Study of Subclinical Thyroid Disorders in Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND

Thyroid disease is more common in people with diabetes mellitus than in general population. Among thyroid disorders, subclinical hypothyroidism is more common than the overt form. Hypothyroidism is associated with dyslipidaemia, hypertension and cardiac disease. Subclinical hypothyroidism has also been reported to have these features. With this background, we aimed to determine the prevalence of subclinical thyroid disorder and its influence on the metabolic profile of patients with type 2 diabetes mellitus (DM).

METHODS

234 type 2 diabetes patients, 117 males and 117 females, who were previously not known to have thyroid disease, were screened for thyroid dysfunction using serum free T3, free T4, and thyroid stimulating hormone (TSH) levels. Patients were evaluated for clinical features of thyroid disease and investigated for microvascular complications of DM, dyslipidaemia and cardiac disease. Individuals with subclinical hypothyroidism were further screened for anti-thyroid peroxidase (TPO) antibodies.

RESULTS

In this study, subclinical hypothyroidism was present in 29 (12.4 %) of 234 type 2 diabetics; no case of subclinical hyperthyroidism was detected. 25 of these 29 patients with subclinical hypothyroidism were females. Elevated TPO antibody levels were present in 82.8 % (24 out of 29) subclinical hypothyroidism (SCH) patients. SCH was found to be associated with higher body mass index (BMI) and patients aged more than 50 years. No significant difference was found in glycaemic profile or lipid profile between patients with SCH and euthyroid subjects. There was no significant difference among SCH patients with and without microvascular complications. Left Ventricle (LV) diastolic dysfunction was present in 34.4 % of SCH patients.

CONCLUSIONS

SCH is common among type 2 diabetics, especially in females and most commonly due to autoimmune thyroid disease. SCH in type 2 DM is associated with a higher BMI and an older age group, but it does not seem to have an influence on glycaemic profile, lipid profile or microvascular complications of diabetes.

KEYWORDS

Thyroid Stimulating Hormone (TSH), Type 2 Diabetes Mellitus (T2DM), Subclinical Hypothyroidism (SCH), BMI, Anti–TPO (Thyroid Peroxidase) Antibody

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BACKGROUND

Thyroid disease is common in the general population, and its prevalence increases with age.[1] Hypothyroidism is more common than hyperthyroidism; it can be autoimmune in origin, presenting as either primary atrophic hypothyroidism or Hashimoto's thyroiditis. A recent study from Kerala, shows prevalence of hypothyroidism as 3.9 % and subclinical hypothyroidism as 9.4 %.[2]

Subclinical hypothyroidism (SCH) is defined as a serum thyroid stimulating hormone (TSH) level above normal despite normal levels of serum free thyroxine. In various studies, it has been shown to be associated with elevation in serum total cholesterol, triglycerides (TGL), low density cholesterol (LDL-C), coronary artery disease (CAD), LV diastolic dysfunction, LV systolic dysfunction with exercise and increased peripheral vascular resistance, thereby increasing the risk of CAD.[1]

The prevalence of thyroid disease in diabetic patients is significantly higher than in general population.[1] Apart from autoimmune aetiology linked to the higher prevalence of thyroid disease in diabetes, it has also been observed that thyroid function is intrinsically linked to insulin resistance; common factors are responsible for both increased TSH levels and insulin resistance.[3] Hypothyroidism in diabetes may lower the exogenous insulin requirement due to reduced rate of insulin degradation.

In type 2 DM, prevalence of thyroid disease has been found to be as high as 31 %, the most common disorder being subclinical hypothyroidism, followed by subclinical hyperthyroidism, overt hypothyroidism and overt hyperthyroidism.[4] Various studies have been done to look at thyroid status in patients with diabetes and its effect on diabetes control and complications, but results have been variable. Since Indian-diabetic population is large and diverse, we decided to estimate the occurrence of thyroid disorders in patients with T2DM in South India and to ascertain whether subclinical hypothyroidism had an effect on their metabolic profile and complications or not.

