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Relationship of thyroid dysfunction and its manifestations in diabetes mellitus patients in the Kingdom of Saudi Arabia

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Abstract. – OBJECTIVE: Both diabetes mellitus (DM) and thyroid dysfunction (TD) are endocrinopathies that are frequently inclined to coexist in patients. Most studies avoid explicitly supporting or opposing testing thyroid function for diabetic patients as a baseline. The association between hypothyroidism and diabetes is considerable when assessing thyroid functions in diabetic individuals based on clinical suspicion. Therefore, this study aimed to assess the relationship between thyroid dysfunction and its manifestations in DM patients in the Kingdom of Saudi Arabia.

SUBJECTS AND METHODS: **The study included 301 DM subjects. A questionnaire divided into two sections was administered to all participants. The first section involved questions about diabetes control, monitoring, and disease severity. The second section included questions about thyroid disease and the 14-item Hypothyroidism Clinical Prediction (HCP) score we created for our research. The HCP score was obtained by summing up all discrete scores for different symptoms of hypothyroidism. ROC curve analysis was used to assess the predicted hypothyroidism cases based on the most precise cut-off point for the HCP overall score (highest sensitivity and specificity). HCP discriminant ability for detecting hypothyroid cases was assessed considering the Area Under the Curve (AUC) as a measurement.**

RESULTS: **Almost 53 (17.6%) diabetes mellitus subjects were previously diagnosed with hypothyroidism. Comparatively, regarding the given cut-off point, the total number of predicted hypothyroidism cases using the HCP score was 149 (49.5%). The most reported symptoms included tiredness (75%), followed by irritability (72%), and difficulty in losing weight (65%). Hypothyroidism was detected/predicted among 60.1% of female diabetics *vs.* 44.2% of males with recorded statistical significance (*p*=.006).**

CONCLUSIONS: **This study further proves a significant association between diabetes and hypothyroidism in Saudi Arabia. We recommend periodic screening for thyroid dysfunction in the diabetic population in specific cases; since some patients with diabetes are more likely to have hypothyroidism based on their clinical presentation.**

Key Words:
Diabetes mellitus, Thyroid dysfunction, Saudi Arabia.

Introduction

Diabetes mellitus and thyroid disease are two of the most common endocrine diseases encountered in clinical practice[1,2]. As for diabetes mellitus (DM), many studies[3,4] agreed that DM is a disorder of global epidemic, with many different regions showing a substantial increase in prevalence. DM, as in the past and the current era, is one of the most prevalent diseases worldwide, reaching a prevalence of 9.3% globally in adult subjects[5,6]. In particular, Saudi Arabia has a surprisingly high prevalence rate compared to other nations, reaching almost 30% of people suffering from DM overall in the population[7,8]. Moreover, there are two types of diabetes, the most common being type 2 DM, which is caused by insulin resistance that results in carbohydrate derangement and raises the blood glucose level[9,10]. The other is type 1 DM (T1DM), an autoimmune process that destroys the cells that produce insulin. As studies[11-13] suggested, T1DM and autoimmune thyroid diseases are frequently associated together in the same patients. However, the relationship between T2DM and thyroid disease is more complicated[14]. Secondly, hypothyroidism is a significant and common endocrine disorder reported world-

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wide[15]. In Saudi Arabia, a study[16] demonstrated a total prevalence of hypothyroidism of 25.3%. Hypothyroidism or thyroid dysfunction can be classified according to the function of the thyroid gland into primary and secondary hypothyroidism[17]. Also, it can be either acquired or congenital; many factors can influence the prevalence of hypothyroidism, including but not limited to age, gender, recent pregnancy, and history of autoimmune disease[15].

Furthermore, the co-occurrence of type 2 diabetes mellitus (T2DM) and hypothyroidism is a trend often observed in clinical practice. This is alarming because of the well-established and significant connection between these two disease disorders[1]. As such, some studies[18,19] showed that patients with these endocrinopathies and their complex interdependent interactions are at an increased risk for cardiovascular events and, notably, diabetes microvascular complications like diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy. On the other hand, a retrospective case-control study[20] negated the presence of any association after adjusting the confounding factors between hypothyroidism and T2DM micro-vascular complications. At present, clinical recommendations[21-23] remain neutral on the issue of monitoring thyroid function in individuals with T2DM, neither advocating for nor opposing it. Conversely, others[24] recommend thyroid screening as a baseline but are against routine screening in patients with T2DM. Many studies[25-27] showed a strong association between type 2 diabetes mellitus (T2DM) and hypothyroidism. One study[27] conducted in rural south India showed the prevalence of clinical and subclinical hypothyroidism in individuals with type 2 diabetes mellitus to be 3.2% and 14.1%, respectively. Another study[26] that aimed to identify the rate of primary hypothyroidism in diabetic patients (cases) and compared it to another group without diabetes (controls), found that the rate in the case group was 5.7% and the control group was 1.8%.

