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Investigation of Thyroid Dysfunctions Among Type-1 and Type-2 Diabetes Mellitus Patients

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ABSTRACT

Background and Objective: Thyroid function plays a crucial role in controlling physiological processes. Diabetes and thyroid dysfunctions are two common endocrinological conditions that can be seen in the same patient at the same time. This study aims to investigate thyroid dysfunctions in patients with diabetes mellitus (DM) and to determine the risk factors for thyroid diseases accompanying diabetes. **Materials and Methods:** The 10297 patients were included in the study. All of the patients were diagnosed with DM. For this retrospective study, medical records of all patients were reviewed and serum T3, T4, TSH and HbA1c results were recorded. **Results:** All patients were categorized as overt hypothyroidism, overt hyperthyroidism, subclinical hypothyroidism, subclinical hyperthyroidism and euthyroidism according to T4 and TSH results. It was found that thyroid dysfunctions were more common in women and their incidence increased with age. **Conclusion:** Subclinical thyroid dysfunctions were found to be higher than overt dysfunctions. This is very important for patients with thyroid dysfunction accompanied by diabetes. Screening is recommended to reveal this condition, which is also related to age and gender.

KEYWORDS

Diabetes mellitus, thyroid dysfunctions, thyroid hormone abnormalities, HbA1c, autoimmune diseases, subclinical thyroid dysfunctions

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INTRODUCTION

Although diabetes mellitus and thyroid diseases are seen at different rates in different populations, they are among the most common chronic endocrine diseases[1]. Type 1 diabetes accounts for approximately 10% of all diabetes cases. Its incidence is increasing all over the world. Major challenges in the management of type 1 diabetes and its complications remain[2]. Type 1 diabetes and type 2 diabetes are heterogeneous diseases. Classification of diabetes is important in choosing the treatment protocol. It is not obvious that some individuals have type 1 or type 2 diabetes at diagnosis[3]. Diabetes mellitus is the disease of the century, the global prevalence of which has nearly doubled in the last fifty years, especially in the adult population. Approximately half of those who died due to diabetes mellitus and related complications were patients under the age of 70[4]. The prevalence of diabetes has increased steadily in the United States, from 7.5% in 1988-1989 to approximately 14% in 2016-2018[5]. The T1D disease develops

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froma background of autoimmunity and absolute insulin deficiency occurs as a result of the destruction of β cells of the pancreas and covers 5-10% of diabetes patients while the pathogenesis of T2D disease is much more complex and contains many pathways that interact with each other. The T2D disease in which insulin resistance is at the forefront may be a component of metabolic syndrome, T2D patients have higher Body Mass Index (BMI) measurements and the disease can occur in the presence of environmental triggers such as different types of viruses and various toxins, more than 90% of the diabetes patients have T2D disease. The T2D patients have high insulin levels at the earlier stage of the disease nevertheless low insulin levels and tissue unresponsiveness to insulin can sometimes occur in the same patient[6].

The incidence of type 1 diabetes can vary significantly around the world. With some exceptions, the incidence of T1D increases as one moves north of the equator. This situation is associated with a decrease in seasonal temperatures. Age at disease onset and islet autoimmunity have been reported to be higher in autumn and winter. The incidence of T2D is increasing in the United States, especially among young people. However, there is a close relationship between increasing age and the risk of developing T2D. Approximately 25% of individuals over the age of 65 in America have diabetes and approximately half of this age group has prediabetes. Studies have shown that T1D has a much more advanced characterization than T2D. Studies of patients with T1D and their first-degree relatives show that the persistent presence of two or more autoantibodies is almost certainly the cause of diabetes. Elevated glucose and HbA1c levels enable diagnosis before the clinical onset of diabetes and the onset of diabetic ketoacidosis (DKA)[7,8]. When hyperglycemia occurs, all diabetics have the same risk of developing chronic complications. However, progression rates may differ. Decreased β-cell insulin secretion in response to hyperglycemia appears to be the common denominator in both T1D and T2D. In both T1D and T2D, various genetic and environmental factors can cause progressive loss of β-cell mass and/or function, manifesting clinically as hyperglycemia[7]. Three stages are defined in the development of T1D. Stage 1 is characterized by the presence of two or more islet autoantibodies with normoglycemia or the presence of β-cell autoimmunity and is presymptomatic. Stage 2 is characterized by the presence of dysglycemia and β-cell autoimmunity and is presymptomatic. Stage 3 is the beginning of symptomatic disease. This staging classification is standardized for T1D[8].

