a routine specific screening test for TSH and T3 levels every 2 years. In addition, thyroid antibody levels are also screened yearly to check the TD among diabetic pregnant women. This test should be done in the first trimester of pregnancy, along with other basic tests in antenatal care. If weight changes during the first semester, then screen the test every 6 months. Start thyroid management immediately if an abnormality is found (Palma et al. 2013). Both types of TD, hypothyroidism, and hyperthyroidism, affect insulin and glucose metabolism. This relationship has an indirectly related L and U-shaped association which leads to metabolic syndrome in a different population of diabetes.

There are several limitations of this study. First, it is a cross-sectional study that did not determine the causality of the association between risk factors and outcome. Second is the study's selection bias because these patients are already under medical treatment. The major strength of this study is the sample size (n= 338), which is higher than other studies conducted in the Kingdom of Saudi Arabia. The study found a high prevalence of TD among diabetic patients, specifically SC-hypothyroidism, which recommends regular screening of TD among these patients and early diagnosis and prompt treatment started. There is a need to make the physician aware of screening diabetic patients routinely and identifying the risk factors which may lead to cardiovascular diseases.

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