Prevalence Of Thyroid Disorders In Diabetic Patients Referred To Kosar Hospital In Semnan During 2014-2020

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Abstract:

Introduction and aim: One of the problems of the diabetic community is thyroid disorders, which doubles the problems of these patients. The present study was conducted to investigate the prevalence of thyroid disorders in diabetic patients and related factors.

Materials and Methods: In this cross-sectional study, 400 outpatients with diabetes, from 2014 to 2020, were selected by available sampling method and after extracting information and clinical and laboratory data from the clinical records of research units, the frequency of effective variables was analyzed using statistical analysis software.

Results: The findings of the present study demonstrated that 142 patients (35.5%) had thyroid disorders; The most common thyroid disorders were clinical hypothyroidism (22.0%), subclinical hypothyroidism (11.0%), and hyperthyroidism (2.5%), respectively. Also, 49 patients (32.4%) had high anti-TPO antibody titers and among the patients with positive anti-TPO antibodies, 91.8% (45 patients) had thyroid disorders. There was a statistically significant relationship between the level of anti-TPO and the type of thyroid disorder in diabetic patients (P 00 0.001); Thus, 16.3% had Hashimoto's disease and 6.1% had Graves' disease.

Conclusion: Thyroid disorders are relatively common in diabetic patients. Due to the high prevalence of diabetes in Iran, knowing the epidemiology of thyroid disorders in diabetic patients can help long-term planning for diagnosis, prevention, and early treatment of these disorders.

Keywords: Diabetes, Clinical Hypothyroidism, Subclinical Hypothyroidism, Hyperthyroidism.

1. INTRODUCTION

It is estimated that by 2030 the number of diabetics in the world would reach about 366 million, which is nearly 4.4% of the population [1]. In Iran, the prevalence of diabetes is estimated at 7.7%, which is also increasing [2]. Disorders of metabolic regulation due to diabetes mellitus could cause secondary pathophysiological changes in various organs of the body, which cause many problems for a person with diabetes and the public health system. In the United States, diabetes mellitus is a major cause of chronic renal failure, non-traumatic lower-extremity amputations, and adult blindness [3, 4].

Diabetes may be associated with autoimmune disorders such as autoimmune thyroid disease, Addison's disease, and celiac disease [5]. Thyroid disorders and diabetes mellitus are the most common endocrine disorders [6]. Thyroid hormones play an important role in regulating carbohydrate metabolism [7]. Diabetes mellitus and thyroid disorders are both due to dysfunction of the endocrine system, which regulates the body's metabolism [8]. Both insulin and thyroid hormones are involved in cellular metabolism, and an increase or decrease in each of them can cause disorders [9]. Thyroid dysfunction impairs metabolic control in diabetic patients [10, 11] and increases the risk of cardiovascular diseases [12]. Thyroid disorders can be a major problem for controlling blood sugar in diabetics. Hypothyroidism can reduce the need for insulin in diabetic patients and hyperthyroidism can impair glucose tolerance or control [6]. Subclinical hypothyroidism causes recurrent hypoglycemic attacks [13], because the rate at which glucose is excreted from the liver is reduced due

to decreased gluconeogenesis [14], thereby controlling carbohydrate metabolism in the body [10]. The prevalence of thyroid diseases in type 1 diabetic patients has been reported from 7.3 to 20% according to some studies conducted so far [15, 16].

Thyroid autoimmune diseases are characterized by the high titer of thyroid autoantibodies [17]. The prevalence of thyroid antibodies in patients with diabetes varies between 3% to 50% in different countries, depending on age, sex, duration of diabetes, and race [18]. The rate of positiveness of antithyroid antibodies in patients that are newly diagnosed with diabetes has been reported between 10 to 30% [17]. Monitoring of thyroid disease in type 1 diabetic patients, as soon as diabetes is diagnosed, should be performed with TSH hormone and must be repeated every 1 to 2 years, also, anti-TPO and anti-TG levels should be assessed [19].