Identifying individualized treatments for diabetes in the future will require better characterization of the many pathways leading to β-cell death or dysfunction. Classifications regarding diabetes focus on both the pathophysiology of the underlying β-cell dysfunction and the disease stage that may be related to glucose levels[7]. Hyperglycemia caused by the disease because of various pathologies causes different complications. Glycated hemoglobin A1C (HbA1C) evaluates chronic glycemia and elevates when there is long-term hyperglycemia, therefore HbA1C levels correlate with the risk of diabetes complications[9]. Complications are classified as acute and chronic and they can be life-threatening. While diabetic ketoacidosis or nonketotic hyperosmolar syndrome is present among acute complications, chronic complications have a wide spectrum including microvascular complications such as nephropathy, retinopathy, neuropathy and macrovascular complications such as cerebrovascular events, heart diseases and peripheral vascular diseases which can lead to amputations especially in the lower extremity[6,10].

Effective patient self-management is critical to prevent acute complications and reduce the risk of long-term complications. In order to do that, first, lifestyle changes should be made and regular exercise should be done, various diabetes medications should be used consistently and in combination most of the time, blood glucose levels should be monitored regularly and necessary actions should be taken when the blood glucose value is outside of the normal ranges[11]. Diabetes and thyroid dysfunctions represent the two most common endocrinological conditions seen in adults and may occur in the same patient simultaneously[12]. Previous studies indicated the prevalence of TD in diabetic patients is greater than in the general population, ranging from 10.3 to 33%[13,14]. The spectrum of thyroid diseases is quite wide. Subclinical thyroid diseases are diseases that do not have obvious symptoms and are biochemically

determined; however, they can cause complications, especially in the cardiovascular system. In these patients, the treatment is determined by considering the patient's age, TSH and cholesterol levels and comorbidities such as diabetes[15].

The most common autoimmune disease group seen in the clinic is autoimmune thyroiditis, these are known as Hashimoto's and Graves' diseases and can occur in the presence of various antibodies such as serum thyroid peroxidase (TPO) and thyroglobulin (Tg) antibodies[16]. Different studies stated that Hashimoto's thyroiditis is the most common autoimmune disease and autoimmune thyroid diseases may accompany 15-50% of T1D patients[17]. Thyroid hormones stimulate hyperglycemia via multiple mechanisms, including regulation of insulin sensitivity and its synergistic effects with catecholamines, leading to increased glycogenolysis[18]. Undiagnosed and untreated thyroid diseases can worsen metabolic control, hinder the management of diabetes and have a negative impact on the prognosis of the disease[19]. The relationship between diabetes and thyroid dysfunctions has been examined in various studies. It has been demonstrated in previous studies that DM patients with subclinical hypothyroidism are at higher risk of complications like nephropathy and cardiovascular events and early thyroxine replacement therapy in individuals with hypothyroid disease accompanying diabetes reduces the risks of various complications, especially in the cardiovascular system[20].

Even without subclinical disease, patients with a TSH level above 2.5 mIU/L have an increased risk of developing complications of diabetes mellitus such as retinopathy and renal dysfunction, which can be fatal, compared to patients who do not have elevated TSH levels[21]. It has been shown that metformin treatment reduces TSH levels without interfering with thyroid hormone levels and there is a decrease in nodular size after metformin treatment in patients with insulin resistance and small thyroid nodular goiter[22,23]. This study aims to investigate thyroid dysfunctions among T1D and T2D patients in Turkey, to develop limited data, determine the risk factors for thyroid diseases accompanying diabetes and examine the necessity of regular thyroid screening in diabetes mellitus patients.

