Prevalence of subclinical thyroid disorders in type 2 diabetes mellitus

Background: Subclinical thyroid disorders usually do not produce symptoms of thyroid disease until they turn into overt thyroid disease. Thyroid disease is more common in people with diabetes mellitus than in the general population and it is important to detect thyroid disorder before its clinical manifestation. Subclinical hypothyroidism (SCH) can produce dyslipidemia, obesity thus resulting increased predisposition to coronary artery disease. Subclinical hyperthyroidism can aggravate hyperglycemia and impair blood sugar control. Objectives: Our objective is to determine the prevalence of subclinical thyroid disorders in patients with type 2 diabetes mellitus (T2DM) and to analyze the clinical and metabolic profile of patients with this dual endocrine disorder. Methods and Results: One hundred consecutive type 2 diabetic patients without clinical manifestations of thyroid disorders were screened for SCH and subclinical hyperthyroidism using serum free T3, free T4 and thyroid stimulating hormone (TSH) levels. Individuals of subclinical thyroid disease were further screened for thyroperoxidase (TPO) antibodies. SCH was detected in 13% of type 2 diabetic patients and none had subclinical hyperthyroidism in our study. SCH was common among females with type 2 diabetes (84.6%). Elevated TPO antibody levels were present in 84.6% SCH patients. Diabetic retinopathy among SCH patients showed significant association with higher serum TSH levels. Left ventricular diastolic dysfunction was present in 30.8% of SCH patients. Conclusion: SCH is common among type 2 diabetic patients, especially in females. It is most commonly secondary to autoimmune thyroid disease. Microvascular complications are commonly observed in this group of patients with dual endocrinal disorder and treating physician should be aware of the impact and should routinely screen SCH to prevent complications.

Key words: Anti-thyroperoxidase antibody, diabetic retinopathy, left ventricular diastolic dysfunction, subclinical hypothyroidism, subclinical hyperthyroidism, type 2 diabetes mellitus

INTRODUCTION

The prevalence of thyroid disease in the diabetic patients is significantly higher than in the general population.[1] Apart from autoimmune etiology linked to the higher prevalence of thyroid disease in diabetes mellitus; it has also been observed that thyroid function is intrinsically linked to insulin resistance. It has also been stated that common factors simultaneously are responsible for increased thyroid stimulating hormone (TSH) levels and insulin resistance.[2]

In type 2 diabetes mellitus (T2DM), 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.[3] Subclinical hypothyroidism (SCH) is defined as a serum TSH level above normal despite normal levels of serum free thyroxine.[4,5]

SCH, in various studies, has been shown to be associated with elevation in serum lipids, coronary artery disease and left ventricular (LV) diastolic dysfunction, LV systolic dysfunction with exercise, increased peripheral vascular resistance and mental depression.

Objectives
1. To determine the percentage of subclinical thyroid disorders in patients with T2DM.
2. To study the clinical and metabolic profile of patients with this dual endocrine disorder.
MATERIALS AND METHODS

This study was done at department of general medicine, Kempegowda Institute of Medical Sciences, Bangalore. This is a cross-sectional observational descriptive study. A total of consecutive 100 type 2 diabetic patients (50 male and 50 female patients) aged >40 years, with no past history of thyroid disorder were included in the study. Patients younger than 40 years of age on drugs known to alter thyroid hormonal levels, seriously ill-patients, patients previously diagnosed with thyroid disorder and on medication, patients with the chronic conditions known to alter thyroid function, such as hepatic dysfunction, pregnancy and psychiatric illness were excluded from the study. Written informed consent was taken from all patients and the study was approved by institutional ethical committee. All the study participants underwent detailed history, clinical examination and laboratory investigations using pro forma designed for this study. Special emphasis was given to symptoms and signs of hypothyroidism and hyperthyroidism.

All patients were subjected to following investigations: Fasting blood sugar (FBS), post-prandial blood sugar (PPBS), hemoglobin A1c (HbA1c) Serum free T3, free T4, TSH, Fasting lipid profile, ECG, 2D Echocardiography, Ophthalmological evaluation (fundus examination), Urine routine, Blood urea, serum creatinine. Serum anti-thyroperoxidase (TPO) antibody assay was done in patients detected to have subclinical thyroid disease.

