Prevalence of thyroid dysfunction among type 2 diabetic patients attending the Diabetes Clinic, National Hospital of Sri Lanka

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Abstract

Objective: To determine the prevalence of thyroid dysfunction (TD) and to identify risk factors which are associated with TD in Type 2 Diabetic (T2DM) patients attending the Diabetes Clinic, National Hospital of Sri Lanka

Method: A descriptive cross sectional study was carried out at the Diabetes Clinic, National Hospital of Sri Lanka. Study subjects were selected by simple random sampling method and data was collected using an interviewer administered data collection form. TD was assessed by performing 3rd generation TSH and when required FT4/FT3 levels were measured. Statistical analysis was done using Pearson's Chi-square test, Fisher exact test, Mann Whitney U test and Wilcoxon Rank Sum test and P value < 0.05 was considered as significant.

Results: TD was detected in 83 out of 393 T2DM subjects.The prevalence of TD among study subjects was 21.1% (95% CI:17.2-25.5%). The most common TD categories were subclinical hypothyroidism (9.4%, 95% CI:6.7-12.7%) and overt hypothyroidism (6.1%, 95% CI:3.9-8.9%). Subclinical hyperthyroidism and overt hyperthyroidism were detected only in 5.1% (95% CI:3.1-7.8%) and 0.5% (95% CI:0.1-1.8%) of cases respectively. The presence of TD was strongly associated with female sex (p<0.01) advancing age (p<0.01),the presence of goitre (p< 0.01) and a positive family history of thyroid disorder among 1st degree relatives (p=0.02).There was no association between the presence of TD and the duration of T2DM, presence of hypertension or chronic complications of DM, type of antidiabetic drugs used, current glycaemic control, body mass index (BMI) and total cholesterol level.

Conclusion: The prevalence of TD was 21.1% and higher prevalence was seen in T2DM patients with female sex, advancing age, presence of goitre and positive family history of thyroid disorder among 1st degree relatives.

Introduction

T2DM has become one of the major non communicable diseases worldwide and the prevalence has risen steadily over the past few decades. In Sri Lanka, the prevalence of T2DM in 2006 was 10.3% and the projected prevalence for the year 2030 is 13.9% (1).

The prevalence of TD among normal subjects varies according to the studied population. In a population-based study done in India on 971 adult subjects, the prevalence of overt and subclinical hypothyroidism was 3.9% and 9.4% respectively. Same study revealed that overt and subclinical hyperthyroidism was present in 1.3% and 1.6% of subjects respectively (2). In the NHANES III study, it was shown that 4.6% of the US population had hypothyroidism (0.3% overt and 4.3% subclinical) and 1.3% had hyperthyroidism (0.5% overt and 0.7% subclinical) (3).

Since both T2DM and TD are common diseases, researches were carried out to explore the possible association between these two endocrinopathies. The first report showing the association between diabetes and TD was published in 1979 (4). Since then several studies from different countries had been done to estimate the prevalence of TD among diabetic patients. The reported prevalence of TD among diabetic patients ranges from 12.3% to 32.4% (5-10). In addition, diabetic women are more frequently affected than men and hypothyroidism (either overt or subclinical) is more common than hyperthyroidism (8). Most of the studies demonstrated

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that the prevalence of TD was higher in diabetic population as compared to general population.

T2DM patients have an increased risk of developing cardiovascular disease which leads to significant mortality and morbidity. Multiple risk factor modification is considered as a key strategy in reducing the cardiovascular risk. TD also (including both subclinical hypothyroidism and hyperthyroidism) has also been linked to increased cardiovascular risk (11). A meta-analysis (including 25,977 participants, 2020 with subclinical hypothyroidism) showed an increased risk of coronary heart disease events and increased risk of cardiovascular and/or all-cause mortality at higher serum TSH concentrations (12). With regard to subclinical hyperthyroidism, a cross-sectional study (in 24,000 older patients) showed that the relative risk of atrial fibrillation in this group was 5.2 compared to euthyroid controls (13). Also a meta-analysis showed a significantly increased risk of all-cause mortality (HR 1.41, 95% CI 1.12-1.79) in patients with subclinical hyperthyroidism (14). Therefore it is reasonable to postulate that the combination of both T2DM and TD may have added cardiovascular risk. So it might be possible to reduce the cardiovascular risk in this subset of T2DM patients by early identification and treatment of TD.

On the other hand, few studies have explored the effects of subclinical thyroid dysfunction on microvascular complications of diabetes. In one cross-sectional study which included 588 subjects, subclinical hypothyroidism was associated with a higher frequency of nephropathy and incident cardiovascular events in patients with T2DM (15). In another study of 1170 subjects, type 2 diabetic patients with subclinical hypothyroidism had a higher prevalence of retinopathy especially the sight-threatening form, when compared with their type 2 diabetic euthyroid counterparts (16).