MATERIALS AND METHODS

Study design: This study was conducted using the data of 11757 patients who applied to the Sultan Abdülhamid Han Training and Research Hospital of the University of Health Sciences in Istanbul between 04 January, 2016 and 10 October, .2021 and were diagnosed with type 1 or type 2 diabetes mellitus. Patient data were taken from the Nucleus Database between 01 October, 2021 to 20 November, 2021. Ethics committee approval was obtained with decision no. 30/6 (2021) of the Scientific Research Ethics Committee. All procedures were followed in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all individual participants included in the study.

This is a single-center study that involved data from 10297 patients (4275 males and 6022 females), a representative number of Turkish patients with diabetes, aged between 18-100 years who applied to Istanbul Training and Research Hospital between 04.01.2016-10.10.2021 and were diagnosed with type 1 or type 2 diabetes mellitus according to the ADA "Classification and Diagnosis of Diabetes Guideline"[3]. The data used in the study are; gender, age, admission diagnoses as type-1 or type-2 DM, TSH, T4 and HbA1c results. The data was taken from the Nucleus Database between 01 October, 2021 to 20 November, 2021. The number of data checked before the exclusion filters were applied is given in Table 1. The recurrent applications of the patients were not considered and only the results recorded at the first admission to the hospital were included in the study. The TSH results of the patients were categorized as <0.4 mIU/L low, 0.4-4.05 mIU/L normal and $\geq$4.05 mIU/L high; T4 results were categorized as <0.9 ng/dL low, 0.9-1.75 ng/dL normal and $\geq$1.75 ng/dl high. The HbA1c cut-off values were determined as 5 and 15. Thyroid functions of patients were categorized according to the ATA Guidelines and they evaluated as follows: Overt hypothyroidism when T4 is low and TSH is high, subclinical

Table 1: Number of data checked before applying exclusion filters

Year	TSH	T4	HbA1C
2016	3.353	25.570	10.599
2017	4.490	32.022	20.238
2018	5.792	45.390	18.836
2019	7.991	52.196	27.084
2020	5.748	40.437	27.186
2021	4.743	33.330	35.503
Total	32.122	228.995	139.446

Table 2: Patient groups not included in the study and their numerical distribution

Thyroid hormone levels	Frequency
TSH high+T4 high	3
TSH N+T4 low	51
TSH N+T4 high	1440
TSH low+T low	55

hypothyroidism when TSH is high but T4 is normal, euthyroid when both TSH and T4 results are between normal ranges, subclinical hyperthyroidism when TSH is low but T4 is normal, overt hyperthyroidism when TSH is low and T4 is high. Patients under the age of 18 and with longer than 7 days between T4-TSH measurements and longer than 90 days between TSH and HbA1c measurements were not included in the study. Besides, patients with thyroid function abnormalities, which may occur due to a possible secondary/tertiary cause, who may not fall under the category of primary thyroid diseases were excluded from the study; these patients are the patient groups with low TSH and T4 values together, high TSH and T4 values together, low or high T4 values when TSH is within normal limits and the number of patients in these groups is given in Table 2. As a result of the exclusion criteria, the number of patients, which was 14.382 at the beginning, decreased to 10.297.

Statistical analysis: The data were processed on IBM SPSS v25.0 and percentage, Chi-square analysis, standard deviation and median values were used in descriptive statistics. The statistical significance level of p-value less than 0.05 was accepted as statistically significant.

RESULTS

This study included 4275 (41.5%) males and 6022 females (58.5%), a total of 10297 patients; 408 of whom were diagnosed with type-1 diabetes (insulin dependent diabetes mellitus, 4%) and 9889 with type-2 diabetes (insulin independent diabetes mellitus, 96%). The age of the patient's distribution is given in text (Table 3). The TSH results were as follows, 710% (6.9 %) with low, 8696 with normal (84.5%) and 891 with high (8.7%) results and T4 results were as 306% with low (3%), 9939% with normal (96.5%) and 52% with high (0.5%). Thyroid functions were determined according to TSH and T4 values and showed the prevalence of thyroid dysfunctions of 1582/10297% (15.4%) in our population. The distribution was as follows: Overt hypothyroidism 287, subclinical hypothyroidism 604, euthyroid 8715, subclinical hyperthyroidism 639 and overt hyperthyroidism 52 (Table 4). It has been shown that HbA1c median value and HbA1c categorization distribution by gender, both HbA1c median value and the percentage of HbA1c in the "diabetes" category is higher in men (Table 5). When thyroid functions and gender were compared, it was found that both hypothyroidism and hyperthyroidism were more common in women and a significant relationship was found between gender and thyroid function (Table 6). The median HbA1c value of T1D patients was 8 while it was 6.9 in T2D patients. When the diagnosis of admission and thyroid dysfunctions were compared, no significant relationship was found and the distribution of thyroid dysfunction among type 1 and type 2 diabetes patients was similar (Table 7). However, the most common dysfunction in T1D patients was subclinical hypothyroidism, while it was subclinical hyperthyroidism in T2D patients. The relationship between age and thyroid dysfunctions was found to be significant ($p < 0.001$) and

