Prevalence of Thyroid Dysfunction in Patients with Type 2 Diabetes Mellitus in Mumbai, Maharashtra, India: A Cross-sectional Study

ABSTRACT

Introduction: India bears a high burden of Type 2 Diabetes Mellitus (T2DM) and Thyroid Dysfunction (TD). Though the coexistence of T2DM and TD has been evaluated, such studies from the perspective of metropolitan cities, including Mumbai, are lacking.

Aim: To assess the prevalence of TD in patients with T2DM and to evaluate the association of TD with glycaemic control, duration, and complications of T2DM.

Materials and Methods: The present observational cross-sectional study was performed in the Department of General Medicine, The Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India, from January 2016 to December 2017. The study involved 220 diagnosed patients with T2DM, of either gender, aged 18 years or more. All patients were evaluated for TD by performing thyroid profile (T3, T4 and Thyroid Stimulating Hormone (TSH)). The association of TD prevalence with age, gender, Body Mass Index (BMI), duration of T2DM, Glycated Haemoglobin (HbA1c), and complications was assessed. The qualitative and quantitative parameters were compared with Chi-square and independent sample t-test, respectively, with a p-value <0.05 considered statistically significant.

Results: The patients were predominantly males, 127 (57.7%) with a mean±Standard Deviation (SD) age and BMI of 63.4±14.02 years and 25.9±4.5 Kg/m², respectively. The prevalence of TD was 36.8%. The predominant TD in patients with T2DM was subclinical hypothyroidism (75.9%). TD was significantly associated with advancing age (p-value=0.0167). However, gender and BMI were not significantly associated with TD. Poor glycaemic control was significantly associated with subclinical hypothyroidism (p-value=0.0255). The duration of TD was significantly associated with the prevalence of subclinical hypothyroidism (p-value=0.0144), primary hypothyroidism (p-value=0.0257), and subclinical hyperthyroidism (p-value=0.0310). TD was found to be significantly associated with both micro and macrovascular complications of T2DM (all p-values <0.05).

Conclusion: In Mumbai, the prevalence of T2DM-associated TD was 36.8%. TD was significantly associated with advancing age, duration of T2DM, high HbA1c levels, and both micro and macrovascular complications.

Keywords: Complications, Glycaemic control, Hypothyroidism, Macrovascular

INTRODUCTION

The coexistence of TD with T2DM is known, and its prevalence in patients with T2DM is reported to be 16% [1-3]. Specifically, in this group of patients, the prevalence of subclinical hypothyroidism, hypothyroidism, and hyperthyroidism is 4-18%, 6-20% and 2-4%, respectively [4,5]. Following China, India is home to the second largest number of diagnosed and undiagnosed patients with diabetes [6]. Moreover, in India, goitre is an endemic disease [7]. In patients with T2DM, poor glycaemic control leads to an increased incidence of TD [8]. However, the association between T2DM and TD is not clear. Impaired glycaemic control is thought to alter thyroid function either by changing TSH levels at the hypothalamic level or by changing the conversion of T4 to T3 in peripheral tissues [5]. Once TD sets in, it influences insulin metabolism and further aggravates insulin resistance, leading to worsening of glycaemic control, which in turn deteriorates thyroid function further [9]. This results in a vicious cycle of events that leads to a poor prognosis in patients with T2DM due to complications-related morbidity.

The association between TD and T2DM has been assessed among patients residing in the Northern, Eastern, Western and Southern parts of India [10-17]. Moreover, metropolitan cities in India, including Mumbai, have a high burden of T2DM [18]. However, the association between TD and T2DM has not been assessed among patients residing in Mumbai. Thus, the present study was performed to assess the prevalence of TD in patients with T2DM and evaluate the association of TD with glycaemic control, duration and complications of T2DM.

MATERIALS AND METHODS

The present observational cross-sectional study was performed in the Department of General Medicine, The Grant Government Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India, from January 2016 to December 2017. The study began after the approval of the study protocol by the Institutional Ethics Committee (IEC/PG/317/Dec/2015) and obtaining written informed consent from the patients.