The relatively high prevalence of both endocrinopathies and adverse impact of TD on diabetes and its complications highlight the importance of screening diabetic patients for TD. However, screening has been currently recommended only in children and adolescents with type 1 diabetes. With regards to adults with T2DM, there is no consensus as to whether screening for thyroid disorders should be mandatory.

To the best of our knowledge no studies have been done to estimate the prevalence of TD in T2DM patients in Sri Lanka. Therefore, the main objective of the study is to determine the prevalence of TD in T2DM patients attending the Diabetes Clinic, National Hospital of Sri Lanka. We also tried to identify any risk factors which are associated with TD in the above population.

Materials and methods

This was a descriptive cross sectional study carried out at the Diabetes Clinic, National Hospital of Sri Lanka. Ethical approval was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Colombo. Patients were recruited to the study after obtaining informed written consent.

T2DM patients who were above the age of 20 years and who had at least 3 previous clinic visits were included in the study. Diagnosis of diabetes was based on American Diabetes Association criteria (17). Simple random sampling method was used to select the subjects for the study. Data was collected through an interviewer administered data collection form. Medical officers at the clinic filled this form by questioning the patient and going through their previous health records. This data included the duration of diabetes, presence of diabetic complications and other comorbid conditions (eg. hypertension, dyslipidaemia), current anti-diabetic medications, past history of thyroid disorder and family history of thyroid disorder among first degree relatives. Patients who reported taking thyroxine, carbimazole, methimazole or propylthiouracil, and those with a history of thyroidectomy or radioactive iodine treatment were identified as having TD.

Anthropometric measurements (height and weight) were measured according to the standard methods using calibrated equipment (18). All these measurements were done by two specially trained diabetes nursing officers at the clinic. Body mass index was calculated by using the following formula – BMI = weight in kgs / (height in meters)^2.

Blood pressure was recorded as the mean of two consecutive measurements in the sitting position taken 10 minutes apart. Hypertension was defined as BP levels ≥ 140/90 mm Hg or the use of anti-hypertensive drugs. A trained medical officer determined the presence of goitre by palpation method.

Fasting venous blood samples were obtained for glucose, total cholesterol and 3rd generation TSH estimations from all patients who participated in the study. 3rd generation TSH assay was done at the biochemical laboratory of Faculty of Medicine, Colombo using chemiluescence method. Further evaluation with free T4 (free T3 if necessary) was done using the same blood sample in patients who had TSH values which were outside the normal range.

Thyroid dysfunction prevalence for the entire study group and each subcategory were separately identified and 95% confident intervals were determined assuming normal distribution and exact binomial distribution. Group comparisons were performed using Pearson's Chi-square

test, Fisher exact test, Mann Whitney U test and Wilcoxon rank sum test as appropriate. A P value < 0.05 was considered significant. Analysis was by the SAS System (version 9.0; Cary, USA).

Results

This study included 405 subjects with T2DM who were attending the Diabetic Clinic, National Hospital of Sri Lanka. Data from 393 subjects were used for statistical analysis and 12 patients were excluded because they had not given blood samples for the estimation of TSH. The basic (disease and treatment) characteristics of T2DM study subjects are shown in Table 1. The median age was 57 years and the ages ranged from 25 to 80 years. The median duration of diabetes was 8 years. Among study subjects, 276 (70%) had hypertension and 341 (87%) were on statins. The microvascular and macrovascular complications were present in 123 (31%) and 33 (8%) patients respectively.

Eighty three patients out of 393 diabetic patients had TD. Therefore the prevalence of TD among study subjects was 21.1% (95% CI:17.2 - 25.5%). The prevalence of TD among females and males were 24.7% and 8.9% respectively. A significantly higher prevalence of TD was observed in females than in males ($p<0.01$).

The distribution of TD into four main categories was shown in Table 2. The most common TD category was subclinical hypothyroidism (9.4%). This was followed by overt hypothyroidism (6.1%). Subclinical hyperthyroidism and overt hyperthyroidism were detected in 5.1% and 0.5% of cases respectively.

Among 83 patients with TD, only 16 (19.3%) patients were already diagnosed as having some form of TD (clinical hypothyroidism or clinical hyperthyroidism). All the subjects with subclinical TD were newly detected during the study.