METHODS

This descriptive, cross-sectional study was performed at a tertiary care, university hospital near Chengalpattu in Tamil Nadu. A total of 234 patients with type 2 DM with equal number of men and women were included in the study. Inclusion criteria were subjects without history of thyroid disorder, above 18 years of age and willing to give informed consent. Patients with known thyroid disorder, critically ill patients, those on drugs known to alter thyroid levels, patients with hepatic dysfunction and psychiatric illnesses were excluded. Pregnant women were also excluded. The study was approved by the institutional ethics committee.

In all patients a detailed clinical history was taken and all underwent a complete physical examination, with emphasis on symptoms and signs suggestive of thyroid dysfunction. A diabetic profile was done which included fasting blood sugar (FBS), post prandial blood sugar (PPBS), glycosylated haemoglobin (HbA_{1C}), urine albumin excretion, fundus examination and neurological examination for presence of peripheral neuropathy. Serum freeT3, freeT4, TSH was measured in all. In those who were detected to have subclinical thyroid disease serum anti-thyroid peroxidase antibody (anti-TPO) titres were measured by immunoenzymatic assay using 0.5 ml of patient's serum sample. Values > 9.0 IU / ml were interpreted as elevated.

Subclinical hypothyroidism was defined as serum TSH value between 4.2 µIU / ml and 10 µIU / ml, with normal levels of serum free T4 (0.93 – 1.7 ng / dl). Subclinical hyperthyroidism was defined as serum TSH < 0.27 µIU / ml, with normal levels of serum free T3 (2.0 – 4.4 pg / ml) and serum free T4 (0.93 – 1.7 ng / dl).

Statistical Analysis

The collected data was analysed statistically by computing the standard quantities namely mean, standard deviation, standard error of mean, and percentages. The difference between different parameters based on quantitative variables were compared using Student's t test for independent samples and the difference was considered statistically significant when the p value < 0.05.

RESULTS

A total of 234 patients with diabetes underwent thyroid function testing. Out of the 234, 84.2 % were euthyroid (normal serum TSH, free T4 and free T3), 12.4 % patients (n = 29) had subclinical hypothyroidism (serum TSH > 4.2 µIU / ml with normal levels of serum free T4), and the remaining 3.4 % (n = 8) had overt primary hypothyroidism (serum TSH ≥ 10 µIU / ml and serum free T4 ≤ 0.93 ng / dl). None had subclinical or overt hyperthyroidism. Among the 29 patients with subclinical hypothyroidism, serum levels of anti–TPO antibodies were elevated in 24 patients (82.8 %). 22 of them were females and 2 were males.

	Thyroid Function				
Gender	Euthyroidism [n (%)]	Subclinical Hypothyroidism [n (%)]	Overt Hypothyroidism [n (%)]	Total	P Value
Female	86 (73.5)	25 (21.4)	6 (5.1)	117 (50)	
Male	111 (94.9)	4 (3.4)	2 (1.7)	117 (50)	0.000 (S)
Total	**197 (84.2)**	**29 (12.4)**	**8 (3.4)**	**23 4100)**	

Table 1. Gender Distribution of Thyroid Status

Among the 29 patients of subclinical hypothyroidism, 25 were females (21.4 %) and 4 were males (3.4 %). (P value 0.000) (Table 1).

Age Group	Total Number of Patients	SCH	P Value
< 51 years	45	2 (4.4)	
51 – 60 years	112	15 (13.4)	0.000 (S)
> 60 years	77	12 (15.6)	

Table 2. Age Distribution among SCH Patients

Age more than 50 years was significantly associated with presence of subclinical hypothyroidism. (P value 0.000) (Table 2).

BMI of euthyroid and subclinical hypothyroid patients was compared. SCH patients had a mean BMI of 27.322 with SD ± 4.135 whereas euthyroid patients had a mean BMI of 29.724 with SD ± 3.791, which was statistically significant (p value 0.002). (Table 3).

