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Original Article

Thyroid dysfunction prevalence and relation to glycemic control in patients with type 2 diabetes mellitus

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ABSTRACT

Objective: It is usually difficult to clinically identify thyroid abnormalities in diabetics as features of thyroid dysfunction may simulate diabetes symptoms or complications. So, assessing thyroid dysfunction prevalence in patients with type 2 diabetes mellitus (DM) would help better control of DM and its complications. Several studies reported this prevalence, however, some included small sample size or lacked a control group. We aimed to determine thyroid dysfunction prevalence in diabetic patients as well as its relation to glycemic control.

Methods: A cross-sectional study included 200 patients having type 2 DM and 200 apparently healthy controls. Each participant was tested for fasting and 2-h post-prandial blood glucose, glycated haemoglobin (HbA1C), thyroid function tests: thyroid-stimulating hormone (TSH), free tri-iodothyronine (FT3), free thyroxine (FT4), serum total cholesterol and triglycerides and thyroid antibodies; anti-thyroid peroxidase (*anti*-TPO) and anti-thyroglobulin (*anti*-Tg) for hypothyroidism only.

Results: There was a significant increase in serum TSH and T3 levels in diabetics when compared with the controls, ($P < 0.001$, $P = 0.001$), respectively. Thyroid dysfunction was significantly more prevalent in patients with HbA1c $\geq$ 8%, ($P = 0.0001$), and in those having longer diabetes duration, ($P < 0.001$).

Conclusion: There was a higher prevalence of thyroid dysfunction among patients with type 2 DM. This dysfunction increased with the rise of HbA1c. This could suggest that poor glycemic control may have a role in the development of thyroid dysfunction in type 2 DM patients. Subclinical hypothyroidism was the most prevalent type of thyroid dysfunction in diabetic patients.

1. Introduction

Hyperglycemia is the hallmark of the metabolic abnormalities in diabetes mellitus (DM) due to dysfunction of the pancreatic β cells [1]. The second most common endocrinal pathology, after DM, is thyroid dysfunction [2].

Both conditions can interact with each other in several ways. The abnormalities present in insulin resistance as increased insulin degradation, increased glucagon secretion, increased hepatic glucose production, and enhanced catecholamines are considered as an integral part in the pathogenesis of hyperthyroidism [3,4].

Subclinical hypothyroidism had been connected to insulin resistance in several studies. This connection is thought to be due to imbalance of lipid metabolism and the occurrence of metabolic syndrome [5].

Elevated hepatic glucose output and upregulated glycogenolysis present in thyrotoxicosis, both lead to glucose intolerance with subsequent aggravation of blood glucose level elevation in diabetics [6]. While in hypothyroidism, the main metabolic features of the disease have an impact on glucose metabolism through diminished glucose output from the liver, gluconeogenesis and reduced glucose catabolism [7].

Sometimes it is difficult to diagnose thyroid abnormalities in diabetics based on the clinical picture of the patient as features of hyperthyroidism may simulate features of hyperglycemia such as: weight reduction in spite of increased appetite and tiredness. Similarly, hypothyroidism could be confused with the development

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of diabetic nephropathy as the patient may present with increased weight, edema, pallor and easy fatigability [8].

Several authors studied the association between type 2DM and thyroid dysfunction [2,6], however, some of these studies had small sample sizes or lacked a control group. Moreover, these studies reported a high incidence of diabetic complications in patients with thyroid dysfunction; hence, we need to assess thyroid dysfunction prevalence in patients with type 2 DM to help better control of DM and to decrease its complications.

In this work we aimed to assess the thyroid function in patients with type 2 DM and apparently healthy controls, attending our University Hospital, in an attempt to determine the prevalence of thyroid dysfunction in those patients as well as its relation to glycemic control.

2. Subjects and methods

2.1. Study design

This cross-sectional study was performed on 400 subjects. Two hundred diabetic patients were recruited from the outpatient clinic of Internal Medicine department, in Tanta University Hospital, plus 200 apparently healthy controls. The study was conducted in the period from November 2017 to November 2018.

2.2. Study groups

2.2.1. Group I

This group included 200 patients diagnosed to have type 2 DM. All the patients in the diabetic group were confirmed to be diabetics based on the American Diabetes Association (ADA) 2018 criteria for diagnosis of DM [9]. They were 126 females and 74 males. They received treatment in the form of insulin, or oral hypoglycemic agents.

2.2.2. Group II

This group included 200 apparently healthy non-diabetic individuals (control group). They were 116 females and 84 males.