Despite the high prevalence of DM in Saudi Arabia, most of the studies performed on this topic were not done in the Saudi population. For this reason, our study aims to investigate the relationship between thyroid dysfunction and its manifestations in DM patients in the Kingdom of Saudi Arabia. It also provides the basis for promoting early treatment and prevention of thyroid dysfunction in DM patients, which in turn would improve life quality and reduce healthcare costs.

Subjects and Methods

Study Design and Data Collection

A cross-sectional survey was done to find the relationship between hypothyroidism and its manifestations in 301 diabetes mellitus subjects in the Kingdom of Saudi Arabia. Data was collected through an online self-administered questionnaire using Google Forms, and the link was shared publicly *via* social media platforms. The enrolment lasted from July 2022 to December 2022. Inclusion criteria included adult type 1 or type 2 diabetic patients and participants older than 18 years old. Exclusion criteria included subjects below the age of 18 years and patients not diagnosed with diabetes mellitus. Data collected included demographic parameters of participants, including gender, age, weight, height, residence, level of education, job, smoking status, diagnosis of DM, and the type of DM. The Ethical Committee at the University of Hail approved this study, and written informed consent was obtained from participants before they filled out the survey.

Development of the Questionnaire

The research team designed the survey to assess and measure the relationship between thyroid dysfunction and its symptoms in diabetic patients in the Kingdom of Saudi Arabia. The questionnaire was divided into two sections with a total of 38 questions. The first section involved questions about diabetes control, monitoring, and disease severity. This includes monitoring the glucose levels on a certain basis, the duration of DM, and the management used in DM, and any associated comorbidities or complications related to DM. The second section involves questions about thyroid disease, which include any thyroid disease diagnosis and medications given, and lastly, the 14-item Hypothyroidism Clinical Prediction (HCP) score that we specifically invented for the purpose of our research. The language validation was concluded by using two independent translators to translate from English to Arabic and cross-translated from Arabic back to English (Table I).

Statistical Analysis

After data were extracted, it was revised, coded, and analyzed using the IBM SPSS version 22 statistical software (IBM Corp., Armonk, NY, USA). All statistical analysis was performed using two-tailed tests. A p-value lower than 0.05 was considered statistically significant. Descriptive analysis based on frequency and percentage

Table I. The 14-items of Hypothyroidism Clinical Prediction (HCP) score.

Score criteria	Yes (1)	No (0)
Score criteria	(1)	(0)
Female gender	(1)	(0)
I feel exhausted most of the time	(1)	(0)
I have muscle stiffness and recurrent muscle aches	(1)	(0)
My skin and hair are dry, pale and has rough surface	(1)	(0)
I feel cold most of the time even when other feel comfortable	(1)	(0)
I have a lot of negative thought and feel depressed	(1)	(0)
I have constipation	(1)	(0)
I find it difficult to lose weight or gain weight	(1)	(0)
For women, I have irregular menstrual cycles	(1)	(0)
My face is puffy or swollen	(1)	(0)
I woke up early without intention	(1)	(0)
My skin has become blue in color	(1)	(0)
I often feel irritable	(1)	(0)
My memory is worse than usual	(1)	(0)
The maximal score is 14 points		

distribution was done for all categorical variables, while mean with standard deviation was used to display numeric variables. The Hypothyroidism Clinical Prediction (HCP) score was obtained by summing up all discrete scores for the typical symptoms of hypothyroidism. ROC curve analysis was used to assess the predicted hypothyroidism cases based on the most precise cut-off point for the HCP overall score (highest sensitivity and specificity). The best cut-off point was assessed using the Youden index method[28]. HCP discriminant ability for detecting hypothyroid cases was assessed using Area under Curve (AUC). Symptoms of hypothyroidism among study cases were graphed. Cross tabulation was used to assess the factors associated with hypothyroidism (diagnosed and predicted) among diabetic patients using Pearson's Chi-square and the exact probability test for small frequencies.