In TD group, a goitre was present in 20.5% of subjects. In contrast, patients with normal TSH had goitres only in 5.5%. There was a significant association between TD and the presence of goitre ($p < 0.01$) in T2DM patients. Higher percentage of subjects in TD group (10.8%) gave a positive family history of thyroid disorder among 1st degree relatives when compared with euthyroid group (4.2%) and this association was also statistically significant ($p= 0.02$).

Table 1. Basic (disease and treatment) characteristics of T2DM study subjects

Characteristics of T2DM subjects		*M(IQR) or N(%)*
Median age (years)		57 (50-62)
Gender female		303 (77%)
Duration of diabetes (years)		8 (5-13)
Presence of diabetic complications	microvascular	123 (31%)
	macrovascular	33 (8%)
Presence of hypertension		276 (70%)
Statin use		341 (87%)
Anti-diabetic drug use	Metformin	366 (93%)
	Sulphonylureas	211 (54%)
	Insulin	133 (34%)
Acarbose		36 (9%)
Glitazone		14 (4%)
Glycaemic control	Mean FBS (mmol/L)	6.6 (5.2 - 7.8)
	Mean PPBS (mmol/L)	7.7 (6.3-10)
Total cholesterol (mg/dL)		188 (164 - 214)
BMI (kg/m^2)		26.2 (23.3-28.9)
Presence of goitre		34 (8.6%)
Past history of thyroid disorder		35 (9%)
Family history of thyroid disorder in a 1st degree relative		22 (6%)
TSH value (mU/L)		1.29 (0.8 - 2.31)

M: Median, IQR: Interquartile range, N: Number, %: Percent

Table 2. Prevalence of thyroid dysfunction according to main categories

Category	*Number of patients*	*Prevalence (95% CI)*
Overt hypothyroidism	24	6.1% (3.9-8.9)
Subclinical hypothyroidism	37	9.4% (6.7-12.7)
Overt hyperthyroidism	2	0.5% (0.1-1.8)
Subclinical hyperthyroidism	20	5.1% (3.1-7.8)
Total	83	21.1% (17.2-25.5)

The median age was significantly higher in T2DM patients with TD than those without TD (60 vs 56, $p < 0.01$). The highest prevalence of TD (38.1%) was observed in patients aged more than 65 years. The prevalence of TD in age groups 50 to 64 years and aged less than 50 years were 20.6% and 12.3 % respectively.

Detection of TD was not associated with duration of diabetes (p=0.42), presence of hypertension (p=0.20), or recent glycaemic control (p=0.17 and 0.12) based on FBS and PPBS respectively. Also the presence of microvascular (p=0.31 for retinopathy, p=0.80 for nephropathy and p=0.28 for neuropathy) and macrovascular complications (p=0.76 for IHD) of diabetes wasn't significantly associated with TD among our T2DM patients. There were no patients with TD who had either CVA or PVD. Also this study demonstrated that there was no association between the presence of TD and being on different types of anti-diabetic medications (p=0.26 for metformin, p= 0.17 for sulphonylureas and p=0.81 for insulin, p=0.49

Table 3. Clinical and laboratory characteristics of T2DM patients with thyroid dysfunction 83 (21.1%) vs without thyroid dysfunction 310 (78.9%)

Characteristics of T2DM subjects	*Diabetic subjects without thyroid dysfunction M (IQR) or N(%)*	*Diabetic subjects with thyroid dysfunction M (IQR) or N(%)*	*P value*
Age (years)	60 (55-65)	56 (49-61)	<0.01
Gender Female	75 (90.4%)	228 (73.5%)	<0.01
Male	8 (9.6%)	82 (26.5%)	
Duration of diabetes (years)	8 (6-14)	8 (5-13)	0.42
Presence of goitre	17 (20.5%)	17 (5.5%)	<0.01
Family history of thyroid disorder in a 1st degree relative	9 (10.8%)	13 (4.2%)	0.02
Presence of hypertension	63 (75.9%)	213 (68.7%)	0.20
Anti-diabetic drug use: Metformin	75 (90.4%)	291 (93.9%)	0.26
Sulphonylureas	39 (47.0%)	172 (55.5%)	0.17
Insulin	29 (34.9%)	104 (33.5%)	0.81
Acarbose	7 (8.4%)	29 (9.3%)	0.80
Glitazone	4 (4.8%)	10 (3.2%)	0.49
BMI (kg/m^2)	26.0 (23.2-28.7)	26.8 (23.9-29.2)	0.31
Glycaemic control: FBS (mmol/L)	6.2 (5 - 7.8)	6.5 (5.65 -7.55)	0.17
PPBS (mmol/L)	7.7 (6.2 - 9.8)	8.2 (6.8 - 10.5)	0.12
Total cholesterol (mg/dL)	184 (164 - 212)	196 (160 - 224)	0.35
TSH value (mU/L)	1.2 (0.85 -1.86)	4.4 (0.26-6.56)	<0.01

for glitazone and p=0.80 for acarbose). Also data analysis did not reveal any association between BMI and the presence of TD (p=0.31).

