Original Research Article

Double Trouble: an observational study of thyroid dysfunction in South Indian subjects with type 2 diabetes

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Abstract

Objective: Studies conducted in subjects with type 2 diabetes have shown increased prevalence of overt hypothyroidism and subclinical hypothyroidism. Hence, we designed a study to find out the prevalence of thyroid dysfunction in south Indian subjects with type 2 diabetes. **Research Design and Methods:** 400 subjects with type 2 diabetes attending the out-patient department of Karnataka Institute of Endocrinology and Research, Bangalore were randomly selected. 200 relatives who accompanied the subjects without diabetes were recruited as controls. BMI, waist circumference, blood pressure, fasting plasma glucose, post prandial plasma glucose, HbA1c, lipid profile, and thyroid profile of these subjects were determined. **Results:** 400 subjects with type 2 diabetes and 200 subjects without diabetes were included in the study. They were in the age group of 25 to 75 years. Thyroid dysfunction was present in 13% of non diabetic controls. Subclinical hypothyroidism was present in 7%, overt hypothyroidism in 5% and hyperthyroidism in 1% of the controls. Thyroid dysfunction was present in 24% of subjects with type 2 diabetes. Subclinical hypothyroidism was present in 11.25%, overt hypothyroidism in 12% and hyperthyroidism in 0.75% of the 400 subjects with type 2 diabetes. **Conclusions:** Hypothyroidism especially subclinical hypothyroidism is more common in south Indian subjects with type 2 diabetes. Hence, it is indispensable to investigate for thyroid dysfunction in subjects with type 2 diabetes. Failure to recognize the presence of thyroid dysfunction may be a primary cause of poor glycemic control often encountered in some subjects with type 2 diabetes, despite appropriate anti diabetic therapy. This highlights the need for the routine evaluation of thyroid function in subjects with type 2 diabetes.

Keywords: Hypothyroidism, Diabetes, Hyperthyroidism, Insulin.

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Introduction

Diabetes mellitus (DM), a common endocrine metabolic disorder, is a leading cause of death worldwide [1]. It is characterized by hyperglycemia resulting from a variable interaction of hereditary and environmental factors and is due to the combination of insulin resistance and defective secretion of insulin by pancreatic β-cells or both [2]. 415 million people worldwide have diabetes in 2015; by 2040 this will rise to 642 million. The number of people with type 2 diabetes is increasing in every country. 80% of people with diabetes live in low and middle-income countries. India has 69.2 million people with type 2 diabetes and it will increase to 123.5 million by 2040 [3]. Thyroid disorders are also very common in the general population and it is second only to diabetes as the most common endocrine disorder. As a result, it is very common for an individual to be affected by both thyroid diseases and diabetes. The first report showing the association between diabetes and thyroid dysfunction were published in 1979 [4, 5]. Since then, several studies have estimated the prevalence of thyroid dysfunction among diabetes patients to be varying from 2.2 to 17% [6, 7]. Till date, not much data is available about thyroid diseases in south Indian subjects with type 2 diabetes. The aim of the present study was to evaluate the prevalence of thyroid dysfunction in south Indian subjects with type 2 diabetes.

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Both insulin and thyroid hormones are involved in cellular metabolism and excess and deficit of any one can result in functional derangement of the other [8]. Thyroid disease is a pathological state that adversely affects diabetic control and is commonly found in most forms of DM which is associated with advanced age in type 2 diabetes and autoimmune diseases in type 1diabetes. DM appears to influence thyroid function at two sites; firstly at the level of hypothalamic control of TSH release and secondly at the conversion of T4 to T3 in the peripheral tissue.

Marked hyperglycemia causes reversible reduction of the activity and hepatic concentration of T4-5-deiodinase, low serum concentration of T3, elevated levels of reverse T3 and low, normal, or high level of T4 [9]. Since thyroid hormone regulates metabolism and diabetes can alter metabolism of food, the metabolism may be further affected by the combination of thyroid disease and diabetes.

Research Design and Methods

400 subjects with type 2 diabetes attending the out-patient department of Karnataka Institute of Endocrinology and Research, Bangalore were randomly selected. The 200 relatives without diabetes who accompanied diabetic subjects were selected as controls. BMI, waist circumference, blood pressure, fasting plasma glucose, post prandial plasma glucose, HBA1c, lipid profile, and thyroid profile of these subjects were determined.