2.3. Inclusion criteria

Patients diagnosed to have type 2 DM with age ranging from 30 to 65 years were included in the study group.

2.4. Exclusion criteria

Patients having any of the following were excluded from the study: known history of thyroid disease, surgery of the thyroid gland, exposure to radiation of the thyroid gland, pregnancy, receiving medications known to modify the thyroid functions such as lithium, amiodarone, etc., unstable cardiac disease, renal impairment (including diabetic nephropathy), liver cirrhosis, malignancies, or other types of DM such as drug-induced, gestational DM, or type 1 DM.

The study complied with the Declaration of Helsinki and ethical approval was obtained by the Local Faculty review board (approval number: 31843/10/17). A written informed consent was obtained from all participants before enrollment in the study.

2.5. Study work up

All included subjects were subjected to complete history taking and clinical examination with special stress on clinical findings of hypothyroidism or hyperthyroidism. Laboratory tests included: Fasting blood glucose, fasting insulin level, 2 h post-prandial blood glucose, HbA1c, complete blood count, thyroid function tests: thyroid-stimulating hormone (TSH), free tri-iodothyronine (FT3), free thyroxine (FT4), total serum cholesterol and triglycerides, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), blood urea, serum creatinine, and thyroid antibodies; anti-thyroid peroxidase (*anti*-TPO) and anti-thyroglobulin (*anti*-Tg), for hypothyroidism only. The normal reference ranges of thyroid functions were; TSH: 0.27–4.2 mIU/L, FT3: 2–4.4 Pg/ml and FT4: 0.93–1.7 ng/dl.

2.6. Statistical analysis

Once data were collected, a code sheet was developed. Organization, tabulation, presentation and analysis of data were performed by using SPSS Version 23, IBM Corp., Armonk, NY, USA. Numerical data were presented as mean and standard deviation (SD). For quantitative non-parametric data; Mann-Whitney *U* test and Spearman correlation were used. Categorical data were presented as number and percentage and Chi-squared test was used for statistical analysis. The level of significance was adopted at $p < 0.05$.

3. Results

The demographic data and some laboratory results are mentioned in Table 1.

3.1. Thyroid hormones and serum insulin levels

The levels of serum insulin, FT3 and TSH were significantly higher in the group of diabetic patients (group I) compared to the controls (group II), ($P < 0.001$, $= 0.001$ and <0.001 respectively), denoting the higher prevalence of thyroid dysfunction in diabetic patients, while the FT4 levels were non-significantly higher in diabetics than controls ($P = 0.177$) (Table 1).

3.2. Types of thyroid dysfunction

Out of the 200 diabetic patients, 29% had thyroid dysfunction in the form of; overt hypothyroidism (7%), all of them were females, subclinical hypothyroidism (13%), overt hyperthyroidism (3%), and subclinical hyperthyroidism (6%). On the other hand in the control group, (5%) had thyroid dysfunction and they were all females, (2%) had subclinical hyperthyroidism, (3%) had subclinical hypothyroidism, and the rest of controls had normal thyroid functions (Table 2).

3.3. Thyroid antibodies in hypothyroid participants

Thyroid antibodies were +ve in 8/14 females having overt hypothyroidism, 6 were +ve for *anti*-TPO alone, while 2 were +ve for both antibodies. The thyroid antibodies were detected in 16/26 patients having subclinical hypothyroidism, 12 of them were +ve for *anti*-TPO, 2 female patients were +ve for *anti*-TG, and 2 male patients were +ve for both *anti*-TPO and *anti*-TG. In the controls, 2 females out of the 6 females having subclinical hypothyroidism were +ve for *anti*-TPO (Table 3).

3.4. Thyroid dysfunction prevalence in relation to glycemic control and duration of diabetes

In the group of diabetic patients, the prevalence of thyroid dysfunction was analyzed in relation to glycemic control. Thyroid dysfunction was significantly more prevalent in patients with HbA1c $\geq$ 8% (poor glycemic control) than patients who had lower

Table 1
Demographic and laboratory data of the studied groups.