Sample size calculation: Considering a 29% prevalence of TD in patients with T2DM [19], α of 0.05, and β of 0.2, the sample size was calculated as 220 patients.

Inclusion criteria: Patients diagnosed with T2DM, of either gender, aged 18 years or older were included in the study.

Exclusion criteria: Patients with secondary, gestational and type 1 diabetes mellitus and pre-existing TD were excluded from the study.

Study Procedure

The patients visiting the outdoor and indoor facilities of the tertiary care Institute were screened using a well-structured case record form. In all patients, a detailed history was obtained. Subsequently, physical examinations and laboratory investigations (including HbA1c and serum T3, T4 and TSH) were performed. Patient details, including age, sex, weight, height, BMI, heart rate, respiratory rate, blood pressure, serum thyroid profile (T3, T4 and TSH), HbA1c and duration of diabetes, were recorded. Patients were also evaluated for the presence of micro and macrovascular complications, including Coronary Artery Disease (CAD) (on the basis of electrocardiogram evaluation or
history of angina, myocardial infarction, or coronary angiography and angioplasty, retinopathy (assessed by an ophthalmologist, based on the International Clinical Classification of Diabetic Retinopathy) [20], nephropathy (urine analysis for albumin and creatinine), neuropathy (evaluation of pain perception, vibration sense, temperature sense, monofilament testing, and reflex testing), and cerebrovascular disease (based on history or clinically by checking peripheral pulsation and performing arterial doppler in suspected patients). Fasting state blood samples were collected from the patients. The samples were analysed for thyroid profile and HbA1c levels using an Enzyme-linked Immunosorbent Assay (ELISA) kit. The diagnosis of diabetes was based on the American Diabetes Association guidelines, and patients having HbA1c >7% were categorised as having poor glycaemic control [21].

Thyroid function tests were interpreted as follows [22]:

a) Primary/ overt hypothyroidism: If TSH levels were increased in the presence of reduced T3 and T4 levels;

b) Subclinical hypothyroidism: If TSH levels were increased in the presence of normal levels of T3 and T4;

c) Overt/ primary hyperthyroidism: If TSH levels were reduced in the presence of increased levels of T3 and T4;

d) Subclinical hyperthyroidism: When the levels of TSH were reduced in the presence of normal levels of T3 and T4.

STATISTICAL ANALYSIS

The quantitative and qualitative parameters were represented as mean±standard deviation and median (interquartile range) or frequency (percentage), respectively. The qualitative parameters were compared using the Chi-square test. The independent sample t-test was used to compare the mean values. A p-value of <0.05 was considered statistically significant. The data was analysed with Statistical Package for the Social Sciences (SPSS) (IBM, Armonk, NY, USA) software version 19.0 for Windows.

RESULTS

The mean±SD age of the study population was 63.4±14.02 years, with male predominance, 127 (57.7%). The demographic and clinical characteristics of the study population were depicted in Table/Fig-1. The prevalence of TD was 36.8%.

Of the 81 patients with TD, 54 (66.7%) were hypothyroid [13 (24.1%) primary and 41 (75.9%) subclinical] and 27 (33.3%) were hyperthyroid [7 (25.9%) primary and 20 (74.1%) subclinical] [Table/ Fig-2]. The effect of BMI on TD was assessed, and no significant association was observed between them (euthyroid: 26.50±1.99, and TD: 26.50±1.79, p-value=0.587). Similarly, TD was not significantly associated with gender (p-value=0.674). However, TD had a statistically significant association with increasing age (p-value=0.0167) [Table/Fig-3, Table/Fig-4]. Table/Fig-4 depicts the mean serum levels of T3, T4, and TSH in patients with T2DM.