Results

A total of 301 diabetic patients were included. Patients' ages ranged from 20 to more than 70 years, with a mean age of 38.2±12.7 years old. 163 (54.2%) participants were female. As for body mass index, 104 (34.6%) patients were overweight and 128 (42.5%) were obese. Among the subjects involved in the study, 60 (19.9%) were smokers, 83 (27.6%) complained of hypertension, 24 (8%) had coronary artery disease (CAD), and 145 (48.2%) reported high lipid levels (Table II).

124 (41.2%) were type 1 diabetic patients and 177 (58.8%) were type 2 diabetics. A total of 27 (9%) were diabetic for less than a year, 98 (32.6%) were diabetic for 1-5 years, and 41 (13.6%) were diabetic for more than 20 years. A total of 95 of the study patients measured their blood glucose level regularly, where 101 (33.6%) had good diabetic control, 74 (24.6%) had fair control, and 126 (41.9%) had poor diabetic control. 196 (65.1%) of

Table II. Bio-demographic data of diabetic patients in Saudi Arabia.

Bio-demographic data	No.	%
Age		
20-29	89	29.6%
30-39	35	11.6%
40-49	64	21.3%
50-59	62	20.6%
60-69	31	10.3%
70+	20	6.6%
Gender		
Male	138	45.8%
Female	163	54.2%
Body mass index (BMI)		
Normal weight	69	22.9%
Overweight	104	34.6%
Obese	128	42.5%
Smoking		
Yes	60	19.9%
No	241	80.1%
Hypertension		
Yes	83	27.6%
No	218	72.4%
Coronary artery disease (CAD)		
Yes	24	8.0%
No	277	92.0%
High lipid levels		
Yes	145	48.2%
No	156	51.8%

Table III. Clinical data, types of management, and complications of diabetes among study patients in Saudi Arabia.

Diabetes data	No.	%
Type of DM		
Type 1 DM	124	41.2%
Type 2 DM	177	58.8%
Duration of DM		
<1 year	27	9.0%
1-5 years	98	32.6%
6-10 years	69	22.9%
11-20 years	66	21.9%
>20 years	41	13.6%
Monitor the glucose levels regularly		
Always	120	39.9%
Sometimes	166	55.1%
Never	15	5.0%
Diabetes control		
Good control	101	33.6%
Fair control	74	24.6%
Poor control	126	41.9%
Management used for DM		
Oral antidiabetic drugs	196	65.1%
Insulin Injections	167	55.5%
Healthy diet and exercise	75	24.9%
Years of using insulin if prescribed		
1-6 months	17	8.1%
6 months-1 year	26	12.4%
More than 1 year	54	25.8%
Since diagnosis	112	53.6%
Complications of DM		
Diabetic retinopathy	64	21.3%
Diabetic neuropathy	38	12.6%
Diabetic nephropathy	9	3.0%
No complications	213	70.8%

DM, Diabetes mellitus.

the participants were on oral anti-diabetic drugs, 167 (55.5%) were on insulin injections, and 75 (24.9%) patients practiced a healthy diet and exercise. As for diabetic complications, the most reported included diabetic retinopathy (21.3%), diabetic neuropathy (12.6%), and diabetic nephropathy (3%), while 70.8% had no complications reported (Table III).

53 (17.6%) diabetic patients were diagnosed with hypothyroidism, and 40 (75.5%) of them were on levothyroxine. A total of 145 (48.2%) patients underwent thyroid function tests (Table IV).

The Receiver Operating Characteristic (ROC) curve illustrates the efficacy of the Hypothyroidism Clinical Prediction (HCP) score in detecting cases of hypothyroidism. The HCP score showed a very good significant discriminant ability for hypothyroidism, where (AUC=.758; p=.001) a Hypothyroidism Clinical Prediction (HCP) score of 12.5 or higher indicated a positive test result, which may signal the presence of hypothyroidism with a sensitivity of 82% and specificity of 56%. This suggests a strong probability of correctly identifying individuals without the illness, effectively excluding hypothyroidism. In reference to the given cut-off point, the total number of predicted hypothyroidism cases was 149 (49.5%) (Figure 1).