Parameter	Diabetics (n = 200)	Controls (n = 200)	P value
Age (years)	54.15 ± 4.6	53.9 ± 4.9	0.628
Sex (F)	126(63%)	116(58%)	0.47
BMI(kg/m2)	38.7 ± 2.8	30.8 ± 4.7	<0.001*
Fasting blood glucose (mg/dl)	147.86 ± 17.7	90.4 ± 10.9	<0.001*
Post prandial blood glucose(mg/dl)	256.39 ± 34.1	120.34 ± 19.3	<0.001*
HbA1c(%)	7.8 ± 1.1	3.78 ± 0.7	<0.001*
ALT(IU/L)	34.76 ± 12	22.46 ± 6.9	<0.001*
AST (IU/L)	42.51 ± 14.4	31.99 ± 9.5	<0.001*
Serum Urea(mg/dl)	17.58 ± 6.9	10.78 ± 3.0	<0.001*
Serum creatinine(mg/dl)	1.16 ± 0.7	0.89 ± 0.18	<0.001*
Total Cholesterol(mg/dl)	261.60 ± 39.3	95.22 ± 17.7	<0.001*
Triglyceride(mg/dl)	156.63 ± 35.3	102.36 ± 16.4	<0.001*
Serum insulin (mIU/ml)	12.78 ± 3.1	10.09 ± 1.2	<0.001*
Serum FT3 (pg/ml)	2.99 ± 0.8	2.78 ± 0.3	0.001*
Serum FT4 (ng/dl)	1.08 ± 0.2	1.04 ± 0.1	0.177
Serum TSH (mIU/L)	2.94 ± 1.8	2.10 ± 0.7	<0.001*

Data are presented as mean ± SD (standard deviation) or number and percentage; n, number of patients. BMI, body mass index; HbA1c, glycated haemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotranferase; FT3, Free Tri-iodothyronine; FT4, Free Thyroxine; TSH, Thyroid Stimulating Hormone; *P-value <0.05.

Table 2
Thyroid profile in the studied groups.

Thyroid function	Diabetics (n = 200)			Controls (n = 200)		
	Male (n = 74)	Female (n = 126)	Total (n = 200)	Male (n = 84)	Female (n = 116)	Total (n = 200)
Normal thyroid function	62(83.8%)	80(63.5%)	142	84(100%)	106(91.4%)	190
Overt hypothyroidism	0(0.0%)	14(11.1%)	14	0	0	0
Subclinical hypothyroidism	6(8.1%)	20(15.9%)	26	0	6(5.2%)	6
Overt hyperthyroidism	4(5.4%)	2(1.6%)	6	0	0	0
Subclinical hyperthyroidism	2(2.7%)	10(7.9%)	12	0	4(3.4%)	4

n, number of patients.

Table 3
Distribution of *anti*-TPO and *anti*-TG in overt or subclinical hypothyroidism.

Parameter	Diabetics				Controls
	Overt hypothyroidism (n = 14)	Subclinical hypothyroidism (n = 26)			Subclinical hypothyroidism (n = 6)
	Female(n = 14)	Male(n = 6)	Female(n = 20)	Total(n = 26)	Female (n = 6)
Anti-TPO	6(42.9%)	2(33.3%)	10(50%)	12(46.2%)	2 (33.3%)
Anti-TG	0	0	2(10%)	2(7.7%)	0
Anti-TPO + *Anti*-TG	2(14.3%)	2(33.3%)	0	2(7.7%)	0
Total	8(57.2%)	4(66.6%)	12(60%)	16(61.6%)	2 (33.3%)

n, number of patients; *anti*-TPO, anti-thyroid peroxidase; *anti*-TG, anti-thyroglobulin.

Table 4
Comparison between normal and abnormal thyroid profile of diabetic patients regarding some parameters.

Parameter	Normal thyroid function(n = 142)	Thyroid dysfunction(n = 58)	P value
Duration of disease (years)	6.1 ± 2.1	8.8 ± 1.3	<0.001*
Fasting Blood Glucose (mg/dl)	143.8 ± 16.4	157.8 ± 17.2	<0.001*
2-h Post Prandial Blood Glucose (mg/dl)	248.2 ± 35.6	276.4 ± 19.1	<0.001*
HbA1c (%):	7.4 ± 0.9	8.7 ± 1.2	<0.001*
HbA1c < 7	60(42.3%)	2(3.4%)	0.0001*
HbA1c 7-8	50(35.2%)	20(34.5%)	0.9442
HbA1c ≥ 8	32(22.5%)	36(62.1%)	0.0001*
Serum insulin (miu/ml)	12.9 ± 3.0	12.6 ± 3.2	0.008*
Serum FT3 (pg/ml)	3.0 ± 0.4	2.9 ± 1.3	0.298
Serum F4 (ng/dl)	1.1 ± 0.1	1.1 ± 0.4	0.041*
Serum TSH (mIU/Ll)	2.4 ± 0.4	4.3 ± 2.9	0.001*
Serum Cholesterol (mg/dl)	257.0 ± 40.9	272.8 ± 33.2	<0.001*
Serum Triglyceride (mg/dl)	151.6 ± 36.6	169.0 ± 28.9	<0.001*

Data are presented as mean ± SD (standard deviation) or number and percentage; n, number of patients; HbA1c, Glycated haemoglobin; FT3, Free Tri-iodothyronine; FT4, Free Thyroxine; TSH, Thyroid Stimulating Hormone; *P-value <0.05.