the increase in dysfunction correlated with increasing age is seen in a text (Table 8). The median values of TSH, T4 and HbA1c according to the age ranges of the patients are shown in text (Table 9). The HbA1c value tends to increase with age in diabetic patients, but it reaches a plateau after the age of 60. As a result of the comparison of HbA1c categorization and thyroid dysfunction, it was determined that there was no statistically significant difference (Table 10).

Table 3: Distribution of age ranges of the patients included in the study

Age range	Frequency (n)	Percentage (%)
18-29	378	3.7
30-39	560	5.4
40-49	1715	16.7
50-59	2995	29.1
60-69	2686	26.1
70-79	1476	14.3
80-100	487	4.7
Total	10297	100

Table 4: Distribution of thyroid functions categorization of patients included in the study

Thyroid status	Frequency (n)	Percentage (%)
Hypothyroidism (T4-low,TSH-high)	287	2.8
Subclinical hypothyroidism (TSH-high,T4-normal)	604	5.9
Euthyroid (T4-N , TSH-N)	8715	84.6
Subclinical hyperthyroidism (TSH-low, T4-N)	639	6.2
Hyperthyroidism (TSH-low, T4-high)	52	0.5
Total	10297	100

Table 5: HbA1c median value and HbA1c categorization distribution by gender

Gender	HbA1c median value	Normal (n) (HbA1c<5.4)	Prediabetes (n) (HbA1c: 5.5-6.4)	Diabetes (n) (HbA1c>6.5)	Total (n)
Female	6	528 (8.7%)	1737 (28.8%)	3757 (62.3 %)	6022
Male	7.30	291 (6.8%)	959 (22.4%)	3025 (70.7%)	4275
Total		819 (7.9%)	2696 (26.1%)	6782 (65.8%)	10297

Table 6: Distribution of thyroid functions by gender

Gender	Overt hypothyroidism	Subclinical hypothyroidism	Euthyroid	Subclinical hyperthyroidism	Overt hyperthyroidism	Total	p-value
Male	103 (2.4%)	180 (4.2%)	3738 (87.4%)	238 (5.50%)	16 (0.30%)	4275	<0.001
Female	184 (3.00%)	424 (7.00%)	4977 (82.6%)	401 (6.60%)	36 (0.50%)	6022	
Total	287 (2.7%)	604 (5.8%)	8715 (84.6%)	639 (6.20%)	52 (0.50%)	10297	

Table 7: Distribution of thyroid functions by diabetes diagnosis

Diagnosis	Overt hypothyroidism	Subclinical hypothyroidism	Euthyroid	Subclinical hyperthyroidism	Overt hyperthyroidism	Total
Type 1	17 (4.1%)	29 (7.1%)	339 (83.2%)	22 (5.4%)	1 (0.2%)	407
Type 2	270 (2.7%)	575 (5.8%)	8376 (84.7%)	617 (6.2%)	51 (0.5%)	9889
Total	287 (2.8%)	604 (5.9%)	8715 (84.6%)	639 (6.2%)	52 (0.5%)	10297

