

# Thyroid dysfunction in patients with type 2 diabetes mellitus and its association with diabetic complications

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## ABSTRACT

**Background and Aims:** Patients with type 2 diabetes mellitus are more prone to thyroid disorders. Hypothyroidism in them leads to an aggravation of microvascular complications. Diabetic patients with hypothyroidism also are at an increased risk of cardiovascular disease. Screening for thyroid dysfunction in diabetic patients will allow early treatment of hypothyroidism. The aim of this study was to assess the level of thyroid dysfunction in patients with type 2 diabetes mellitus and to identify the association of thyroid dysfunction with diabetic complications. **Methods:** This is a cross-sectional study that was conducted at departments of Medicine & Endocrinology in JIPMER, Pondicherry, between June 2016 and May 2019. 331 patients with type 2 diabetes mellitus attending the out-patient department without any prior history of thyroid disease, chronic liver disease or acute illness were recruited for the study. All subjects were screened for diabetic complications (nephropathy, neuropathy, retinopathy & cardiovascular disease). Thyroid function test was done in all subjects using chemiluminescent immunoassay method. **Results:** Hypothyroidism was seen in 13.9%, while hyperthyroidism was observed in 3.6% of the study subjects. Thyroid dysfunction was more common among females than males. No correlation was seen between thyroid dysfunction and diabetic complications in the study subjects. **Conclusion:** The prevalence of thyroid dysfunction is 17.5% in patients with type 2 diabetes mellitus. Thyroid dysfunction did not have any correlation with diabetic complications.

**Keywords:** Diabetic complications, thyroid dysfunction, type 2 diabetes mellitus

## Introduction

Patients with type 2 diabetes mellitus are more prone to develop thyroid disorders. Many diabetic patients show features of thyroid dysfunction over a period of time.<sup>[1]</sup> Insulin resistance plays an important role in the development of hypothyroidism in patients with type 2 diabetes mellitus. Hypothyroidism in diabetic patients leads to an aggravation of dyslipidemia, hypertension

and cardiovascular disease.<sup>[2]</sup> Thus, it is necessary to recognize and treat hypothyroidism in diabetic patients to prevent worsening of diabetic complications.<sup>[3]</sup> Hypothyroidism can be diagnosed with the help of a simple blood test which is readily and easily available. This can be performed by the primary care physician involved in treating diabetic patients. Early treatment of thyroid dysfunction in diabetic patients will help in normalizing their glycemic status and lipid profile.

Diabetic patients with sub-clinical hypothyroidism have been reported to be associated with an increased risk of nephropathy and cardiovascular disease.<sup>[4,5]</sup> Micro-angiopathic complications of diabetes like retinopathy and neuropathy can worsen in the

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Received: 11-05-2020

Revised: 14-06-2020

Accepted: 24-06-2020

Published: 25-08-2020

### Access this article online

#### Quick Response Code:



Website:  
www.jfmpc.com

DOI:  
10.4103/jfmpc.jfmpc\_838\_20

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**How to cite this article:** Mehalingam V, Sahoo J, Bobby Z, Vinod KV. Thyroid dysfunction in patients with type 2 diabetes mellitus and its association with diabetic complications. J Family Med Prim Care 2020;9:4277-81.

presence of co-existing hypothyroidism due to dyslipidemia. Screening for thyroid abnormalities in diabetic patients will allow early treatment of sub-clinical and overt thyroid dysfunction.<sup>[6]</sup> This study was done to estimate the prevalence of thyroid dysfunction in a south Indian population with type 2 diabetes mellitus and examine its association with diabetic complications.

## Aims and Objectives

1. To estimate the prevalence of thyroid dysfunction in patients with type 2 diabetes mellitus
2. To study the association of thyroid dysfunction with diabetic complications.

## Methods

This cross-sectional study was conducted in the Medicine and Endocrinology OPDs of a tertiary care teaching hospital in southern India from June 2016 to May 2019 after obtaining clearance from the Institutional Ethics Committee (*IEC Ref. No. JIP/IEC/SC/2014/1/1508*).

Considering a prevalence of 32% of thyroid dysfunction in diabetic patients seen in a previous study with an absolute precision of 5% at 5% level of significance, the sample size was calculated to be 331 (using the sample size formula for proportions)<sup>[1]</sup> Convenient sampling technique was used to include diabetic patients attending the Medicine and Endocrinology OPDs of the hospital. Patients with known thyroid disease, acute illness and chronic liver disease were excluded from the study.