The prevalence of anti-TPO in patients with diabetes, who are clinically euthyroid, is between 10 to 21.8 percent [20], but the development of autoimmune thyroid disease in patients with high titers of these antibodies is observed in about 50% of cases, within 3 to 4 years [18]. Anti-TPO is more valuable in predicting autoimmune thyroid disease, in comparison with anti-TG [19, 21].

Since failure to diagnose and treat thyroid disorders in diabetic patients with metabolic control disorders increases the complications and mortality of diabetes, in order to develop appropriate diagnosis and treatment programs, it is necessary to investigate the epidemiology of thyroid disorders in diabetic patients; however, in our country, no comprehensive study has been conducted on thyroid disorders in patients with Diabetes Mellitus; Therefore, this study was conducted to assess the prevalence of thyroid diseases in patients with diabetes, in order to collect more information about thyroid disorders and their association with diabetes mellitus, whereas this information can be effective in the timely diagnosis of thyroid disorders in diabetic patients in Iran.

2. MATERIALS AND METHODS

Study Design

In this cross-sectional study, 400 outpatients with diabetes, who referred to the endocrine clinic of Kosar Hospital in Semnan, during 2014-2020, were selected by convenience sampling method and after extracting information and clinical and laboratory data from the clinical records of research units, the frequency of effective variables was analyzed using statistical analysis software. The present research was performed after registering the plan in the ethics council of Semnan University of Medical Sciences and receiving the code of ethics; in addition, all the information was used confidentially and only for the purpose of conducting the research plan.

Inclusion and Exclusion Criteria

Inclusion criteria were complete patient satisfaction, fasting blood sugar level equal to or greater than 126 mg/dl, and other symptoms of diabetes such as polyuria, retinopathy, nephropathy, neuropathy, or weight gain. Exclusion criteria included dissatisfaction with participation in the study, smokers, distortion or serious defect of clinical records, specific diseases such as cancer, liver disorder, kidney disorder, chronic infection, hematuria, heart failure, fever, severe hyperglycemia, severe hypertension, and consumption of drugs that affect thyroid tests such as glucocorticoids, oral contraceptives, and nonsteroidal anti-inflammatory drugs.

Data Collection

In this study, the data collection tool was a researcher-made checklist. Demographic and general information including age, gender, and body mass index, was extracted from the clinical records of research units. Clinical information including the type of diabetes treatment, duration of diabetes diagnosis, family history of diabetes, and complications of diabetes (neuropathy, retinopathy, nephropathy) was extracted from the clinical records of research units. Laboratory information including fasting blood sugar levels, hemoglobin A1C, TSH, FT4, and anti-TPO antibodies, was also extracted from the clinical records of research units.

Procedure

After obtaining the necessary permits, the required information was extracted and recorded by referring to the clinical records archive of outpatients in the educational and research center. Then, demographic, clinical, and laboratory information were collected. In case of minor defects in the information of the research units, the researcher of the project (medical student), after calling the number listed in the individual's clinical file and providing a full explanation of the study process, received additional information and completed the file. Finally, the collected data were statistically analyzed. It should be noted that in this study, information about TSH was recorded for all patients, but, only in case of disorder in this hormone, information about other hormones as well as anti-TPO was recorded. If the titer of anti-TPO was higher than 50 units per milliliter, the antibody levels were considered abnormal, and the patient was diagnosed with autoimmune thyroid disease. The definition of subclinical hypothyroidism is based on normal T4 and increased TSH, clinical hypothyroidism is based on decreased T4 and increased TSH, and hyperthyroidism is based on increased T4 and decreased TSH. In this study, the normal level of serum TSH was considered between 0.4 and 4.2 units per ml [15].

Also, the normal level of total T4 in men was considered 4.4 to 11 units and in women was considered 4.8 to 12 units [2]. In addition, the normal level of T3 was considered 80 to 180 ng/dL, the normal level of FT4 was contemplated 0.7 to 1.9 ng/dL, and the normal level of FT3 was considered 2.3 to 4.1 pg/mL.

Data Analysis

After collecting information, Spss software version 23 was used to compare the studied groups. Data were analyzed using the paired t-test, Pearson correlation coefficient, and chi-square. In all tests, the confidence level was 95% and the significance level was considered less than 5%.