Table 8: Distribution of thyroid functions by age

Age ranges/ Thyroid functions	Overt hypothyroidism	Subclinical hypothyroidism	Euthyroid	Subclinical hyperthyroidism	Overt hyperthyroidism	Total
18-29	7 (1.8%)	18 (4.7%)	344 (91.0%)	8 (2.1%)	1 (0.2%)	378
30-39	8 (1.4%)	30 (5.3%)	493 (88.0%)	27 (4.8%)	2 (0.3%)	560
40-49	47 (2.7%)	77 (4.4%)	1476 (86.0%)	101 (5.8%)	14(0.8%)	1715
50-59	97 (3.2%)	176 (5.8%)	2546 (85%)	167 (5.5%)	9 (0.3%)	2995
60-69	73 (2.7%)	168 (6.2%)	2241 (83.4%)	192 (7.1%)	12 (0.4%)	2686
70-79	38 (2.5%)	100 (6.7%)	1231 (83.4%)	94 (6.3%)	13 (0.8%)	1476
80-100	17 (3.4%)	35 (7.1%)	384 (78.8%)	50 (10.2%)	1 (0.2%)	487
Tole	287 (2.7%)	604 (5.8%)	8715 (84.6%)	639 (6.2%)	52 (0.5%)	10297

Table 9: TSH, T4 and HbA1c median values of age ranges

Age range	TSH median value	T4 median value	HbA1c median value
18-29	1.70	1.03	5.09
30-39	1.51	1.04	6.06
40-49	1.46	1.04	6.90
50-59	1.47	1.06	7.00
60-69	1.42	1.07	7.1
70-79	1.41	1.09	7.1
80-100	1.32	1.08	6.90

Table 10: Comparison of HbA1c categorization and thyroid dysfunctions

	Overt hypothyroidism	Subclinical hypothyroidism	Euthyroid	Subclinical hyperthyroidism	Overt hyperthyroidism	Total	p-value
Normal	21 (2.5%)	39 (4.7%)	715 (87.3%)	39 (4.7%)	5 (0.6%)	819	0.264
Prediabetes	76 (2.8%)	153 (5.6%)	2300 (85.3%)	152 (5.6%)	15 (0.5%)	2696	
Diabetes	190 (2.8 %)	412 (6 %)	5700 (84%)	448 (6.6 %)	32 (0.4 %)	6782	
Total	287 (2.7%)	604 (5.8%)	8715 (84.6%)	639 (6.2%)	52 (0.5%)	10297	

DISCUSSION

The T1D and T2D are polygenic diseases where many variants, with different effects, contribute to overall disease risk. Despite the genetic basis of diabetes, the prevalence of both T1D and T2D is increasing more than genetic variations. Therefore, it is being considered that environmental factors also play a very important role in both types of diabetes[7].

In the present study, thyroid functions were determined from the most common to rare as euthyroid, subclinical hyperthyroidism, subclinical hypothyroidism, overt hypothyroidism and overt hyperthyroidism. In various studies in the literature, it was stated that the most common thyroid condition other than the euthyroid state was subclinical hypothyroidism, the prevalence of overt and subclinical hyperthyroidism was lower than 0.3 and 1%, respectively[24-26].

In a report published by the National Guideline Center (UK) in 2019, it was reported that hypothyroidism is common in 2% of the UK population and more than 5% of people over the age of 60[27]. In the same publication, it was reported that the rate of hypothyroidism in women is 5-10 times higher than in men[27]. Current study concluded that hypothyroidism was seen in approximately 4.2% of the entire population. In addition, it is stated that it is common in approximately 4.5% of people over the age of 60 in our country. In these respects, current study results overlap with the National Guideline Center (UK) in terms of the incidence in the whole population; It has been determined that the rate of individuals over the age of 60 in our country has increased dramatically compared to the UK. It is possible to attribute this situation to many factors such as genetics, environmental factors, nutritional habits and inadequate diabetes follow-up. However, long-term consequences of hypothyroidism include increased cardiovascular risk factors, that involve cardiovascular disease and hypercholesterolemia. These effects can also be alleviated when hypothyroidism is treated effectively. Nevertheless, there are still some differences in the first and second-line follow-up and treatment of thyroid dysfunctions in our country as in the rest of the world. There is a need for standardization of thyroid hormone replacement strategies and follow-up protocols, especially in patients with hypothyroidism.

Remarkably, the subclinical thyroid dysfunctions detected in our study were higher than the overt dysfunctions and it can be thought that when the dysfunction is detected biochemically before it occurs clinically, it can be stopped before it progresses to the overt disease and that the treatment of thyroid dysfunction can prevent the worsening of the prognosis of diabetes as a result of avoiding possible glycemic index disrupting metabolic pathologies.