Data regarding age and duration of diabetes were noted in the proforma of the study subjects. Assessment of body mass index (BMI) was done in all the subjects. Body weight was measured using an electronic scale to the nearest 0.1 kg. Subjects were asked to stand straight and relaxed with minimum clothing. Height was measured to the nearest 0.1 cm by using the wall-mounted stadiometer. The height of the subjects was taken in the standing position, without footwear keeping head in the Frankfurt plane. BMI was subsequently calculated dividing the body weight in kilograms by the square of height in meters. BMI between 25 and 29.9 kg/m<sup>2</sup> was taken as overweight while BMI above 30 kg/m<sup>2</sup> was taken as obesity for the purpose of this study. Blood pressure was measured in the study subjects with the help of a digital BP instrument. Subjects with BP above 140/90 mm Hg were considered to be hypertensive for the purpose of this study.

The laboratory investigations that were performed were glycosylated hemoglobin, fasting lipid profile and urine albumin. Screening for diabetic retinopathy was done by dilated fundus examination. Diabetic retinopathy was classified as non-proliferative (NPDR) or proliferative (PDR) in the study subjects. NPDR was further sub-divided into mild, moderate and severe categories. Twelve lead electrocardiogram (ECG) was

taken for evaluation of cardiovascular disease. Study subjects with changes suggestive of ischemia on ECG were considered to have ischemic heart disease. Vibration perception threshold (VPT) was performed in subjects clinically suspected to have diabetic neuropathy. Based on VPT findings, the study subjects were defined as not having neuropathy, mild or severe neuropathy. Diabetic nephropathy was considered to be present if there was albuminuria. Microalbuminuria was defined as urinary albumin excretion of 30-300 mg/day while macroalbuminuria was defined as presence of urinary albumin of more than 300 mg/day. Microalbuminuria was estimated with the help of nephelometry technique in the biochemistry laboratory.

## Biochemical analysis

Serum TSH (Thyroid Stimulating Hormone), free T<sub>3</sub> (Triiodothyronine) and free T<sub>4</sub> (Thyroxine) were assessed in the fasting serum samples of the study subjects using chemiluminescent immunoassay method technology (ADVIA Centaur XP, Siemens Healthcare Global, USA). The normal range of TSH was 0.35-5.5 mU/L, 2.3-4.2 pg/ml for free T<sub>3</sub> and 0.89-1.76 ng/dL for free T<sub>4</sub>. Sub-clinical hypothyroidism was defined as subjects with TSH value between 5-10 mU/L and normal free T<sub>3</sub> & T<sub>4</sub> levels. Overt hypothyroidism was present in subjects with TSH value above 10 mU/L and low free T<sub>3</sub> & T<sub>4</sub> levels. Sub-clinical hyperthyroidism was defined as low TSH with normal free T<sub>3</sub> & T<sub>4</sub> levels. Overt hyperthyroidism was defined as low TSH with high free T<sub>4</sub> levels. Serum creatinine was estimated by using enzymatic Jaffe's method. Lipid profile was also done for all the study subjects. Dyslipidemia was considered to be present if total serum cholesterol was above 200 mg/dL. Glycosylated hemoglobin was done in all study subjects by high performance liquid chromatography (HPLC) technique in the laboratory.

## Statistical analysis

Data on continuous variables like age, duration of diabetes, BMI, HbA1c and lipid profile were expressed as mean with standard deviation (SD). Independent student's t test was done to compare continuous variables between two independent groups. Categorical variables like proportion of subjects having thyroid dysfunction, hypertension, dyslipidemia, obesity and diabetic complications were expressed as a percentage and were analyzed by Chi-square test ( $\chi^2$ ). All statistical analysis was carried out at 5% level of significance and *P* value below 0.05 was considered as significant.

## Results

A total of 331 participants were included in this study. The baseline characteristics of the study subjects are given in Table 1. The mean duration of diabetes was  $6.37 \pm 2.41$  years and the mean glycosylated hemoglobin was  $9.3 \pm 2.66\%$  among the study population.

The age and gender of the study subjects are given in Table 2. The maximum number of diabetic patients included in this study were in the age group of 41-70 years.