Thyroid Function	N	Mean BMI	Std. Deviation	P Value
Euthyroidism	197	27.3228	4.13507	0.002 (S)
Subclinical hypothyroidism	29	29.7241	3.79178	

Table 3. Comparison of BMI between SCH Patients and Euthyroid Subjects

Among the 29 subclinical hypothyroid patients, 15 patients had dyslipidaemia. All the 15 patients were previously diagnosed with dyslipidaemia and were on medication for the same. Lipid profiles of euthyroid patients were compared with those who had subclinical hypothyroidism. Mean serum levels of triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol were elevated and high-density lipoprotein (HDL) cholesterol levels were reduced in patients with subclinical hypothyroidism but this difference was not statistically significant. There was also no significant association between thyroid status and glycaemic parameters. (Table 4)

Study Variable	Thyroid Status	N	Mean	Std. Deviation	P Value
FBS (mg %)	Euthyroidism	197	155.81	58.80974	0.370
	Subclinical hypothyroidism	29	147.48	37.96391	(NS)
PPBS (mg %)	Euthyroidism	197	236.64	80.67967	0.924
	Subclinical hypothyroidism	29	237.62	68.23406	(NS)
HbA1C (%)	Euthyroidism	197	8.0254	2.18909	0.775
	Subclinical hypothyroidism	29	7.7690	1.88644	(NS)
Cholesterol (mg %)	Euthyroidism	197	164.43	32.35788	0.107
	Subclinical hypothyroidism	29	177.83	29.35749	(NS)
LDL-C (mg %)	Euthyroidism	197	95.5025	28.68880	0.337
	Subclinical hypothyroidism	29	104.03	27.76236	(NS)
HDL-C (mg %)	Euthyroidism	197	39.9995	6.85325	0.220
	Subclinical hypothyroidism	29	37.8172	4.15186	(NS)
TGL (mg %)	Euthyroidism	197	148.39	74.64285	0.074
	Subclinical hypothyroidism	29	180.24	67.55244	(NS)

Table 4. Glycaemic Profile, Lipid Profile and Thyroid Status

Diabetic Complications

Among 29 SCH patients, 17 patients had one or more microvascular complication of DM i.e. nephropathy / retinopathy / neuropathy. 15 SCH patients had diabetic retinopathy, 7 SCH patients had diabetic nephropathy and 17 SCH patients had diabetic neuropathy.

The 17 SCH patients with diabetic microvascular complications had mean duration of DM of 10.4 years, mean HbA 1c of 7.49 %, and mean TSH of 5.28 µIU / ml. 8 out of the 17 patients had systemic hypertension and were on treatment for the same. None of the 17 patients were smokers. SCH patients with and without diabetic microvascular complications were compared with respect to duration of DM, serum HbA 1c levels, and serum TSH. Statistically significant difference was observed between the two groups in duration of DM only (p value 0.000). (Table 5)

Study Variable	SCH Patients	N	Mean	Std. Deviation	P Value
Duration of DM	With microvascular complication	17	10.4 years	2.00367	0.000 (S)
	Without microvascular complication	12	6.16 years	1.52753	
	Total	29	8.68 years	2.80438	
HbA1C	With microvascular complication	17	7.49 %	2.08131	0.739 (NS)
	Without microvascular complication	12	7.71 %	1.12398	
	Total	29	7.58 %	1.72745	
TSH	With microvascular complication	17	5.28 µIU / ml	2.62622	0.253 (NS)
	Without microvascular complication	12	8.93 µIU / ml	19.84094	
	Total	29	7.62 µIU / ml	12.90774	

Table 5. Comparison between SCH Patients with and without Diabetic Microvascular Complications

Diabetic retinopathy was detected in 15 SCH patients. All 15 of these patients had non-proliferative diabetic retinopathy. Diabetic nephropathy was observed in 7 SCH patients. Diabetic neuropathy was present in 17 SCH patients in the form of bilateral lower limb sensory-motor polyneuropathy. With all three microvascular complications, significant association was present only with duration of diabetes: p value was 0.000 for diabetic retinopathy and neuropathy and 0.010 for diabetic nephropathy.

2D echocardiography was performed in all patients with subclinical hypothyroidism. Echocardiogram was normal in 19, while 5 patients each had LV diastolic dysfunction and LV diastolic dysfunction with concentric LV hypertrophy respectively. All ten patients with echo findings had history of hypertension and were on medication for the same.

