Thyroid Abnormality in Patients with Type 2 Diabetes Mellitus - A Cross-Sectional Study from Mumbai

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ABSTRACT

BACKGROUND

Type 2 diabetes mellitus (DM) and thyroid dysfunction have long term sequalae on cardiovascular health. The present study was conducted to assess the spectrum of abnormalities in patients of type 2 DM with thyroid disorders.

METHODS

This case-control study included 52 patients of type 2 DM with thyroid dysfunction (cases) and 52 patients of type 2 DM without thyroid dysfunction (controls). Laboratory investigations like thyroid profile, lipid profile and glycosylated haemoglobin were measured for all the patients.

RESULTS

Subclinical hypothyroidism was the most common thyroid abnormality. Mean body mass index (BMI) was found to be similar in the two patient groups. We observed a higher mean HbA1c levels in patients with thyroid dysfunction as compared to those without thyroid dysfunction (8.75% vs 7.16%, P value < 0.01). Among the lipid profile parameters, mean triglyceride levels and total cholesterol levels were also found to be significantly higher in patients with thyroid dysfunction as compared to those without thyroid dysfunction. Urine Protein Creatinine Ratio (UPCR) was also found to be significantly higher among patients with thyroid dysfunction. Furthermore, we observed mean BMI, HbA1c, mean total cholesterol and UPCR to be significantly higher among cases with hypothyroidism as compared to those with hyperthyroidism. Mean triglyceride levels were similar in the two patient groups.

CONCLUSIONS

We recommend that all type 2 DM patients should have a baseline evaluation of thyroid function.

KEYWORDS

Diabetes Mellitus, Dyslipidaemia, Hypothyroidism

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BACKGROUND

Both type 2 diabetes mellitus (DM) and thyroid dysfunction are chronic diseases that have long term sequalae on cardiovascular health. In 2017, International Diabetes Federation (IDF) reported prevalence of DM to be approximately 425 million with India being the diabetic capital of the world.[1] As per a meta-analysis, thyroid dysfunction is present in 3.82% of the general population.[2] The prevalence of thyroid dysfunction is higher among patients with type 2 DM, ranging from 9.9 to 48%.[3] This wide variation in the prevalence can be due to the use of varied definitions for diagnosing thyroid dysfunction. Thyroid hormone can act on various organs to affect glucose metabolism. Thyroid hormones are antagonists of insulin, both insulin and thyroid hormones are involved in cellular metabolism and excess or deficit of any one can result in functional derangement of the other. It increases gastrointestinal motility and enhances glucose absorption.[4] In the liver, it increases the activity of phosphoenolpyruvate carboxykinase (PEPCK), an enzyme that enhances gluconeogenesis. This hepatic gluconeogenesis may occur through the direct effect of the thyroid hormone or indirectly via glucagon or catecholamine. Likewise, diabetes also affects thyroid function by altering the thyroid-stimulating hormone (TSH) level and impairing the conversion of thyroxine (T4) to triiodothyronine (T3) in the peripheral tissues.[5] Insulin controls TSH release and the conversion of T4 to T3 in the peripheral tissue. Marked hyperglycaemia causes reversible reduction of the activity and hepatic concentration of T4-5-deiodinase. Few studies in the past have investigated the underlying biochemical, genetic, and hormonal abnormalities.[6] Because the clinical features of thyroid dysfunction may mimic those of DM, many cases remain undiagnosed. The present study was conducted to assess the spectrum of abnormalities in patients of type 2 DM with thyroid disorders.

METHODS

This comparative cross-sectional study was conducted at a tertiary level healthcare facility in Mumbai. We included patients who had an established diagnosis of type 2 DM with thyroid dysfunction from April 2017 to September 2018. These patients were enrolled from the outpatient department of General Medicine, Geriatric, Endocrine and Diabetic clinics. Jali et al. reported the prevalence of thyroid dysfunction of 16.2% in patients with type 2 DM.[7] The sample size of the study was calculated using the formula n = (Zα / 2) 2 * (pq) / e2, where Zα/2 is the Z value at 5% error (1.96), p is the prevalence, q is 1 - p and e is allowable error, which was taken as 10 %. Using the formula, the sample size was calculated to be 52, which were patients with an established diagnosis of diabetes mellitus and thyroid dysfunction. We also included same number of age and gender matched controls which were patients with diabetes mellitus without any thyroid dysfunction. We excluded patients with type 1 diabetes mellitus, pregnancy, those with drug induced thyroid disorder and those on corticosteroids. The purpose of the study was explained to the patients and their informed written consent was obtained before enrolment in the study. The study was approved by the Institutional Ethics Committee (Ref number D0201701 / Dated 25.01.2017).