When thyroid functions and gender were compared, it was found that both hypothyroidism and hyperthyroidism were more common in women[15]. In an article published in 2020, Turner *et al.*[28] reported that the frequency of thyroid dysfunction in patients with diabetes increases with age and is higher in women than in men. In current study, a significant relationship was found between gender and thyroid function ($p<0.001$). When the reasons why women are at risk for thyroid dysfunction are examined; it can be thought that their glycemic index may be worse than men's. In the study conducted with T2D patients, Mogre *et al.*[29] suggested that this condition develops because women are more prone to have autoimmune diseases. Furthermore, when the reason for hypothyroidism is autoimmune thyroiditis, which is the most common cause, this condition shares a common genetic origin with T1D. Barmpari *et al.*[30] and Duntas *et al.*[31] stated that T1D and autoimmune thyroid disease are based on a related genetic susceptibility and that there is a complex interaction of common signaling pathways. The ADA recommends regular screening of newly diagnosed type1 diabetes patients at the time of diagnosis and periodically after, in terms of the possibility of developing prospective accompanying autoimmune thyroid diseases[3].

A rising HbA1c level is the first indicator of the clinical onset of diabetes, making diagnosis feasible well before diabetic ketoacidosis. The HbA1c values and standard deviations were found like the studies in the literature. In present study, the HbA1c value tends to increase with age in diabetic patients, but it reaches a plateau after the age of 60. Similar to current findings, Edqvist *et al.*[32] investigated the relationship between the age of onset of diabetes and HbA1c levels and, found that those diagnosed with diabetes before the age of 15 had higher hba1c levels than those diagnosed older ages and that HbA1c in both groups tended to increase until the age of 45, but was stable after this age with slight decreases[32].

Subclinical thyroid dysfunction includes both subclinical hypothyroidism and subclinical hyperthyroidism. Various publications have reported that the prevalence of both conditions increases with age and that in patients>70 years of age, approximately 5% of the population has either of these two conditions. It is also known that most of these patients return to euthyroid state after a certain follow-up and only a few of them progress to overt hypothyroidism or hyperthyroidism. No statistically significant difference was found in present study when the diagnosis (T1D and T2D) and thyroid dysfunctions were compared ($p>0.005$). It was found that the distribution of thyroid dysfunction in T1D and T2D patients were similar. The lack of a significant relationship between DM type and thyroid dysfunctions is consistent with the literature. In their study, Barmpari *et al.*[30] reported no statistically significant difference in the prevalence of hypothyroidism between T1DM and T2DM patients. However, the most common dysfunction in patients diagnosed with T1D was subclinical hypothyroidism, while the most common dysfunction in patients diagnosed with T2D was subclinical hyperthyroidism. The result found in T1D patients was consistent with the literature and it has been stated in many publications that the most common thyroid dysfunction in T1D patients is hypothyroidism.

The fact that the study included a higher number of patients compared to similar studies in the literature increases the reliability of the study results. The retrospective nature of the study and the large number of patients limited the ability to obtain additional examinations from the patients and the inclusion of the patients' clinics in the study. It is recommended that patients thyroid imaging results, such as ultrasound sonography test (USG) or scintigraphy, be included in future studies.

CONCLUSION

In the present study, it was determined that the development of thyroid dysfunction in patients with diabetes mellitus is associated with age and gender. It was determined that the most common thyroid dysfunction in the patient group was subclinical hyperthyroidism, followed by subclinical hypothyroidism. As a result of the data obtained in this study, it is strongly recommended that diabetes mellitus patients, especially women, should be screened for thyroid autoimmunity and dysfunctions.

SIGNIFICANCE STATEMENT

The aim of this study is to investigate thyroid dysfunctions in patients with diabetes mellitus (DM) and to determine the risk factors for thyroid diseases accompanying diabetes. It was found that thyroid dysfunctions were more common in women and their incidence increased with age. As a result of the research, supports diabetic patients to have regular thyroid function checks, as recommended in the ADA guidelines.

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