3. RESULTS

The mean and standard deviation of the age of diabetic patients studied were 55.77 and 13.13 years, respectively (P = 0.863). Table 1 shows the distribution of thyroid disorders in diabetic patients by gender. According to this table, there was no statistically significant relationship between gender and the type of thyroid disorder in diabetic patients (P = 0.793).

Table 1: Age and gender of patients with diabetes

Thyroid disorder	Age group (years)							
	Child (≤18)		Young (19-29)		Middle-aged (30-59)		Elderly (60≤)	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
without disorder (euthyroid)	5	71.4	2	40.0	129	62.0	122	67.8
Subclinical hypothyroidism	-	-	1	20.0	24	11.5	19	10.6
Clinical hypothyroidism	2	28.6	2	40.0	50	24.0	34	18.9
Hyperthyroidism	-	-	-	-	5	2.4	5	2.8
Total	7	100	5	100	208	100	180	100
Thyroid disorder	Gender				P-value			
	Female		Male					

	Frequency	Percentage	Frequency	Percentage	
without disorder (euthyroid)	187	63.8	71	66.4	0.793
Subclinical hypothyroidism	35	11.9	9	8.4	
Clinical hypothyroidism	64	21.8	24	22.4	
Hyperthyroidism	7	2.4	3	2.8	
Total	293	100	107	100	-

Among the studied patients, overall, 35.5% (142 patients) had thyroid disorders; The most common thyroid disorders were clinical hypothyroidism (0.22%), subclinical hypothyroidism (0.11%), and hyperthyroidism (2.5%), respectively (Table 2).

Table 2: Distribution of thyroid disorders in diabetic patients studied

Thyroid disorder	Frequency	Percentage
without disorder (euthyroid)	258	5.64
Subclinical hypothyroidism	44	0.11
Clinical hypothyroidism	88	0.22
Hyperthyroidism	10	5.2
Total	400	100

The mean duration of diabetes diagnosis in the studied patients was 7.28 years. According to Table 3, in most of the subjects (82.5%), less than 10 years had passed since they were diagnosed with diabetes. There was no statistically significant relationship between the duration of diabetes diagnosis and the type of thyroid disorder in diabetic patients (P = 0.051).

Table 3: Distribution of thyroid disorders in diabetic patients based on the duration of diabetes diagnosis

Thyroid disorder	Duration of diabetes diagnosis (years)						
	≤10		11-20		21<		P-value
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
without disorder (euthyroid)	199	3.60	47	0.81	12	100	0.051
Subclinical hypothyroidism	39	8.11	5	6.8	-	-	
Clinical hypothyroidism	83	2.25	5	6.8	-	-	
Hyperthyroidism	9	7.2	1	7.1	-	-	
Total	330	100	58	100	12	100	-

Among diabetic patients, 37% had diabetic neuropathy. There was a statistically significant relationship between diabetic neuropathy and type of thyroid disorder in the studied diabetic patients (P = 0.001). The most common thyroid disorders in patients with diabetic neuropathy were clinical hypothyroidism (21.6%) and subclinical hypothyroidism (6.8%), respectively. Also, 0.17% had diabetic retinopathy. According to Table 4, there was a statistically significant relationship between diabetic retinopathy and the type of thyroid disorder in the diabetic patients (P = 0.030); Accordingly,

the most common thyroid disorders in patients with diabetic retinopathy were clinical hypothyroidism (10.3%) and subclinical hypothyroidism (4.4%), respectively. Also, 23.8% of patients had diabetic nephropathy and there was no statistically significant relationship between diabetic nephropathy and the type of thyroid disorder in diabetic patients (P = 0.059).