SCH was defined as serum TSH> 4.2 μIU/ml, with normal levels of serum free T4 (0.93-1.7 ng/dl). Anti-TPO antibodies were measured by immunoenzymatic assay using 0.5 ml of patient’s serum sample and values >9.0 IU/ml were interpreted as elevated.

Statistical analysis

Descriptive statistics were presented as mean ± standard deviation for continuous measures while absolute values and percentages for categorical measures. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) 16 statistical software (SPSS Inc., Chicago, Illinois, USA). A P < 0.05 was considered to be statistically significant throughout the analysis. The difference between different parameters based on quantitative variables are compared using Student’s t test for independent samples and the difference is considered statistically significant when the P < 0.05.

RESULTS

In the present study, a total number of 100 patients of T2DM underwent thyroid function test including serum free T3, free T4 and TSH. Based on the above biochemical values, it was determined that out of the 100 patients [Table 1], 84 were euthyroid (serum TSH, serum free T4, serum free T3 within normal limits), 13 patients had SCH (serum TSH > 4.2 μIU/ml with normal levels of serum free T3) and the remaining 3 had overt primary hypothyroidism (serum TSH > 4.2 μIU/ml and serum Free T4 < 0.93 ng/dl) [Table 1]. None had subclinical or overt hyperthyroidism.

Among the 13 patients of subclinical hypothyroidism, 11 were female and 2 were male patients. Therefore, the percentages of SCH among female and male patients were 22% and 4% respectively.

The mean age in SCH patients was 58.77 ± 5.47 years, whereas the mean age in euthyroid patients was 56.98 ± 7.49 years, the difference was not statistically significant (P value: 0.304).

Clinical profile of subclinical hypothyroid patients

Among the 13 subclinical hypothyroid patients detected in the study, 3 (23%) patients had clinical features suggestive of hypothyroidism. Goiter was detected in 2 (15.4%) patients of SCH. Table 2 enlists the clinical profile of patients SCH patients who presented with each clinical feature of hypothyroidism.

SCH patients having symptoms/signs of hypothyroidism were compared with SCH patients without symptoms/signs of hypothyroidism with respect to serum free T3, free T4 and TSH values [Table 3]. Statistically significant difference was noted in all the above three biochemical variables between the two groups.

Blood pressure

The mean SBP of the 13 SCH patients was 137.38 ± 11.59 mm Hg, whereas, the mean DBP was 79.69 ± 8.40 mm Hg. Systemic hypertension was present in 6 (46%) of the 13 SCH patients. All the above 6 patients were known cases of hypertension and were on regular antihypertensive drug treatment; and had a mean duration of hypertension of 5.5 ± 3.94 years.

Body mass index (BMI)

BMI, which was calculated for all 100 T2DM patients was used to compare the 13 SCH patients with 84 euthyroid subjects. SCH patients had a mean BMI of 29.70 ± 3.77 kg/m2 whereas euthyroid patients had a mean BMI of 27.35 ± 4.36 kg/m2, which was not statistically significant (P value 0.054).

Chronic complications of diabetes mellitus

Microvascular complications

Among 13 SCH patients, 6 (46%) had one or more microvascular complication of DM i.e., nephropathy/retinopathy/neuropathy.
(46%) SCH patients had diabetic retinopathy, 3 (23%) SCH patients had diabetic nephropathy, 2 (15%) SCH patients had diabetic neuropathy.

The 6 SCH patients with diabetic microvascular complication had a mean duration of DM of 8.83 years, mean HbA1c of 7.61% and mean TSH of 7.21 μIU/ml. Three out of the 6 patients had systemic hypertension and were on treatment for the same. SCH patients with diabetic microvascular complication were compared with SCH patients without microvascular complication [Table 4], with respect to the duration of DM, serum HbA1c levels and serum TSH. Statistically significant difference was observed between the two groups in duration of DM (P value 0.002), serum TSH level (P value 0.004), but not in serum HbA1c level.

**Diabetic retinopathy**

Diabetic retinopathy was detected in 6 SCH patients, i.e. 46% of SCH patients in the study. All 6 of these patients had non-proliferative diabetic retinopathy. None of the SCH patients had any evidence of proliferative diabetic retinopathy or macular edema.

SCH patients with diabetic retinopathy were compared with SCH patients without retinopathy with respect to the duration of DM, serum HbA1c levels and serum TSH.