Overt hypothyroidism was defined as a clinical syndrome of hypothyroidism associated with elevated TSH and decreased serum levels of T_4 or T_3. Subclinical hypothyroidism was defined as a condition without typical symptoms of hypothyroidism, elevated TSH (>4.5 μU/mL), and normal circulating thyroid hormones. Overt hyperthyroidism was defined as a condition with elevated T3 and T4, TSH <.01 μU/Ml with symptoms of hyperthyroidism [10]. Body mass index (BMI) was defined as weight in kilogram divided by height in square meters.

Statistical Methods- Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1were used for the analysis of the data. Microsoft word and Excel have been used to generate graphs, tables etc**.**

Analysis of variance (ANOVA) was used to find the significance of study parameters between three or more groups of patients, Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Levens test for homogeneity of variance was performed to assess the homogeneity of variance.

Results

400 subjects with type 2 diabetes were studied and 200 subjects without diabetes accompanying the patients were used as controls. The age distribution of the type 2 diabetes subjects ranged from 25 to 75 years. Body mass index of type 2 diabetes subjects were <25 in 29.5%, 25 to 30 in 44.5% and >30 in 26%. Waist circumference of the subjects were less than 80 cms in 9.5%, 80–90 cms in 27.5%, 90-100 cms in 36% and >100 in 27% (Table 1).

Family history of the subjects with type 2 diabetes showed that in 20.3% of the subjects have a father with diabetes, and another 20.3% had mother with diabetes. Both parents had diabetes in 11.5%. Positive family history was found in 52% of the type 2 diabetes subjects. Duration of diabetes ranged from 0 to >20 years. 9% were newly diagnosed. 29.25% had duration 0f <5 years, 22% had duration of 5 to 10 years and 39.75% had duration of >10 years. 45.8% of the diabetes subjects had hypertension in this study.

Thyroid dysfunction was present in 24% of type 2 individuals with diabetes. Subclinical hypothyroidism was present in 11.25%, overt hypothyroidism in 12% and hyperthyroidism in 0.75% of the 400 type 2 diabetes subjects (Table 3). In the overt hypothyroidism group, 70.8% were females and in the subclinical hypothyroid group, 40% were females.

Thyroid dysfunction was present in 13% of non diabetic controls. Subclinical hypothyroidism was present in 7%, overt hypothyroidism in 5% and hyperthyroidism in 1% of 200 non diabetic controls (Table 3). Thyroid dysfunction was

associated with the longer duration of diabetes more than 5 years which was statistically significant. (Table 4) There was no statistically significant difference in the plasma glucose variables and HbA1C between the thyroid groups (Table 5). A statistically significant association was found among the different thyroid variables (Table 6).

There was no statistical significant difference between total cholesterol, triglycerides, HDL, LDL levels between normal, subclinical and overt hypothyroidism in type 2 diabetes individuals in our study (Table 7).

Table-1: Presents the sex and age distribution of subjects with and without diabetes.

Group	Sex	Percentage	Mean age in years	Mean BMI	Mean waist circumference in cms
Type 2 subjects with diabetes N= 400	Male Female	59 41	55.85±9.6	27.2±9.6	93.64±11.12
Subjects without diabetes N=200	Male Female	59 41	55.1±8.9	26.89±8.9	92.59±11.02

Table-2: Age distribution of individuals studied.

Age in years	Number of patients	%
30-40	23	5.9
40-50	76	19.3
50-60	153	38.5
60-70	111	28.0
>70	29	7.7
Total	**400**	**100.0**

Table-3: Comparison of Thyroid dysfunction in type 2 diabetes individuals and controls.

Diagnosis	Number of diabetes patients	Percentage of diabetes patients	Number of controls	Percentage of controls
Euthyroid	304	76	174	87
Sub clinical hypothyroid	45	11.25	14	7
Hypo thyroid	48	12.0	10	5
Hyper thyroid	3	0.75	2	1
Total	**400**	**100.0**	**200**	**100**

Table-4: Comparison of Clinical variables in type 2 diabetic subjects.

Clinical variables	Diagnosis			P value
	Euthyroid	Sub clinical Hypothyroid	Overt Hypo thyroid	
Age in years	54.51±10.53	56.26±9.27	56.79±10.29	0.272
BMI (kg/m^2)	26.61±4.16	27.34±4.69	27.65±4.34	0.208
Waist circumference (cm)	93.41±11.04	93.82±11.97	93.70±11.04	0.969
Duration of diabetes in years	7.91±7.07	11.48±7.96	8.76±7.23	0.019*

Table-5: Comparison of plasma glucose parameters according to diagnosis in type 2 diabetic subjects.

Glucose parameters	Diagnosis			P value
	Euthyroid	Sub clinical Hypothyroid	Hypo thyroid	
FPG(mg/dl)	177.58±70.62	171.60±62.63	158.69±59.77	0.207
PPPG (mg/dl)	280.46±99.70	272.94±85.06	248.54±85.17	0.104
HBA1c(%)	9.05±2.21	8.95±2.17	8.38±1.90	0.140

Table-6: Comparison of thyroid parameters subjects with type 2 diabetes.