Data Collection and Data Analysis

Using a pre-designed semi-structured questionnaire, demographic and anthropometric data of the patients was noted. Medical history was obtained to rule out any study exclusion criteria. About five ml overnight fasting venous blood samples were collected at morning time from each patient. Blood glucose glycated haemoglobin (HbA1c), free triiodothyronine (T3), free tetraiodothyronine (T4), and thyroid-stimulating hormone (TSH) were estimated. Blood glucose and HbA1c were determined using the enzymatic method and by high-pressure liquid chromatography (HPLC) principle, respectively. Serum T3, T4, and TSH were measured by using Chemiluminescence Immunoassay (CLIA). First, we compared the lipid profile, mean glycated haemoglobin and renal function between patients with and without thyroid dysfunction. Then patients with thyroid dysfunction were classified as hypothyroidism and hyperthyroidism and outcome variables were compared between them. Thyroid dysfunction was said to occur if patient's thyroid hormones fall outside the reference range (serum T3 (0.6– 1.8 ng/ml), serum T4 (3.2 – 12.6 microgm/ dl), and TSH level (0.55 – 4.78 (microgm/dl). The data generated from the study was entered into MS Excel, checked for completeness and analysed using SPSS statistical package version 20 (Chicago, USA). Continuous variables were expressed as mean ± SD values. Student's t test was applied for comparing various parameters between patients with and without thyroid dysfunction and hypo- and hyperthyroidism. The data were analysed at 5% levels of significance.

RESULTS

In the present study a total of 104 patients were included during the study period, of which half were those with thyroid dysfunction and rest were age and gender matched controls (without thyroid dysfunction). Of the 52 cases with thyroid dysfunction, 45 were hypothyroid and rest were hyperthyroid. Hypothyroid cases consisted of autoimmune subclinical hypothyroidism (n = 25), autoimmune overt hypothyroidism (n = 14) and subclinical hypothyroidism (n = 6). Hyperthyroid cases consisted of autoimmune subclinical hyperthyroidism (n = 4), autoimmune overt hyperthyroidism (n = 2) and subclinical hyperthyroidism (n = 1). Table 1 describes the comparison of patients who presented with and without thyroid dysfunction. Mean TSH levels were significantly higher in patients with thyroid dysfunction (8.63 ± 4.31 vs 3.07 ± 1.63 microg/dl, p value < 0.001). Mean BMI was found to be similar in the two patient groups. We observed a higher mean HbA1c levels in patients with thyroid dysfunction as compared to those without thyroid dysfunction (8.75% vs 7.16%,

p value < 0.01). Among the lipid profile parameters, mean triglyceride levels and total cholesterol levels were also found to be significantly higher in patients with thyroid dysfunction as compared to those without thyroid dysfunction. Urine Protein Creatinine Ratio (UPCR) was also found to be significantly higher among patients with thyroid dysfunction. Furthermore, table 2 describes the comparison of DM patients with hypothyroidism and hyperthyroidism. We observed mean BMI, HbA1c, mean total cholesterol and UPCR to be significantly higher among cases with hypothyroidism as compared to those with hyperthyroidism. Mean triglyceride levels were similar in the two patient groups.

Variables	Diabetes Mellitus with Thyroid Dysfunction (N = 52) Mean (SD)	Diabetes Mellitus without Thyroid Dysfunction (N = 52) Mean (SD)	P Value
Mean age (years)	59.19 (9.06)	57.06 (8.95)	0.23
Thyroid Stimulating Hormone (μg/dl)	8.63 (4.31)	3.07 (1.63)	< 0.001*
Body Mass Index (kg/m^2)	26.87 (3.0)	25.49 (2.57)	0.34
Glycosylated haemoglobin %	8.75 (2.49)	7.16 (1.08)	< 0.01*
Triglycerides (mg/dl)	186.52 (39.02)	153.77 (30.6)	< 0.01*
Total cholesterol (mg/dl)	246.21 (67.17)	153.77 (30.6)	< 0.01*
Urine Protein to Creatinine Ratio	0.59 (0.23)	0.25 (0.13)	< 0.01*