SCH patients with diabetic retinopathy had a mean serum TSH value of 7.21 ± 1.34 μIU/ml, mean serum HbA1c of 7.61 ± 2.15% and mean duration of DM being 8.83 ± 2.54 years. SCH patients without retinopathy had mean serum TSH of 4.90 ± 0.55 μIU/ml, mean serum HbA1c of 8.04 ± 1.58% and mean duration of DM being 3.85 ± 1.80 years. Statistically significant difference between the two groups was observed in duration of diabetes (P value 0.002) and serum TSH levels (P value 0.004).

**Diabetic nephropathy**

Diabetic nephropathy was observed in 3 SCH patients, comprising 23% of all the SCH patients in the study. All the above 3 patients had nephropathy in the form of microalbuminuria. Blood urea and serum creatinine levels were within normal range in all the SCH patients. Comparison was done between SCH patients with nephropathy and SCH patients without evidence of diabetic nephropathy, based on duration of DM, serum HbA1c levels and serum TSH level.

SCH patients with diabetic nephropathy had a mean serum TSH value of 7.29 ± 1.77 μIU/ml, mean serum HbA1c of 8.73 ± 2.45% and mean duration of DM being 8 ± 2.94 years. SCH patients without nephropathy had mean serum TSH of 5.57 ± 1.17 μIU/ml, mean serum HbA1c of 7.58 ± 1.57% and mean duration of DM being 5.6 ± 3.2 years. No statistically significant difference was found between the two groups in any of the above study variables.

| Table 2: Clinical profile of diabetic patients with subclinical hypothyroidism |
|--------------------------|--------------------------|
| Clinical features       | % of SCH patients with the symptom |
| Symptom of hypothyroidism |     |
| Dry skin                | 23 |
| Fatigue                 | 23 |
| Poorer memory           | 15.4 |
| Cold intolerance        | 7.7 |
| Constipation            | 7.7 |
| Clinical signs of hypothyroidism |     |
| Dry coarse skin         | 23 |
| Cool peripheral extremities | 7.7 |

SCH = Subclinical hypothyroidism

| Table 3: Comparison between the two groups of SCH patients based on presence/absence of clinical features of hypothyroidism, with respect to TFT parameters |
|--------------------------|--------------------------|--------------------------|
| TFT parameters | SCH patients | Number of patients | Mean value±SD | P value |
| Free T<sub>3</sub> with clinical features of hypothyroidism | 3 | 2.77±0.12 ng/dl | 0.038 |
| Free T<sub>3</sub> without clinical features of hypothyroidism | 10 | 2.88±0.55 ng/dl |  |
| Free T<sub>4</sub> with clinical features of hypothyroidism | 3 | 1.01±0.07 ng/dl | 0.032 |
| Free T<sub>4</sub> without clinical features of hypothyroidism | 10 | 1.23±0.14 ng/dl |  |
| TSH with clinical features of hypothyroidism | 3 | 8.15±0.57 μIU/ml | 0.00004 |
| TSH without clinical features of hypothyroidism | 10 | 5.31±1.03 μIU/ml |  |

SCH = Subclinical hypothyroidism, SD = Standard deviation, TSH = Thyroid-stimulating hormone, TFT = Thyroid function tests

| Table 4: Comparison between SCH patients with diabetic microvascular complication and SCH patients without diabetic microvascular complication |
|--------------------------|--------------------------|--------------------------|
| Study variable | SCH patients | No. of patients | Mean value±SD | P value |
| Duration of DM with microvascular complication | 6 | 8.83±2.54 years | 0.002 |
| Duration of DM without microvascular complication | 7 | 3.85±1.80 years |  |
| Serum HbA1C with microvascular complication | 6 | 7.61±2.15% | 0.929 |
| Serum HbA1C without microvascular complication | 7 | 8.04±1.58% |  |
| Serum TSH with microvascular complication | 6 | 7.21±1.34 μIU/ml | 0.004 |
| Serum TSH without microvascular complication | 7 | 4.90±0.55 μIU/ml |  |

SCH = Subclinical hypothyroidism, SD = Standard deviation, DM = Diabetes mellitus, TSH = Thyroid-stimulating hormone, HbA1c = Hemoglobin A1c
**Diabetic neuropathy**

Diabetic neuropathy was present in 2 (15.4%) SCH patients. Both of the 2 patients had bilateral lower limb sensory-motor polyneuropathy. Comparison was performed between SCH patients with diabetic neuropathy and SCH patients without diabetic neuropathy, based on the duration of DM, serum HbA1c levels and serum TSH level.