Total cholesterol level was not associated with the detection of TD among T2DM patients (p=0.35) and this observation was most probably due to the balancing effect on total cholesterol by 2 distinct categories of TD (hyperthyroidism and hypothyroidism) which have completely opposite effects on the lipid profile. In fact, further sub analysis revealed that subjects with hypothyroidism (overt/subclinical) had a statistically significant higher median total cholesterol concentration than their hyperthyroid counterparts (200 vs 164 mg/dL, p=0.02).

Discussion

Our study showed that the prevalence of TD among Sri Lankan T2DM patients attending outpatient clinic was 21.1%. Previous studies from various regions of the world, assessing the prevalence of TD among diabetic patients have shown a wide range of values. However, one consistent observation across all these studies was that there was a higher prevalence of TD in diabetic subjects when compared with normal population. A study from Spain which included 318 subjects reported 32.4% prevalence of TD among type 2 diabetic patients (5). Another Italian study (6) also showed a higher prevalence (31.4%) of TD in diabetic population. In contrast, a study by Perros et al. (7) from Scotland found that the prevalence of TD among type 2 diabetic patients was 13.4%. A Greek study (8) demonstrated a TD prevalence of 12.3% among their diabetic patients. In another study by Akbar et al (9) in Saudi Arabia the association between thyroid dysfunction and type 2 DM was investigated and TD was found in 16% of diabetics. When the data from South Asian countries were considered, an Indian study showed a prevalence of 31.2 % (10). However, the major drawback of this study was the lack of randomization which can lead to the overestimation of prevalence. However, we also found a relatively higher prevalence of TD among our T2DM patients after proper randomization.

Although the exact cause for the higher prevalence of TD among our T2DM population was not known, one of the possible major contributory factors might be the higher degree of insulin resistance. Higher levels of circulating insulin associated with insulin resistance have shown a proliferative effect on thyroid tissue resulting in larger thyroid size with increased formation of nodules (19,20) which can result in TD.

In our T2DM patients, the most common TD categories were subclinical hypothyroidism (9.4%) and overt hypothyroidism (6.1%). Both overt and subclinical hyperthyroidism were seen less frequently. Most of the other studies (6,10) also have shown similar pattern of TD among diabetic patients. Community based studies among normal population in India (21) and USA (3) also demonstrated a similar trend of TD. In general, the data indicate that the presence of T2DM only increase the prevalence without changing the pattern of TD.

It is a well-known fact that both hypothyroidism and hyperthyroidism are seen more commonly in females than in males. In this study, the prevalence of TD among females was significantly higher (24.7% vs 8.9%) and female sex is a risk factor for having TD among T2DM patients. In our study, the prevalence of goitre among study subjects was 8.6%. A community based Sri Lankan study showed that the prevalence of goitre was 6.5% (22). Increased thyroid volume and nodularity due to high insulin levels secondary to insulin resistance and higher median age (57 vs 38 years) may be the most probable explanations for the slightly increased prevalence of goitre observed in our study. As with normal population, the presence of a goitre or family history of thyroid disorder in a 1st degree relative is a risk factor for having TD among T2DM patients.

Majority of patients with overt hypothyroidism and significant number of patients with subclinical hypothyroidism, have high serum total and LDL cholesterol concentrations (23). In contrast, patients with hyperthyroidism have changes in lipid metabolism generally opposite to those described above for hypothyroidism. Serum total and LDL cholesterol concentrations tend to be low (24). In keeping with this observation, hypothyroid subjects (overt/subclinical) in our study had a statistically significant higher median total cholesterol concentration than their hyperthyroid counterparts (200 vs 164 mg/dL, p=0.02).

Several studies have shown that TD was associated with increased cardiovascular risk and mortality (11). However the data from our study indicated that the presence of ischaemic heart disease was not considerably higher in TD group when compared with euthyroid diabetic patients (8.4% vs7.4%, p=0.76).

Conclusion

This study highlights the high prevalence (21.1%) of TD among T2DM patients followed up at the Diabetic Clinic, National Hospital of Sri Lanka and the strong association of TD with female sex, advancing age, presence of goitre and a positive family history of thyroid disorder among 1st degree relatives. Based on this data, we emphasize the importance of the screening for TD in selected patients with T2DM. Also this study would provide baseline data to plan management strategies for the above group of patients and to conduct future research on TD among Sri Lankan T2DM patients in a national level.

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