<table>
<thead>
<tr>
<th>Thyroid dysfunction</th>
<th>Thyroid dysfunction (n=81)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroid (n=54)</td>
<td>41</td>
<td>66.7</td>
</tr>
<tr>
<td>Hyperthyroid (n=27)</td>
<td>20</td>
<td>33.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Euthyroid (n=139)</th>
<th>Thyroid dysfunction (TD) (n=81)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤50</td>
<td>30 (21.58)</td>
<td>6 (7.41)</td>
<td>0.0167</td>
</tr>
<tr>
<td>50-70</td>
<td>102 (73.38)</td>
<td>43 (53.09)</td>
<td></td>
</tr>
<tr>
<td>&gt;70</td>
<td>7 (5.04)</td>
<td>32 (39.50)</td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>83 (59.71)</td>
<td>44 (54.32)</td>
<td>0.674</td>
</tr>
<tr>
<td>Female</td>
<td>56 (40.29)</td>
<td>37 (45.68)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²) (Mean±SD)</td>
<td>26.50±1.99</td>
<td>26.50±1.79</td>
<td>0.587</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Thyroid profile</th>
<th>T3 (µg/mL) (Mean±SD)</th>
<th>T4 (µg/dl) (Mean±SD)</th>
<th>TSH (mIU/L) (Mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euthyroid (n=139)</td>
<td>1.2±0.3</td>
<td>7.1±1.4</td>
<td>2.3±1.1</td>
</tr>
<tr>
<td>Subclinical hypothyroid (n=41)</td>
<td>0.99±0.3</td>
<td>6.7±2.1</td>
<td>8.7±2.9</td>
</tr>
<tr>
<td>Primary hypothyroid (n=13)</td>
<td>0.39±0.17</td>
<td>2.1±0.3</td>
<td>10.1±3.3</td>
</tr>
<tr>
<td>Subclinical hyperthyroid (n=20)</td>
<td>1.4±0.6</td>
<td>7.7±2.1</td>
<td>0.21±0.07</td>
</tr>
<tr>
<td>Primary hyperthyroid (n=7)</td>
<td>3.6±0.45</td>
<td>16.9±3.4</td>
<td>0.18±0.06</td>
</tr>
</tbody>
</table>

The patients were stratified according to the HbA1c levels, and the effect of glycaemic control on the prevalence of TD was assessed. There was a statistically significant association between good glycaemic control and euthyroid status (p-value=0.0182). Similarly, a statistically significant association was observed between poor glycaemic control and subclinical hypothyroidism (p-value=0.0255). However, there was no significant association of glycaemic control with primary hypothyroidism, subclinical hyperthyroidism and primary hyperthyroidism (all p-values>0.05) [Table/Fig-5].