Table 4: Distribution of thyroid disorders in diabetic patients based on diabetic complications

Thyroid disorder	Diabetic neuropathy						
	Yes		No		Unknown		P-value
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
without disorder (euthyroid)	103	6.69	142	0.64	13	3.43	0.001
Subclinical hypothyroidism	10	8.6	30	5.13	4	3.13	
Clinical hypothyroidism	32	6.21	47	2.21	9	0.30	
Hyperthyroidism	3	0.2	3	4.1	4	3.13	
Total	148	100	222	100	30	100	-
	Diabetic retinopathy						
without disorder (euthyroid)	56	4.82	153	7.62	49	7.55	0.030
Subclinical hypothyroidism	3	4.4	29	9.11	12	6.13	
Clinical hypothyroidism	7	3.10	56	0.23	25	4.28	
Hyperthyroidism	2	9.2	6	5.2	2	3.2	
Total	68	100	244	100	88	100	-
	Diabetic nephropathy						
without disorder (euthyroid)	71	7.74	148	5.63	39	2.54	0.059
Subclinical hypothyroidism	7	4.7	30	9.12	7	7.9	
Clinical hypothyroidism	15	8.15	51	9.21	22	6.30	
Hyperthyroidism	2	1.2	4	7.1	4	6.5	
Total	95	100	233	100	72	100	-

83.5% of patients consumed oral medications to control their diabetes. According to Table 5, there was no statistically significant relationship between the type of diabetes treatment and the type of thyroid disorder in diabetic patients (P = 0.718).

Table 5: Distribution of thyroid disorders in diabetic patients based on the type of diabetes treatment

Thyroid disorder	Type of diabetes treatment						
	Oral medication		Insulin		Both		P-value
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
without disorder (euthyroid)	217	0.65	15	5.62	26	9.61	0.718
Subclinical hypothyroidism	34	2.10	3	5.12	7	7.16	
Clinical hypothyroidism	75	5.22	6	0.25	7	7.16	
Hyperthyroidism	8	4.2	-	-	2	8.4	
Total	334	100	24	100	42	100	-

Findings related to fasting blood sugar levels showed that the mean FBS in the studied patients was 139.44 mmol / L. According to Table 6, most of the subjects (49.8%) had FBS levels higher than 126 mmol / L. There was a statistically significant relationship between FBS level and the type of thyroid disorder in diabetic patients (P = 0.001); Accordingly, the most common thyroid disorder in patients with high FBS was clinical hypothyroidism.

Table 6: Distribution of thyroid disorders in diabetic patients based on fasting blood sugar levels

Thyroid disorder	Fasting blood sugar (mmol / L)						
	Normal (<100)		Intermediate (100-125)		High (126<)		P-value
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage	
without disorder (euthyroid)	42	6.63	128	3.64	88	2.65	0.001
Subclinical hypothyroidism	4	1.6	30	1.15	10	4.7	
Clinical hypothyroidism	14	2.21	37	6.18	37	4.27	
Hyperthyroidism	6	1.9	4	0.2	-	-	
Total	66	100	135	100	199	100	-

The mean hemoglobin A_1C in the patients was 8.02%. According to Table 7, there was a statistically significant relationship between hemoglobin A1C levels and the type of thyroid disorder in diabetic patients (P = 0.007). Regarding the frequency of anti-TPO antibodies, 32.4% were positive and had autoimmune thyroid disease. According to Table 7, among patients who were anti-TPO positive, 11.3% had thyroid disorders. Also, the results showed that there was a statistically significant relationship between the level of anti-TPO and the type of thyroid disorder in diabetic patients (P< 0.001). Thus, 16.3% had Hashimoto's disease and 6.1% had Graves' disease.

Table 7: Distribution of Thyroid Disorders in studied Diabetic Patients Based on Hemoglobin A_1C and Anti-TPO Levels

Thyroid disorder	Hemoglobin A_1C (percentage)				P-value
	Normal		High		
	Frequency	Percentage	Frequency	Percentage	
without disorder (euthyroid)	64	7.62	194	1.65	0.007
Subclinical hypothyroidism	12	8.11	32	7.10	
Clinical hypothyroidism	23	5.22	65	8.21	
Hyperthyroidism	3	9.2	7	3.2	
Total	102	100	298	100	-
	Anti-TPO (units/mL)				
	Negative (≤50)		Positive (50<)		
	Frequency	Percentage	Frequency	Percentage	
without disorder (euthyroid)	57	4.56	4	2.8	0.001
Subclinical hypothyroidism	8	1.5	34	4..69	
Clinical hypothyroidism	40	8.25	8	3.16	
Hyperthyroidism	6	9.3	3	1.6	
Total	101	100	49	100	-