Table 1. Comparison of Patients with and without Thyroid Dysfunction

*indicates statistically significant difference at $P<0.05$

Variables	Diabetes Mellitus with Hypothyroidism (N = 45) Mean (SD)	Diabetes Mellitus with Hyperthyroidism (N = 7) Mean (SD)	P Value
Mean age (years)	54.66 (7.56)	52.72 (6.82)	0.87
Thyroid Stimulating Hormone (μg/dl)	9.58 (2.84)	0.13 (0.05)	<0.01*
Body Mass Index (kg/m^2)	27.37 (2.95)	23.61 (1.63)	< 0.01*
Glycosylated haemoglobin %	9.03 (2.57)	6.98 (2.03)	< 0.05*
Triglycerides (mg/dl)	193.55 (39.77)	160.78 (25.01)	0.24
Total cholesterol (mg/dl)	252.6 (69.15)	198.23 (31.93)	< 0.05*
Urine Protein to Creatinine Ratio	0.71 (0.06)	0.21 (0.2)	< 0.01*

Table 2. Comparison of Patients with Hypothyroidism and Hyperthyroidism

*indicates statistically significant difference at $P<0.05$

DISCUSSION

The prevalence of thyroid dysfunction in patients with type 2 DM varies in the literature. Jali et al. reported it to be 16.2% in a study population from Belagavi, India.[7] In their study, gender-specific prevalence found higher in females (25%) compared to males (10.1%). A study in Jordan by Radaideh et al. found the prevalence of thyroid dysfunction to be 12.5%.[8] In another study from Greece reported the prevalence to be 12.3%.[9] Higher prevalence of 29.7%, 32.4% documented in Nigeria[10] and in Spain by Diez et al.[11] respectively. A study from Pune found the prevalence to be 30%[12] and from Manipur to be 31%.[13] In the present study, subclinical hypothyroidism was the most common thyroid dysfunction. Numerous epidemiological studies indicate the higher prevalence of overt hypothyroidism in type 2 diabetes mellitus (T2DM) population than in the general population.[14] However, the relationship between subclinical hypothyroidism (SCH) and T2DM is controversial. Recent studies by Ozair et al.[15] Singh et al.[16] and Vikhe et al.[12] reported subclinical hypothyroidism to be the most common thyroid abnormality in patients with type 2 DM. In addition, mean age of the patients in the present was 59.19 years and 57.06 years for patients with or without thyroid dysfunction. Jali and colleagues made a similar observation in which the prevalence of thyroid dysfunction increased with advancing age.[7] The authors reported that prevalence was found to be low (7.7%) in young age group. Prevalence was increased as the age increased and highest prevalence was found in patients more than 50 years of age (19%). A possible explanation for this would be that older patients might have had undetected diabetes for a longer time. Also, they are more prone to develop insulin resistance and decline in beta cell function over a period of time.[17]

In the study by Ozair et al. the mean BMI of subjects having thyroid dysfunction was more than those who were euthyroid.[15] The mean BMI of the study group was 25.71 ± 4.90 kg / m2. The mean BMI of the thyroid dysfunction group (25.26 ± 5.51 kg / m2) was slightly higher than the BMI of the euthyroid group (24.07 ± 4.93 kg / m2). The difference between the mean BMI of the euthyroid and thyroid dysfunction group was not found to be statistically significant. This is similar to our study, in which mean BMI was found to be similar in the two patient groups. We also observed a higher mean HbA1c levels in patients with thyroid dysfunction as compared to those without thyroid dysfunction (8.75 % vs 7.16 %, P value < 0.01). Similar observations were made by Mishra et al. who found that the mean HbAlc level in diabetics with thyroid dysfunction was (10.33 ± 2.37) higher than those of euthyroid ones (7.16 ± 1.04).[18] Ozair et al. also reported the mean HbA1c of the group having some form of thyroid dysfunction to be higher than the mean HbA1c of the euthyroid population. The mean HbA1c of those with thyroid dysfunction (8.14 ± 1.84 %) was higher than those without any thyroid dysfunction (7.8 ± 1.81%) but the difference was not statistically significant. among those diabetics with thyroid dysfunction highest HbA1c was of those with hyperthyroidism (9.0 ± 1.10%) while lowest was of those with overt hypothyroidism (7.9 ± 1.99%) (Table 4). The mean HbA1c of patients with subclinical hypothyroidism was 8.18 ± 1.81%, which was higher than the overt hypothyroid group but less than the hyperthyroid group. Jali et al. also found a significant association between the presence of thyroid dysfunction and glycaemic control.[7] In their study, poorly controlled type 2 DM patients carried increased risk (27.9%) of development of thyroid dysfunction compared to well controlled diabetic group (14.7 %) (P value = 0.012). However, the prevalence of thyroid dysfunction did not differ according to the duration of T2DM (P value = 0.42).