SCH patients with diabetic neuropathy had a mean serum TSH value of 7.03 ± 1.60 μIU/mL, mean serum HbA1c of 7.87 ± 2.59% and mean duration of DM being 9 ± 3.08 years. SCH patients without neuropathy had mean serum TSH of 5.49 ± 1.21 μIU/mL, mean serum HbA1c of 7.83 ± 1.44% and mean duration of DM being 4.8 ± 2.51 years. Statistically significant difference between the two groups was observed in duration of DM (P = 0.038).

**Macrovascular complications of DM**

Among 13 SCH patients, coronary artery disease was evident in 1 (7.7%) SCH patient with a positive history of ischemic heart disease and was confirmed by 2D echocardiography. There was no clinical evidence of peripheral arterial disease or cerebrovascular disease in any of the thirteen SCH patients in the study.

**Metabolic profile of SCH patients**

**Glycemic profile**

The glycemic profile including FBS, PPBS and serum HbA1c of SCH patients of T2DM was compared with that of euthyroid counterparts in the study. Among the 13 SCH patients, the mean FBS value was 148.23 ± 37.77 mg%, mean PPBS value was 240.30 ± 65.06 mg%, mean serum HbA1c was 7.84 ± 1.87%. Among the 84 euthyroid patients, the mean FBS value was 157.04 ± 60.27 mg%, mean PPBS was 242.09 ± 79.50 mg% and mean serum HbA1c was 8.09 ± 2.15%. Statistically significant difference was not observed in any of the above study variables between the two groups; although, SCH patients had relatively low mean values of FBS, PPBS and serum HbA1c, compared with euthyroid subjects.

**Antidiabetic medications**

Among the 13 SCH patients, 2 (15.4%) patients were on insulin therapy along with oral hypoglycemic agents, 4 (30.8%) patients were on more than 2 classes of oral hypoglycemic drugs, the remaining 7 (53.8%) SCH patients were on not more than 2 classes of oral hypoglycemic drugs.

**Fasting lipid profile**

Among the 13 SCH patients, 6 (46%) patients had dyslipidemia. All the 6 patients were known cases of dyslipidemia and were on medication for the same. The fasting lipid profile of SCH patients of T2DM was compared with that of euthyroid counterparts. Among the 13 SCH patients, the mean serum total cholesterol was 175.69 ± 28.05 mg%, mean serum low-density lipoprotein (LDL) was 102.30 ± 27.3 mg%, mean serum high-density lipoprotein (HDL) was 38.14 ± 4.12 mg%, mean serum triglycerides (TG) was 178 ± 66.03 mg%. Among the 84 euthyroid subjects, the mean serum total cholesterol was 164.35 ± 32.73 mg%, mean serum LDL was 94.64 ± 28.87 mg%, mean serum HDL was 40.06 ± 6.94 mg%, mean serum TG was 151.10 ± 77.03 mg%. Although SCH patients had higher mean values of serum total cholesterol, LDL, TG and lower mean value of serum HDL, compared with euthyroid subjects, the difference was not statistically significant.

**Serum levels of anti-TPO antibodies**

Among the 13 SCH patients, serum level of anti-TPO antibodies was elevated in 11 patients (84.6% of SCH patients). 10 SCH patients with elevated anti-TPO antibody were female, one was male. The remaining 2 SCH patients had serum levels of anti-TPO antibodies within normal limits. Therefore, serum anti-TPO antibody levels were elevated in 91% of female SCH patients and in 50% of male SCH patients.

**DISCUSSION**

SCH is defined as a serum thyroid-stimulating hormone (TSH) level above the upper limit of normal despite normal levels of serum free thyroxine.[10] SCH or mild thyroid failure is a common problem, with a prevalence of 3-8% in the population without known thyroid disease.[7-8] The prevalence increases with age and is higher in women. After the sixth decade of life, the prevalence in men approaches that of women, with a combined prevalence of 10%. Antithyroid antibodies can be detected in 80% of patients with SCH and 80% of patients with SCH have a serum TSH of less than 10 mIU/L.