4. DISCUSSION

The results of the present study showed that among the diabetic patients studied, in total, 35.5% had thyroid disorders; The most common thyroid disorders were clinical hypothyroidism, subclinical hypothyroidism, and hyperthyroidism, respectively. A study by Tudor et al. in 2020 showed that overall, 30% of diabetic patients had thyroid disorders [22]. In another study in 2018, the results showed that the prevalence of thyroid disorders in this group of patients was 28% [23], which was in line with the findings of the present study. In a study by Shun et al. (2014), thyroid dysfunction in diabetic patients was observed in 27% of these patients [18]. In another similar study in Iran, the frequency of thyroid dysfunction was 28.2% in diabetic patients [3]. In other studies, the frequency of

thyroid dysfunction was equal to 37.7% [24] and 28% [25], that these findings were in line with the results of the present study. In contrast, in some studies, the prevalence of thyroid disorder was lower, in comparison with our study. In a study by Khurana et al. In 2016, the prevalence of thyroid disorders among patients was 16% [26]. Also, in a study by Al-Lehibi et al. In 2019, only 8% of patients showed thyroid disorders [22]; The reason for these differences could be differences in the study population, statistical sample size, contextual variables such as genetics and metabolic disorders, as well as differences in measurement methods and tools. In other words, racial and ethnic differences may play a role in differentiating the prevalence of thyroid dysfunction in diabetic patients [1, 4, 5, 12]. In addition, perhaps some other reasons for the differences between the present study and other studies could be differences in iodine and goitrogen consumption in the diet, climate differences, and differences in the prevalence of autoimmune disorders in different communities.

In general, several similar studies have been performed on thyroid disorders, reporting a prevalence of 10 to 50 percent [27-32]; Some studies have attributed this difference in the prevalence of the disease to genetics, associated autoimmune disorders, and chronic stress [12]. There is evidence that genetic factors such as human leukocyte antigen and other genes outside the area of human leukocyte antigen, such as CTLA4 and PTPN2 genes, could have a role in this regard acting [17, 18]. Apart from this, environmental factors are involved in the pathogenesis of thyroid disorders [28].

The findings of the present study showed that 32.4% of cases had a positive anti-TPO titer. In a similar study, it was concluded that 32.3% of the patients had positive anti-TPO titers [29], which was close to the findings of the present study. Findings of other studies in Iran and other parts of the world also showed the titers of this antibody were close to the findings of the present study[30, 31]. However, in a study by Sarfo-Kantanka et al., 14.7% of cases [28] and in a study by Kalantari et al., 5.8% of the subjects had positive anti-TPO titer and, as a result, autoimmune thyroid disease [32]. Which also showed lower frequencies compared to the present study; the reason for these differences can be related to factors such as differences in the size of statistical samples studied and also, differences in measurement tools and methods in different studies.

The results of our study showed that among the diabetic patients who had positive anti-TPO, 11.3% had thyroid disorders. In a study by Hadayek et al. In Bandar Abbas, which was conducted to determine thyroid autoimmune disorders in patients with diabetes in the southern region of Iran, the results showed that 17.6% of patients with positive anti-TPO had thyroid dysfunction [31]; the findings were close to the results of the present study. The results of the present study also demonstrated that there was a statistically significant relationship between the complications of diabetes, including diabetic retinopathy and diabetic neuropathy, and the type of thyroid disorder in diabetic patients studied. A similar study by Yang JK et al. found that the prevalence of diabetic retinopathy was higher in people with subclinical hypothyroidism than in those with normal thyroid [33]. In addition, in a study by Ozair et al. In 2018, the results showed that thyroid disorders were more common in patients with symptoms of retinopathy [23], which was consistent with the results of the present study.