Thyroid hormones, especially T3 have been demonstrated to regulate low density lipoprotein (LDL) receptors by directly binding to thyroid hormone responsive elements (TREs) and controlling sterol regulatory element-

binding protein.[19] Thyroid hormone also induces the hepatic expression of hydroxymethyl glutaryl coenzyme-A reductase, which results in increased cholesterol synthesis. Thus, decreased thyroid hormones lead to reduced expression of LDL receptors and hepatic cholesterol synthesis, which may reduce cellular uptake and catabolism of LDL-C from circulation and finally result in increased levels of circulating TC.[20] In the present study, mean triglyceride levels and total cholesterol levels were also found to be significantly higher in patients with thyroid dysfunction as compared to those without thyroid dysfunction. Similar observations were made by Mishra et al. who found that the lipid level variations in diabetics show higher than normal values of total cholesterol, triglycerides and LDL cholesterol in diabetic patients with thyroid dysfunction when compared to control population and even higher levels than those of euthyroid diabetic individuals. In their study, out of the 50 diabetic patients studied, 7 were found to have thyroid dysfunction. Those with thyroid dysfunction had a mean total cholesterol level of 257.87 mg / dl with a standard deviation of 28.68 while that of the euthyroid diabetics was found to be 204.11 ± 11.35 mg / dl and controls was 180 ± 15.96 mg / dl. A total of 7 out of 50 diabetic patients had a mean tri- glyceride level of 196.62 ± 19.63 mg / dl and that of euthyroid diabetics was 162.26 ± 20.49 mg / dl. The mean level in the controls was 140.18 ± 17.12 mg / dl. The diabetic patients with thyroid dysfunction had a mean LDL cholesterol level of 159.37 ± 16.18 mg / dl and that of euthyroid diabetics was 105.83 ± 12.96 mg / dl while that of controls was 92.18 ± 18.23 mg / dl.[18] In another study, Wolide et al. demonstrated a positive and significant correlation between diabetes, TSH and total cholesterol, LDL and triglyceride.[21] However, in multivariable linear regression, TSH was positively associated only with triglycerides.

Increase in UPCR is an indication of nephropathic changes in patients with type 2 DM. In our study, UPCR was found to be significantly higher among patients with thyroid dysfunction. Furthermore, UPCR was significantly higher among cases with hypothyroidism as compared to those with hyperthyroidism. Likewise, Chen et al. demonstrated that type 2 diabetic patients with subclinical hypothyroidism are associated with an increased risk of nephropathy after adjustment for other factors.[22] In their study, subclinical hypothyroidism was associated with a greater prevalence of diabetic nephropathy. The odds ratio for nephropathy [3.15 (95% CI, 1.48 – 6.69), P value = 0.003) was increased in type 2 DM patients with subclinical hypothyroidism. Additional adjustment for HbA1c, blood pressure, BMI and smoking status did not affect these associations. Recent studies have shown that patients with subclinical hypothyroidism have endothelial dysfunction characterized by impaired vasodilatation and reduced availability of nitric oxide. Endothelial dysfunction has been shown to be the underlying mechanism of diabetic nephropathy, in addition to atherosclerosis.[23]

Therefore, subclinical hypothyroidism may have an important role in the development of diabetic nephropathy, as a result of vascular endothelial dysfunction.

CONCLUSIONS

Hypothyroidism is more common than hyperthyroidism in patients with type 2 DM. Failure to recognise the presence of thyroid dysfunction in patients with type 2 DM may be an underlying cause of poor glycaemic control. It is therefore recommended that all type 2 DM patients should have a baseline evaluation of thyroid function.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
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