Table 5
Correlation between serum insulin, HbA1c levels and thyroid hormone levels in diabetic group.

Thyroid Hormone		Serum Insulin (mIU/ml)	HbA1c (%)
Serum FT3 (pg/ml)	r	0.179	−0.285
	p	0.075	0.004*
Serum FT4 (ng/dl)	r	0.008	−0.193
	p	0.935	0.055
Serum TSH (mIU/L)	r	−0.069	0.214
	p	0.495	0.033*

HbA1c, Glycated haemoglobin; FT3, Free Tri-iodothyronine; FT4, Free Thyroxine; r, Spearman correlation coefficient; p, P-value; *P-value <0.05.

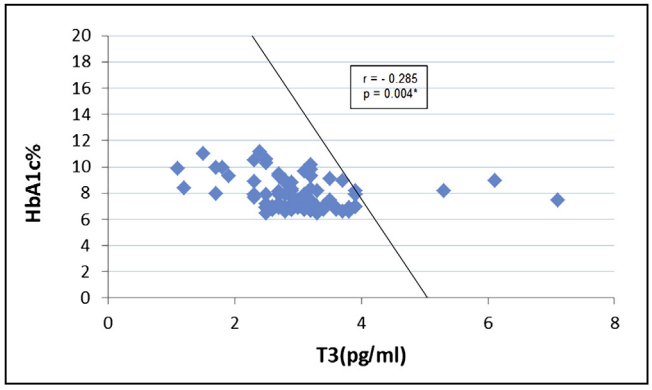

Fig. 1. Correlation between HbA1c levels and T3 level in the diabetic group. Pearson's correlation analysis was used. r: Pearson's correlation coefficient. p: P value, a p value of <0.05 was considered significant (*).

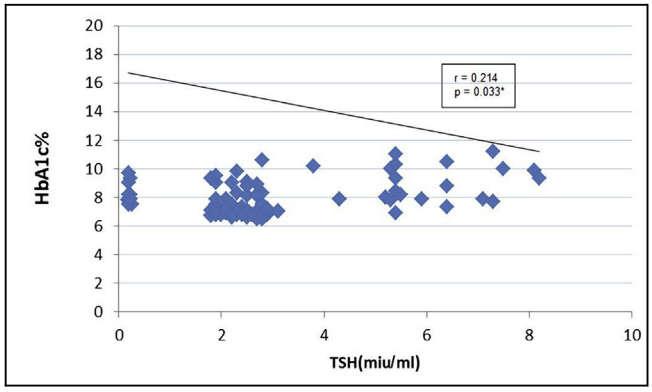

Fig. 2. Correlation between HbA1c levels and TSH level in the diabetic group. Pearson's correlation analysis was used. r: Pearson's correlation coefficient. p: P value, a p value of <0.05 was considered significant (*).

HbA1c levels, (P = 0.0001). A significantly longer diabetes duration was observed in patients having thyroid dysfunction, (P < 0.001) (Table 4).

Levels of serum cholesterol and triglycerides were also significantly higher in diabetics having thyroid dysfunction than in diabetics with normal thyroid function, (P < 0.001) for both (Table 4).

Spearman correlation test was performed to assess the correlation between the levels of thyroid hormones with each of serum insulin and HbA1c (Table 5). There was significant negative correlation between serum FT3 and HbA1c, P = 0.004 (Fig. 1), and significant positive correlation between serum TSH levels and HbA1c, P = 0.033, (Fig. 2).

4. Discussion

In this study, we observed a higher prevalence of thyroid dysfunction, mainly hypothyroidism, in diabetic patients than in apparently healthy controls. Thyroid dysfunction was especially more prevalent in patients having poor glycemic control (HbA1c ≥ 8%), longer diabetes duration and it was associated with significantly higher levels of serum cholesterol and triglycerides. HbA1c levels showed a significant positive correlation with TSH levels and significant negative correlation with FT3 levels.

DM and thyroid disorders are considered the most common endocrinopathies encountered in adult patients. Insulin and thyroid hormones together play interacting vital roles in cellular metabolism; a disturbance in one of them, whether by increase or decrease, may result in an abnormal function of the other [10].