Similar research has shown that patients with subclinical hypothyroidism often show endothelial dysfunction, which may lead to poor vascular function and increase the risk of retinopathy [33, 34]. An association between thyroid hormone levels and retinopathy has also been observed in other studies [35-37]. For this reason, in many studies, it is recommended that people with thyroid disorders, especially subclinical hypothyroidism, be screened for retinopathy. In a study of 1,581 people with normal thyroid function, the results showed that diabetes and diabetic retinopathy were directly related [38].

Retinopathy and neuropathy are two important factors in thyroid disorders that are commonly seen in people with diabetes. Several cellular pathways and potential molecular mechanisms have been proposed to explain these complications in diabetes. In diabetic retinopathy, some mechanisms are involved, including the increased formation of advanced glycation end-products (AGE), abnormal activation of signaling cascades such as activation of the protein kinase C (PKC) pathway, increased oxidative stress, increased hexosamine pathway, and peripheral nerve damage. All of these pathways directly or indirectly disrupt the readjustment of factors such as insulin growth factor (IGF), stroma-derived factor (SDF-1), vascular endothelial growth factor (VEGF), angiopoietins (Ang-2), and tumor necrosis factor (TNF), by increasing oxidative stress, inflammation, and vascular occlusion, which ultimately contribute to the pathogenesis of diabetic retinopathy. In fact, cellular stress caused by high

blood sugar levels disrupts the cellular cascading pathways in long term, leading to diabetic retinopathy and thyroid disorders [39, 40].

There is also a lot of empirical evidence for diabetic neuropathy. In neuropathy, all parts of neurons, from the pericardium to the terminal, are targeted by diabetes. Damage caused by diabetes causes dysfunction of nerve cells and their organs by disrupting important cellular factors such as the oxidation cycle [41]. Nerve cells, like other cells in the body, are affected by the deficiency of thyroid hormones. Schwann cells contain vesicles full of ribosomes that play an important role in the structure of axons by protein synthesis. Therefore, in many cases, Schwann cell damage leads to several changes in axons and their destruction [42-44].

The point of connection between diabetic neuropathy and retinopathy with thyroid disorders is that in diabetic patients, due to changes in the regulation of cellular factors and increased cellular stress, thyroid function is impaired and the process of protein synthesis of thyroid hormone-secreting cells is disrupted. Thyroid hormones play an important role in the structure and function of peripheral nerve regeneration such as Schwann cells and glial cells [45, 46].

Findings have shown that thyroid hormone deficiency is associated with neurological problems and abnormalities in the central nervous system [47]. In general, from the findings of the present study and the molecular mechanism of retinopathy and neuropathy, it can be concluded that all these variables are directly related to each other, diabetes and high blood sugar, in long term, cause tissue damage and thyroid dysfunction, thyroid dysfunction causes nerve damage, and tissue damage causes disruption of cell cycles and important cellular factors and the progression of retinopathy; Due to the role of these factors, it is important to pay attention to the factors that reduce diabetes and improve thyroid function.

Among the limitations of the present cross-sectional study was the inability to control confounders and contextual variables involved in the main variables of this study; Therefore, the analysis of results should be done more carefully. In addition, there are certainly many known and unknown factors that may affect the prevalence of thyroid disorders in diabetics, all of which, especially nutrition, genetics, and how to control metabolic disorders, could not be studied in one research and would require further studies in wider statistical communities. However, in this study, the maximum possible effort was made to achieve accurate results by controlling the limitations that can be eliminated.

5. CONCLUSION

Thyroid disorders, including clinical and subclinical hypothyroidism, and hyperthyroidism, are relatively common in diabetic patients. Due to the high prevalence of diabetes in Iran, knowing the epidemiology of thyroid disorders in diabetic patients can help long-term planning for diagnosis, prevention, and early treatment of these disorders. However, due to the descriptive nature of this study, it is necessary to conduct further interventional studies with long-term and broader follow-up, in order to better generalize the results to other high-risk groups and to obtain more accurate results, while removing the limitations of the present study.

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