Factors Associated with Hypothyroidism (Diagnosed and Predicted) Among Diabetic Patients

Hypothyroidism was detected/predicted among 60.1% of female diabetics *vs.* 44.2% of males with recorded statistical significance (p=.006). Also, 64.1% of diabetics with high lipid profiles had hypothyroidism compared to 42.3% of others without (p=.001) (Figure 2).

Reported Symptoms Among Diabetic Cases with Hypothyroidism

The most reported symptoms included tiredness (75%), followed by irritability (72%), difficulty to lose or gain weight (65%), dry skin and hair (65%), muscle stiffness (65%), feeling cold (58%), and memory disturbance (57%). The least reported symptoms include irregular menstrual cycle for women (35%), puffy or swollen face (29%), and blue skin (19%).

Discussion

This cross-sectional study analysed the relationship between thyroid dysfunction and its manifestations in diabetes mellitus (DM) patients. Our study with 301 diabetic patients found that 53 participants (17.6%) were already diagnosed with hypothyroidism. Similarly, another study[9] found that 18.7% of the study population had hypothyroidism. On the other hand, our results were higher than a study[29] performed in Scotland, which found 13.4% cases of hypothyroidism among type 1 and type 2 DM, and in a study[30] in Jordan, where it was 12.5% among T2DM patients. The Hypothyroidism Clinical Prediction (HCP) score that we used in this study showed a good negative-predictive value; participants with a value of 12.5 or more with the highest sensitivity and specificity (82% and 56%, respectively) were defined as predicted hypothyroidism cases. Those patients typically have hypothyroidism manifestations but did not do thyroid function tests to confirm the diagnosis. Based on the HCP score, it was detect-

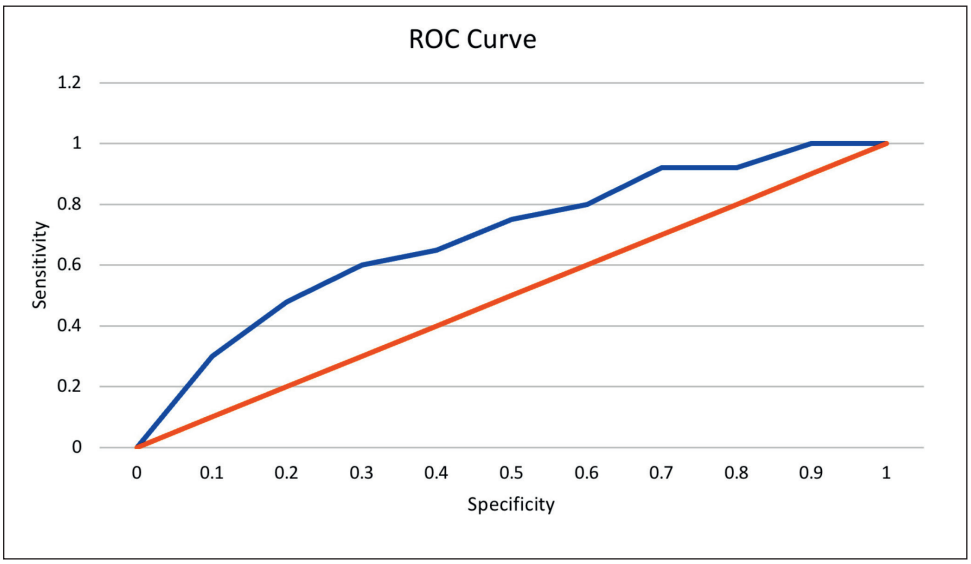

Figure 1. ROC curve for detecting predicted hypothyroidism based on HCP score.

ed/predicted in 129 of our diabetic participants; 60.1% among them were female diabetics, and 44.2% were male diabetics. This amplifies the significance of thyroid function tests to be done to diagnose hypothyroidism in diabetic patients. More than half of our participants (51.8%) were not tested for hypothyroidism. However, despite many studies[9,24] showing the association between the two conditions, there are no established guidelines yet that recommend regular screening for hypothyroidism in diabetic patients, more specifically, type 2 diabetes mellitus. Regarding the manifestations of hypothyroidism in DM patients, we found that fatigue, irritability, and difficulty in losing or gaining weight were the most common symptoms reported by participants. These findings are consistent with the typical symptoms of hypothyroidism, which include fatigue, weight gain, and constipation, among others[31].