DISCUSSION

Studies have varied widely in the prevalence of SCH, from high values in a recent meta-analysis of mostly Chinese studies[5] (6.16 to 18.6 % - pooled value of 10.2 %), to a low value of 4.69 from Nigeria[6] to 10.69[7] in Europe. In the current study, out of 234 patients with T2DM, 37 had thyroid dysfunction (TD). Of these, 29 (12.4 %) had subclinical hypothyroidism. In the meta-analysis[5] mentioned above, there was a 1.93-fold increase in SCH. Indian studies also have reported varied values for example, 31 % thyroid dysfunction in Meerut[8] and 23 % SCH from Kolkata. [9]

Chaturvedi et al. from Meerut also reported that diabetes was associated with higher TSH values. These variations could be due to differences in iodine sufficiency, varying levels of autoimmunity etc. Indian studies have indicated that South India is by and large iodine sufficient[10].

Furthermore, in the current study, of 29 subjects with SCH, 24 had high anti TPO antibody titres, indicating autoimmunity. Thyroid dysfunction is more common in women and in this study also women outnumbered men. This is true of other studies also {Chen et al[11] (Taiwan), Demitrost[12] (Manipur)}.

SCH in the current study was associated with both age greater than 50 years and an increased BMI. Kim et al.[13] showed a similar association with age ($p = 0.014$). In the Manipuri study quoted above, BMI > 25 was associated only with hypothyroidism, similar to another large South Indian study[14], but not with SCH. Correlation of SCH with dyslipidaemia, glycaemic control and diabetic complications have also been dissimilar in various studies.

A metanalysis by Aziz et al.[15] showed significant elevation of total cholesterol and triglycerides with SCH. This meta-analysis included a study by Monzani et al.[16] which measured lipid profile and carotid artery intima media thickness in 45 patients with SCH, at baseline and again after 6 months of levothyroxine replacement. Baseline elevations of total cholesterol, LDL-C (LDL Cholesterol), apolipoprotein B and mean carotid intima media thickness were significantly reduced by the end of the study period. In the current study, elevations were seen in total cholesterol, LDL-C, triglycerides and reduction in HDL-Cholesterol demonstrating an atherogenic profile but the values did not achieve statistical significance. (Table 5)

In another Italian study[17], it was observed that SCH was significantly associated with LV diastolic dysfunction which was reversible on levothyroxine therapy. Imaizumi[18] found an association with ischaemic heart disease (IHD) in patients with SCH and speculates that it may be linked to cardiovascular mortality. A similar association of SCH with IHD was shown in patients older than 65 years by Jia et al[19]. In the current study, 10 patients were already known to have hypertension and cardiovascular disease and were on treatment for the same. The numbers were too small to make significant conclusions.

When we compared patients with and without microvascular diabetic complications within the group with SCH, we found no significant difference. A group from Trivandrum[14] in South India, studied 1152 diabetic patients for thyroid dysfunction retrospectively. They reported no correlation of SCH with BMI and glycaemic control.

But a much smaller study from Kolkata[9] found positive correlation of TSH values with vibration perception threshold and negative correlation with estimated glomerular function rate (eGFR), but no association with albumin-creatinine ratio or retinopathy. A Karnataka[20] study found a significant association of diabetic retinopathy with increased TSH levels. Kamendu.[21] studying 200 patients from rural Bihar reported correlation of thyroid dysfunction with increasing HbA_1c and duration of diabetes < 5 years and surprisingly, more males than females.

The previously mentioned meta-analysis[5] by Han et al. also found increased risk of complications associated with SCH – OR of 1.74 for diabetic nephropathy, 1.42 for retinopathy, 1.85 for peripheral arterial disease and 1.87 for neuropathy. Our study did not find a clinically significant association of SCH with glycaemic control or with diabetic complications, similar to the Trivandrum study.[14]

CONCLUSIONS

We found that subclinical hypothyroidism in our patients with type 2 DM was associated with increasing age and BMI, but did not seem to influence diabetic control or dyslipidaemia significantly. Trials undertaking treatment of these patients with levothyroxine and / or follow-up may be helpful in understanding the true role of subclinical hypothyroidism in diabetes.

A small sample size and lack of follow up were limitations of this current study.

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