Table 3 shows the result of thyroid function test in the study subjects. A majority of study subjects (> 80%) had normal TSH, free T<sub>3</sub> and free T<sub>4</sub> values. Hypothyroidism was seen in 13.9% while hyperthyroidism was seen in only 3.6% of subjects.

Diabetic nephropathy in study subjects was based on the presence of albuminuria. This was further classified into microalbuminuria (<300 mg albumin/gram of creatinine) and macroalbuminuria (>300 mg albumin/gram of creatinine). Tables 4-7 depict the presence of thyroid dysfunction in the study population according to age, gender, duration of diabetes and glycemic status. Both types of thyroid dysfunction (hypothyroidism & hyperthyroidism) were more common in females as compared to males.

Table 8 shows that there was no correlation of thyroid dysfunction with diabetic nephropathy in the study subjects. Similarly, there was no correlation of thyroid dysfunction in diabetic patients with cardiovascular disease, neuropathy and retinopathy. [Tables 9-11].

**Table 1: Baseline characteristics of study participants**

Parameter	Mean	Standard deviation
BMI (kg/m <sup>2</sup> )	26.07	5.82
Duration of diabetes (years)	6.37	2.41
HbA1c (%)	9.3	2.66

**Table 2: Age and gender distribution of study participants**

Male	Female
174	157
Age (years)	
n=331	
21-30	8
31-40	41
41-50	87
51-60	109
61-70	67
71-80	18
>80	1

**Table 3: Thyroid function test results of study participants**

Parameter	Normal range	Increased value	Decreased value
(n=331)			
Serum TSH	273 (82.48%)	46 (13.89%)	12 (3.63%)
Free T <sub>3</sub>	287 (86.71%)	6 (1.82%)	38 (11.49%)
Free T <sub>4</sub>	301 (90.94%)	16 (4.84%)	14 (4.23%)

**Table 4: Thyroid dysfunction in study subjects according to gender**

Gender	Hypothyroidism	Hyperthyroidism
Male	22 (47.83%)	5 (41.66%)
Female	24 (52.17%)	7 (58.33%)
Total	46	12

**Summary**

1. The prevalence of thyroid dysfunction among diabetic patients was 17.5% in this study. Hypothyroidism was more common in the study subjects as compared to hyperthyroidism
2. Thyroid dysfunction was more common among females in this study
3. Hypothyroidism was more common among study subjects having diabetes for more than 5 years
4. There was no correlation of thyroid dysfunction with diabetic complications among the study subjects

**Discussion**

Insulin resistance that is typically seen in patients with type 2 diabetes mellitus plays a major role in the development of thyroid dysfunction in such patients. Thyroid dysfunction can occur in the form of hypothyroidism and hyperthyroidism. Sub-clinical hypothyroidism can also occur in diabetic patients and can contribute to diabetic complications like retinopathy, neuropathy and cardiovascular disease.<sup>[7]</sup>

**Table 5: Thyroid dysfunction in study subjects according to age**

Age group (years)	Hypothyroidism	Hyperthyroidism
21-30	-	1
31-40	5	3
41-50	10	5
51-60	12	1
61-70	14	2
Above 70	5	-

**Table 6: Thyroid dysfunction in study subjects according to duration of diabetes**

Duration of diabetes	Hypothyroidism	Hyperthyroidism
Below 1 year	6	5
1-5 years	16	6
5-10 years	12 (26.08%)	-
Above 10 years	12 (26.08%)	1

**Table 7: Thyroid dysfunction in study subjects according to glycemic status**

HbA1c (%)	Hypothyroidism	Hyperthyroidism
6.5-7	8	3
7.1-8	9	2
8.1-9	8	2
Above 9	21	5

**Table 8: Correlation of thyroid dysfunction with diabetic nephropathy in study participants**

Parameter	Hypothyroidism	Hyperthyroidism	p
Microalbuminuria	39	10	
Macroalbuminuria	7	2	0.99

**Table 9: Correlation of thyroid dysfunction with cardiovascular disease in study participants**

Parameter	Hypothyroidism	Hyperthyroidism	<i>p</i>
Normal ECG	37	10	0.32
Abnormal ECG	9	2	

**Table 10: Correlation of thyroid dysfunction with diabetic neuropathy in study participants**

Parameter	Hypothyroidism	Hyperthyroidism	<i>p</i>
Normal VPT	32	9	0.56
Abnormal VPT			
1. Mild neuropathy	8	0	
2. Severe neuropathy	6	3	