Most of our participants (70.8%) reported no complications related to DM, which could be due to the relatively young age of participants (mean age 38.2±12.7 years old). This is contradicted by the poor blood glucose control seen in 41.9% of our participants, which is considered by some[32] to be the most determinant of diabetes-related complications and death. Nevertheless, about 111 (36.9%) of participants reported complications of DM, most commonly being diabetic retinopathy. Other studies[18-20,25] showed that the coexistence of hypothyroidism and DM increases the risk for diabetic retinopathy, diabetic kidney disease, and cardiovascular disease. In addition, about 48.2% of all participants had high lipid levels; this perhaps results from insulin resistance, which leads to the increased serum level of TSH and, therefore, reduced catabolism of lipoproteins[33-35] coupled with the fact that most of our participants (42.5%) reported a body mass index of more than 30 kg/m^2. This data provides information about a fact that is not particularly surprising; in which, obesity is closely linked to DM and hypothyroidism[36]. Moreover, only 24.9% maintained a healthy diet and exercise, which is an integral part of the management, especially for DM, as shown by the findings in the Diabetes Remission Clinical Trial (DiRECT)[37].

Table IV. Hypothyroidism among diabetic patients in Saudi Arabia.

Hypothyroidism	No.	%
Were you diagnosed before with hypothyroidism?		
Yes	53	17.6%
No	248	82.4%
If yes, are you taking the medication for it (levothyroxine)?		
Yes	40	75.5%
No	13	24.5%
Did you do any thyroid function tests?		
Yes	145	48.2%
No	156	51.8%