This interaction has motivated multiple authors to investigate the inter-relationship between DM and thyroid dysfunction. However, some studies were limited by small sample sizes or lack of control groups [2,6].

So, we aimed to focus the light on the prevalence and types of thyroid dysfunction in patients with type 2 DM in comparison with apparently healthy controls, attending our University hospital, as well as its relation to glycemic control.

DM affects hypothalamic control of TSH release and diminishes the conversion of T4 to T3 in peripheral tissues. Severe hyperglycemia leads to decreased levels of T3 and increased T4. Moreover, high insulin levels associated with DM enhance TSH turnover, increase the levels of FT4 and suppress the levels of T3 by inhibiting hepatic conversion of T4 to T3 [11–13].

In our study, the prevalence of thyroid dysfunction in patients with type 2 DM was 29% compared to only 5% in a sample of apparently healthy non-diabetic population. This was in line with other studies which documented that the overall prevalence of thyroid dysfunction among diabetic patients was 35% [14], 31% [15], while less prevalence of 12.3%, and 12.7% was reported by other authors [16,17].

In the 200 diabetic patients, the most prevalent type of thyroid dysfunction was hypothyroidism, mainly subclinical hypothyroidism. This could be explained by the fact that TRH synthesis decreases in diabetes mellitus [18]. Our results were in accordance with other studies showing a high prevalence of hypothyroidism of 12.5%–32.4% in T2DM [19–21]. Other studies as well stated that subclinical hypothyroidism is the most prevalent type of thyroid dysfunction [22,23]. On the other hand Muhammed and Albustani [24] reported higher prevalence of overt hypothyroidism (87.5%) rather than subclinical hypothyroidism (12%).

The higher prevalence of thyroid dysfunction in T2DM females can be attributed to the direct role estrogen hormone has on thyroid follicular cells, and its effect on thyroxine binding globulin (TBG) [19]. Our study was on the same track with this concept as the overall prevalence of thyroid dysfunction was higher in females especially hypothyroidism. These results agreed with other studies reporting the higher prevalence of thyroid dysfunctions in females [16,21,23,25].

We noticed that the antithyroid antibodies were more prevalent in females which agreed with other studies [24,26]. The more prevalence of thyroid disorders associated with auto-antibodies to the thyroid gland in females, could be linked to the higher rates of thyroiditis among females and the implication of an autoimmune process in the development of thyroid dysfunction among type 2 diabetics [27].

When we analyzed the relation between thyroid dysfunction and glycemic control in diabetic patients, we detected that thyroid dysfunction, in general, was associated with higher HbA1c levels. At a HbA1c level of ≥8%, the prevalence of thyroid dysfunction

significantly increased. On the other hand, a better glycemic control (HbA1c) < 7% was associated with significantly more patients having normal thyroid functions. This could suggest that poor glycemic control may have a role in the development of thyroid dysfunction in Type 2DM patients.

Sreelatha et al. [28] stated that the prevalence of patients with thyroid dysfunction was more when HbA1c was ≥7% (78.57%) when compared to HbA1c <7% (21.4%). On the contrary, Aljabri et al. [21] could not establish significant difference in HbA1c levels between diabetic patients with and without hypothyroidism (P = 0.2).

In this study, patients with thyroid dysfunction had longer duration of DM when compared to patients with normal thyroid function. Similar result was reported by Ahmed [29].

Diabetic patients have an increased risk of high serum lipids due to increased mobilization of free fatty acids from the peripheral stores [26]. Our diabetic patients had a significantly increased serum lipids in comparison to controls. In the subgroup of diabetic patients having thyroid dysfunction, serum cholesterol and triglycerides were found to be significantly higher than those in diabetics with normal thyroid function. Similar results were reported by Ravishankar et al. [26], and Pasupathi et al. [30].

From the previous findings, we recommend regular screening of thyroid dysfunction in patients with type 2 DM, especially those having higher HbA1c, to help early detection and management of thyroid dysfunction; allowing better glycemic control and minimizing diabetic complications.

5. Conclusion

There was a higher prevalence of thyroid dysfunction-mainly hypothyroidism-among patients with type 2 DM when compared to non-diabetic controls. *Anti*-TPO and *anti*-TG were more common in females. HbA1c showed a significant negative correlation with T3 and a significant positive correlation with TSH. This could suggest that poor glycemic control may have a role in the development of thyroid dysfunction in Type 2 DM patients.

Conflicts of interest

None.

Funding

The authors have received no funding for preparation or publication of this work.

Ethical aspects

All procedures performed in studies involving human participants were in accordance with the ethical standards of the local Faculty ethical committee No. 31843/10/17 and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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