**Table 11: Correlation of thyroid dysfunction with diabetic retinopathy in study participants**

Parameter	Hypothyroidism	Hyperthyroidism	<i>p</i>
Normal fundus	32	11	0.55
Mild NPDR	11	0	
Moderate NPDR	3	1	
Severe NPDR	0	0	

The prevalence of thyroid dysfunction among diabetic patients in our study was found to be 17.5%. Hypothyroidism was more common among the study subjects. This is similar to a study done in south India by Jali MV *et al.* that showed the prevalence of thyroid dysfunction among diabetic patients to be 16.2%.<sup>[8]</sup> Another study done in north India showed that prevalence of sub-clinical hypothyroidism in diabetic patients was 18.8%. This study also found that prevalence of thyroid dysfunction was more among females, patients with dyslipidemia and retinopathy and patients with poor glycemic control & long duration of diabetes.<sup>[9]</sup> A retrospective study done by Demitrost L *et al.* showed that hypothyroidism was seen in 11.4% of type 2 diabetic patients while hyperthyroidism was seen in only 1.5% of the cases.<sup>[1]</sup> A study to assess the prevalence of thyroid dysfunction in patients with type 2 diabetes mellitus was done by Diez JJ *et al.* and it was found that 15.1% of the patients had overt hypothyroidism while overt hyperthyroidism was seen in 3.5% of the patients. The study also showed that thyroid dysfunction was not linked to the duration of diabetes, glycosylated hemoglobin and the presence of diabetic complications.<sup>[10]</sup> The study findings are in line with the present study which did not show a correlation between thyroid dysfunction and diabetic complications in the study subjects. However, another study done in Egypt showed that prevalence of thyroid dysfunction increased with an increase in glycosylated hemoglobin which suggests that poor glycemic control could play a role in the occurrence of thyroid dysfunction in diabetic patients.<sup>[11]</sup>

Our study showed that duration of diabetes (more than 5 years) was an important factor in patients with hypothyroidism. However, this was not found in diabetic patients having hyperthyroidism. A study that was done by Metab Al-Geffari *et al.*

showed that duration of diabetes (more than 10 years) was an important risk factor for the development of thyroid dysfunction among type 2 diabetic patients in their study population.<sup>[12]</sup>

Apart from insulin resistance, autoimmunity may also have a role in the development of thyroid dysfunction in patients with type 2 diabetes mellitus. A study done by Radaideh AR *et al.*, showed that 12.5% of diabetic patients were found to have thyroid disease. Among the diabetic patients with thyroid dysfunction, thyroid peroxidase antibody was found to be positive in 8.3% of cases. This study showed that screening for asymptomatic thyroid dysfunction may be helpful in diagnosing thyroid disease among diabetic patients.<sup>[13]</sup>

Hypothyroidism can be associated with an increased risk of nephropathy and cardiovascular disease among diabetic patients. This was shown in a study done by Chen HS *et al.* that found sub-clinical hypothyroidism to be a risk factor for nephropathy and cardiovascular disease among type 2 diabetic patients.<sup>[4]</sup> However, our study showed that there was no correlation of thyroid dysfunction with nephropathy and cardiovascular disease in patients with type 2 diabetes mellitus.

Thyroid dysfunction is a common occurrence among patients with type 2 diabetes mellitus. It is more pronounced in patients with long-standing diabetes and female gender. Treatment of thyroid dysfunction in diabetic patients can improve their morbidity and prevent worsening of diabetic complications.

### Limitation of the study

Anti-thyroid peroxidase (anti TPO) antibody estimation was not done in our study. Thus, the role of thyroid auto-immune antibody in patients developing thyroid dysfunction among type 2 diabetic patients could not be assessed.

### Conclusion

The prevalence of thyroid dysfunction was 17.5% among patients with type 2 diabetes mellitus in this study. Hypothyroidism was more common among the study subjects than hyperthyroidism. There was no correlation of thyroid dysfunction with diabetic complications.

### Acknowledgements

The authors gratefully acknowledge the financial support provided by JIPMER, Puducherry for conducting this study.

### Financial support and sponsorship

JIPMER Intramural Research Grant.

### Conflicts of interest

There are no conflicts of interest.

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