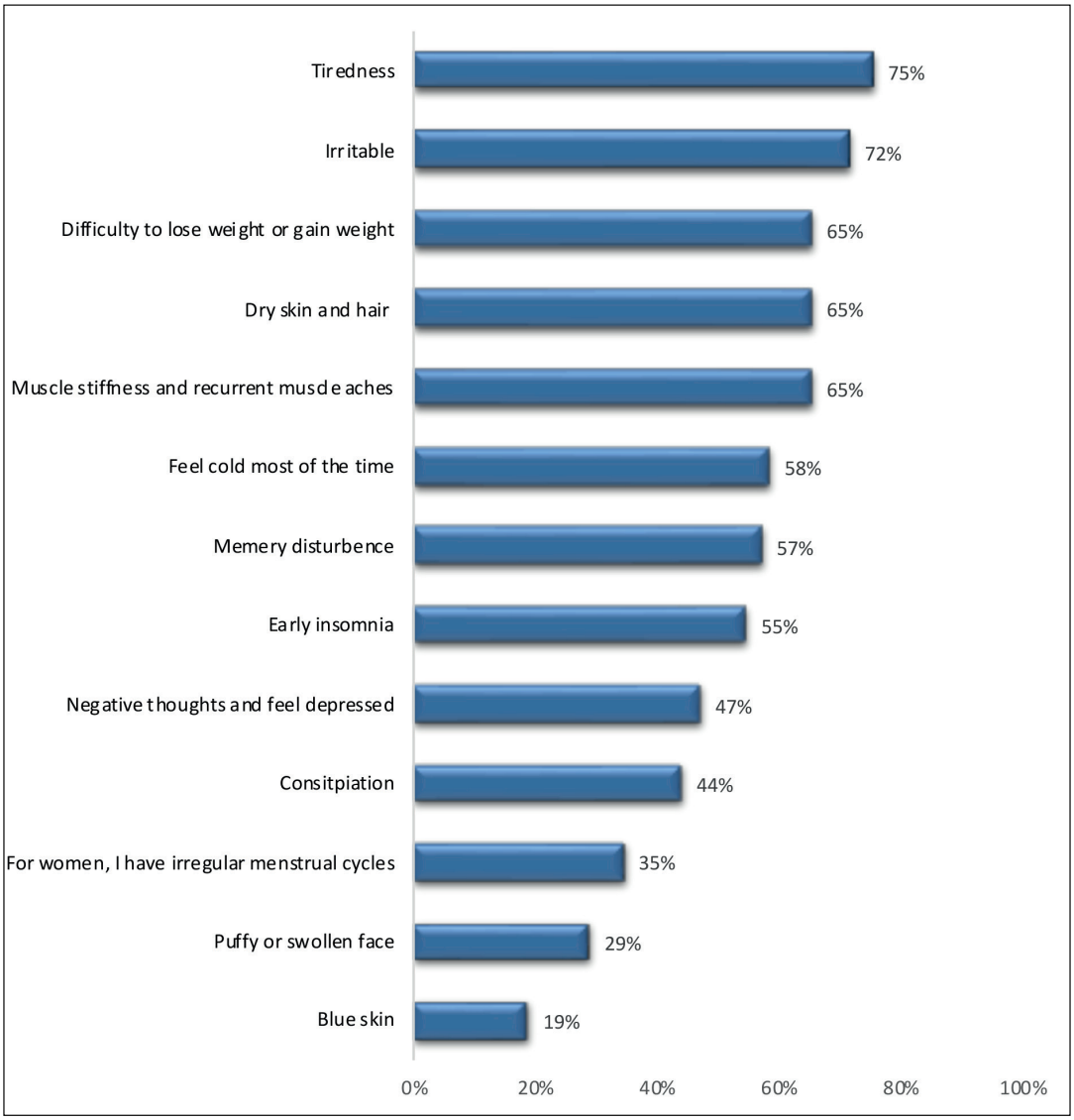

Figure 2. Reported symptoms among diabetic cases with hypothyroidism in Saudi Arabia.

Limitations

Our study has a few strengths and limitations. The strength is that this is the first study highlighting the burden of hypothyroidism in patients with T2DM and identifying the impact of this comorbidity on the prevalence of hypothyroidism. Similarly, the study showed the possibility of many diabetic cases that might have undiagnosed thyroid disease. In addition, it can be assumed that the study represents the population of Saudi Arabia, as the survey was distributed to different regions around the country. On the other hand, there are several limitations to our study. First, this cross-sectional analysis does not have laboratory confirmation to establish a relationship between thyroid-stimulating hormone (TSH) and hypothyroidism-detected/predicted diabetics. Furthermore, the study was limited in its ability to conclude an association between hypothyroidism with gender, age, and duration of diabetes or control of diabetes. Lastly, most patients who were already diagnosed with hypothyroidism are under medical treatment and, therefore, biochemically euthyroid, thus neutralizing the potential consequences of hypothyroidism.

Research[38] on thyroid disease and type 1 diabetes indicated the relationship between thyroid autoantibodies and the expression of glutamic acid decarboxylase antibody (GADA), ZnT8A, and IA-2A in individuals with type 1 diabetes melli-

tus and thyroid disease. This study is important for our understanding of how diabetes and thyroid dysfunction interact.

Another work[39] offers a thorough understanding of the genetics, mechanisms, and state of knowledge surrounding autoimmune thyroid disease. It is essential to comprehend the ways in which autoimmune processes affect thyroid function and how they may affect diabetic conditions.

Conclusions

Overall, our study provides further evidence of a significant association between diabetes and hypothyroidism in Saudi Arabia. We recommend periodic screening for thyroid dysfunction in the diabetic population only in specific cases. As the study shows, some patients with diabetes are more likely to have hypothyroidism in their clinical presentation. All things considered, further research and more comprehensive measures of thyroid functions are needed to confirm and expand on our findings.

Our research offers an initial understanding of the connection between hypothyroidism and diabetes in Saudi Arabia. Nevertheless, these results should be regarded as suggestive rather than definitive because of the limitations of our cross-sectional analysis and the absence of laboratory confirmation in certain cases. We highly recommend conducting more extensive studies to validate and build upon our findings, ideally with larger and more diverse sample sizes. Such research would more successfully inform clinical guidelines and contribute to a clearer understanding of the relationship between these conditions.

Conflict of Interest

The authors declare no conflict of interest regarding this work.

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Data Availability

The experimental data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval

The study "Relationship of Thyroid Dysfunction and its Manifestations in Diabetes Mellitus Patients in the Kingdom of Saudi Arabia" has been reviewed and approved by the Research Ethics Committee (REC) at the University of Hail dated 05/09/2022 under the reference number H-2022-297. The study adheres to the principles outlined in the Declaration of Helsinki.

Informed Consent

All patients and their families provided their informed consent.

Authors' Contributions

All authors contributed evenly to the research's conceptualization, drafting, data analysis, writing, and proofreading.

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