Moreover, the patients were stratified according to the duration of T2DM, and the effect of the duration of T2DM on the prevalence of TD was assessed. The statistical analysis revealed a significant association of the duration of T2DM with the prevalence of euthyroidism (p-value=0.0194), subclinical hypothyroidism...
The evaluation of the relationship between gender and the prevalence of TD did not reveal a significant association (p-value=0.674). Contrarily, other studies by Singh RK et al., (p-value=0.002) and Telwani AA et al., (p-value=0.030) reported a significantly higher prevalence of TD among female patients with T2DM [11,23]. Though a high BMI is reported to be a risk factor for TD in patients with T2DM, the present study did not observe any significant association between BMI and the prevalence of TD (p-value=0.587) [27]. Ozair M et al., reported similar findings (p-value=0.05), while Singh RK et al., (p-value=0.0001), Demitrost L and Ranabir S (p-value=0.016), and Telwani AA et al., (p-value=0.011) reported a significant association between BMI and the prevalence of TD [10-12,23]. These contrary findings could be attributed to differences in the study population. TD is long known to be associated with advancing age. Similarly, the present study observed a significant association between advancing age (≥50 years) and a higher prevalence of TD (p-value=0.0167). This is similar to the findings reported by Jali MV et al., (≥50 years, p-value=0.036), Telwani AA et al., (≥50 years, p-value=0.031), and Khassawneh AH et al., (≥50 years, p-value<0.001) [3,23,28]. The longer duration of T2DM is associated with a higher chance of TD. This may be attributed to the underlying metabolic disturbances that accompany T2DM, which aggravate with time and are supported by coexisting TD. Thus, the evaluation of the relationship between the duration of T2DM and the prevalence of TD revealed a significant association (p-value<0.05). This is consistent with the findings reported by Telwani AA et al., (p-value=0.007) and Ogbonna SU et al., (p-value=0.005) [23,29]. Poor glycaemic control is directly related to the occurrence of TD in patients with T2DM. This may be attributed to the effect of raised blood glucose levels on the hypothalamo-pituitary-thyroid axis that results in low T3 levels. Moreover, raised blood glucose levels associated inhibition of the peripheral conversion of T4 to T3 leading to a low T3 state is also implicated [29]. Based on these findings, a statistically significant association between poor glycaemic control and subclinical hypothyroidism, observed in the present study, is justified. Ogbonna SU and Ezenei IU, reported raised HbA1c levels as a risk factor for TD [27]. In another study, Ogbonna SU et al., reported a positive correlation between HbA1c and TSH and a negative correlation between HbA1c and serum free T3 in the T2DM patients with hypothyroidism [29]. It is reported that higher levels of T4 contribute to hyperglycaemia and thus, in patients with primary hyperthyroidism it might be a contributing factor for higher HbA1c. Moreover, hypothyroidism is also known to increase insulin resistance in patients with T2DM, thereby contributing to the elevated HbA1c [5]. However, the present study did not observe any statistically significant association of HbA1c levels with primary hyperthyroidism, subclinical hyperthyroidism and primary hyperthyroidism. The present study observed a high prevalence of micro and macrovascular complications, and TD was significantly associated with all the complications. Reddy N et al., reported that microvascular complications, especially diabetic retinopathy, were significantly greater among patients with coexisting TD and T2DM. However, a significant association was not observed for diabetic neuropathy and diabetic nephropathy [24]. Jia F et al., observed that subclinical hypothyroidism in patients with T2DM is significantly associated with a high prevalence of coronary heart disease and chronic kidney disease [30]. In a meta-analysis, Han C et al., concluded that subclinical hypothyroidism is significantly associated with increased complications, including diabetic nephropathy, diabetic retinopathy, PVD and diabetic peripheral neuropathy, but not coronary heart disease [4].

Limitations:
The present study had certain limitations. Firstly, the lack of a control group did not allow us to reach a more generalised conclusion from the study. Secondly, antithyroid peroxidase antibodies were not

### DISCUSSION

The present study suggested a high prevalence (36.8%) of TD in patients with T2DM residing in the Western part of India. Studies from various parts of India, by Ozair M et al., (28%), Demitrost L and Ranabir S (31.2%), and Telwani AA et al., (29%) have reported similar findings [10,12,23]. However, studies by Mehalingam V et al., (17.5%) and Reddy N et al., (19.6%) reported lower prevalence, while those reported by Mukherjee S (65.8%) suggested a higher prevalence [Table-Fig-8] [10,12,16,23-25]. The high prevalence of TD in the present study could be attributed to a small sample size and the high burden of thyroid disorders in Mumbai [26].

The analysis of the thyroid profile revealed that subclinical hypothyroidism followed by subclinical hyperthyroidism had the maximum prevalence. These findings are consistent with those of previous studies [10,12,23,24].

### STUDIES

<table>
<thead>
<tr>
<th>Studies</th>
<th>Prevalence of Thyroid Dysfunction (TD) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehalingam V et al., [16]</td>
<td>17.5%</td>
</tr>
<tr>
<td>Reddy N et al., [24]</td>
<td>19.6%</td>
</tr>
<tr>
<td>Ozair M et al., [10]</td>
<td>28%</td>
</tr>
<tr>
<td>Telwani AA et al., [23]</td>
<td>29%</td>
</tr>
<tr>
<td>Demitrost L and Ranabir S, [12]</td>
<td>31.2%</td>
</tr>
<tr>
<td>Mukherjee S, [25]</td>
<td>65.8%</td>
</tr>
<tr>
<td>Present study</td>
<td>36.8%</td>
</tr>
</tbody>
</table>

[Table-Fig-8]: Comparison of prevalence of Thyroid Dysfunction (TD) among various studies [10,12,16,23-25].