Although studies have pointed to some adverse effects of SCH, no consensus exists as to the clinical importance of the adverse effects and the benefits of levothyroxine therapy, particularly for the 80% of patients with SCH who have a TSH of less than 10 mIU/L, because of the different levels of TSH and degrees of thyroid dysfunction in these studies.[9,10] Patients with SCH have a high rate of progression to clinically overt hypothyroidism, 2.6% each year if TPO antibodies are absent and 4.3% if they are present.[11]

The Colorado Health Fair study showed that the mean total cholesterol level was 216 mg/dL for euthyroid patients and 224 mg/dL for patients with SCH.[12] Several randomized studies have shown reduction of LDL cholesterol by levothyroxine therapy. However, most of the studies showing benefit are not categorized for serum TSH levels of 5.0-10.0 mIU/L. A meta-analysis of 13 studies concluded that the lipid profile improved with therapy.[13] In a 2004 review, data were considered insufficient to show benefits of levothyroxine therapy on lipid levels.[14]

Several recent meta-analysis of observational studies found an association between SCH and coronary artery disease.[15-17] Diabetic patients have a higher prevalence of thyroid disorders compared with the normal population. Because patients with one organ-specific autoimmune disease are at risk of developing other autoimmune disorders and thyroid disorders are more common in females, up to 30% of female type 1 diabetic patient have thyroid disease. The
rate of postpartum thyroiditis in diabetic patients is three times that in normal women. A number of reports have also indicated a higher than normal prevalence of thyroid disorders in type 2 diabetic patients, with hypothyroidism being the most common disorder.[10]

Prevalence of thyroid disease in the general population is 6.6%. [11] Perros et al.[11] found that the prevalence of thyroid disease in diabetics is 13.4% and was highest in type 1 diabetic females and lowest in type 2 diabetic males. Celani et al.[8] found that prevalence of thyroid disease in type 2 diabetes was 31.4%, out of which SCH was most common form (48.3%), followed by subclinical hyperthyroidism (24.2%), overt hypothyroidism (23.1%) and overt hyperthyroidism (4.4%). The study even reported that 33% of type 2 diabetics with thyroid disease had high levels of anti-TPO antibodies. Fernández-Real et al.[2] reported that thyroid function tests are intrinsically linked to variables of insulin resistance and endothelial function, therefore implying the possibility that underlying factors lead simultaneously to increased serum TSH, insulin resistance, ensuing dyslipidemia and altered endothelial function. In hypothyroidism, glucose homeostasis is also affected although its clinical impact is less obvious. Decreased glucose disposal (as compared with euthyroid subjects) has been proved in hypothyroid patients. Hyperthyroidism results in unimpaired or decreased liver glucose output thereby compensating for insulin resistance present in peripheral tissues and accounting for the diminished insulin requirement for glycemic control in hypothyroid diabetic patients. Insulin resistance has been also reported in subclinical hypothyroidism, adding one more possible mechanism to the association of sub-clinical hypothyroidism and cardiovascular risk.

Only a few studies have explored the effects of sub-clinical thyroid dysfunction in the diabetic population. Patients with SCH had a higher prevalence of retinopathy, especially the sight-threatening form, when compared with their type 2 diabetic euthyroid counterparts.[19] Both SCH and hyperthyroidism have been linked to increased cardiovascular risk.

In the present study, serum TPO antibody elevation was seen in 11 (84.6%) SCH patients, indicating thyroid disease of autoimmune etiology. In a study by Celani et al.,[8] it was observed that 61.3% SCH patients with T2DM had elevated serum anti-TPO antibody levels. Celani et al.[8] also observed that the remaining 38.7% SCH patients who were negative for anti-TPO antibody, showed decreased serum TSH concentrations when retested after 2 months of adequate treatment for DM.

CONCLUSION

SCH is common among type 2 diabetic patients, especially in females. It is most commonly secondary to autoimmune thyroid disease. Microvascular complications are commonly observed in this group of patients with dual endocrinal disorder treating physicians should routinely screen SCH in patients with diabetes mellitus to prevent complications.

REFERENCES

10. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 2001;86:4585-90.
14. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: Scientific review and guidelines for diagnosis and management. JAMA 2004;291:228-38.