A total of 27 (12.27%) patients had retinopathy. Based on severity, 13 (48.15%), 10 (37.03%) and 4 (14.81%) patients had mild, moderate and severe non proliferative diabetic retinopathy, respectively. Finally, TD was found to be significantly associated with both micro (nephropathy (p-value=0.001); retinopathy (p-value=0.047); neuropathy (p-value=0.008) and macrovascular complications (Peripheral Vascular Disease (PVD) (p-value=0.049); Cardiovascular Disease (CVD) (p-value=0.009); CAD (p-value=0.001) of T2DM [Table-Fig-7].

### LIMITATION(S)

The present study had certain limitations. Firstly, the lack of a control group did not allow us to reach a more generalised conclusion from the study. Secondly, antithyroid peroxidase antibodies were not

### [Table/Fig-6]: Effect of duration of T2DM on the prevalence of Thyroid Dysfunction (TD).

<table>
<thead>
<tr>
<th>Duration of diabetes (years)</th>
<th>Thyroid status</th>
<th>n (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>Euthyroid</td>
<td>31 (7.5)</td>
<td>101 (68.7)</td>
</tr>
<tr>
<td>5-10</td>
<td>Subclinical hypothyroid</td>
<td>4 (10.0)</td>
<td>26 (17.7)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>Primary hypothyroid</td>
<td>2 (5.0)</td>
<td>6 (4.1)</td>
</tr>
<tr>
<td></td>
<td>Subclinical hyperthyroid</td>
<td>2 (5.0)</td>
<td>12 (8.2)</td>
</tr>
<tr>
<td></td>
<td>Primary hyperthyroid</td>
<td>1 (2.5)</td>
<td>2 (1.4)</td>
</tr>
</tbody>
</table>

### [Table/Fig-7]: Association of Thyroid Dysfunction (TD) with complications of T2DM.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Patients with complications (n=75)</th>
<th>Patients with TD and complications (n=56)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrovascular complications, n (%)</td>
<td>PVD: 6 (8)</td>
<td>5 (8.9)</td>
<td>0.049</td>
</tr>
<tr>
<td></td>
<td>CVD: 4 (5.3)</td>
<td>7 (1.1)</td>
<td>0.009</td>
</tr>
<tr>
<td></td>
<td>CAD: 13 (17.3)</td>
<td>10 (17.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Microvascular complications, n (%)</td>
<td>Nephropathy: 30 (40)</td>
<td>22 (39.2)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>Retinopathy: 17 (22.6)</td>
<td>10 (17.8)</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>Neuropathy: 5 (6.6)</td>
<td>5 (8.9)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

[Table/Fig-7]: Association of Thyroid Dysfunction (TD) with complications of T2DM. PVD: Peripheral vascular disease; CVD: Cardiovascular disease; CAD: Coronary artery disease.

The present study had certain limitations. Firstly, the lack of a control group did not allow us to reach a more generalised conclusion from the study. Secondly, antithyroid peroxidase antibodies were not
Maverick Medicorum® (India), for statistical analyses and medical glycaemic control, subclinical hypothyroidism should be suspected. With T2DM have a high prevalence of TD. In diabetics with poor macrovascular complications (PVD, CVD and CAD). The patients with T2DM have a high prevalence of TD. In diabetics with poor glycaemic control, subclinical hypothyroidism should be suspected. TD was significantly associated with the prevalence of euthyroidism, subclinical hypothyroidism, primary hyperthyroidism, and subclinical hyperthyroidism, except primary hyperthyroidism. Moreover, TD was significantly associated with microvascular (nephropathy, retinopathy and neuropathy) and macrovascular complications (PVD, CVD and CAD). The patients with T2DM have a high prevalence of TD. In diabetics with poor glycaemic control, subclinical hypothyroidism should be suspected. TD is significantly associated with micro and macrovascular complications.

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REFERENCES

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