Thyroid parameters	Diagnosis			P value
	Euthyroid	Sub clinical Hypothyroid	Hypo thyroid	
T3	1.77±0.38	1.78±0.33	1.59±0.33	0.006**
T4	105.84±22.78	103.01±23.47	103.19±29.67	0.650
TSH	2.22±1.07	6.53±1.24	8.63±13.87	<0.001**

Table-7: Comparison of Lipid parameters according to diagnosis.

Lipid parameters	Diagnosis			P value
	Euthyroid	Sub clinical Hypothyroid	Hypo thyroid	
Total cholesterol (mg/dl)	180.57±43.09	175.76±47.33	170.47±41.36	0.293
Triglycerides (mg/dl)	176.07±112.39	164.41±99.56	142.56±48.61	0.113
HDL(mg/dl)	40.24±9.48	38.09±7.99	42.02±7.77	0.163
LDL(mg/dl)	103.55±33.78	106.18±42.02	103.81±43.26	0.927
VLDL(mg/dl)	35.22±22.67	32.88±19.92	28.38±9.87	0.116

Discussion

Type 2 diabetes mellitus is a complex metabolic disorder with multiple pathophysiologic abnormalities. Insulin resistance in muscle/liver and β-cell failure represents the core defects [11, 12]. β-Cell failure occurs much earlier in the natural history of T2DM and is more severe than previously thought [13, 14]. Subjects in the upper tertile of impaired glucose tolerance (IGT) are maximally/near-maximally insulin resistant and have lost >80% of their β-cell function. In addition to muscle, liver, and β-cells ("triumvirate") adipocytes (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), α-cells (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (insulin resistance and neurotransmitter dysregulation) play important roles in development of glucose intolerance in T2DM individuals [15]. Collectively, these eight players comprise the "ominous octet" and dictate that *1*) multiple drugs used in combination will be required to correct the multiple pathophysiological defects, *2*) treatment should be based upon reversal of known pathogenic abnormalities and not simply on reducing HbA_{1c}, and *3*) therapy must be started early to prevent/slow progressive β-cell failure that is well established in IGT subjects. A treatment paradigm shift is recommended in which combination therapy is initiated with agents that correct known pathogenic defects in T2DM and produce durable reduction in HbA_{1c} rather than just focusing on the glucose-lowering ability of the drug.

The prevalence of hypothyroidism in India is 11%, compared with only 2% in the UK and 4·6% in the USA. Compared with coastal cities (e.g., Mumbai, Goa, and Chennai), cities located inland (e.g., Kolkata, Delhi, Ahmedabad, Bangalore, and Hyderabad) have a higher prevalence (11·7% vs. 9·5%). According to Ambrish Mithal, chairman of the Medanta Division of Endocrinology and Diabetes (Gurgaon, India), the reason behind the higher mean thyroid stimulating hormone concentration and range in India compared with western countries is possibly linked to long-standing iodine deficiency in the country, which has only been partly corrected over the past 20 years. The highest prevalence of

hypothyroidism (13·1%) is noted in people aged 46–54 years, with people aged 18–35 years being less affected (7·5%). In Western countries the most common cause of primary hypothyroidism is autoimmune thyroiditis. However, in many parts of the world, iodine deficiency remains an important cause [16].

Several population studies have shown higher prevalence of thyroid dysfunction in diabetes. This close link has been attributed to a common genetic background [17]. The association has clinical implication since thyroid hormones have profound effects in the regulation of glucose homeostasis. Thyroid hormones are known to modify of circulating insulin levels and counter regulatory hormones, intestinal absorption, hepatic production and peripheral tissues uptake of insulin. They are also involved in stimulation of gluconeogenesis and glycogenolysis [18]. Ashok kurana et al in their study showed that there was a high prevalence (16%) of thyroid disorders in patients of type 2 diabetes mellitus. Most common thyroid disorder found was subclinical hypothyroidism (7.5%) followed by hypothyroidism (4.5%) which was followed by hyperthyroidism (2.5%) and subclinical hyperthyroidism (1.5%) [19]. Navneet Agrawal et al in their study found that 27.8% had associated thyroid dysfunction, out of that 15.2% had subclinical hypothyroidism, 10.6% had clinical hypothyroidism and 2% had hyperthyroidism [20]. Laloo Demitrost et al in their study found out of the 202 type 2 DM patients included in the study, 61 are males and 141 are females.

The mean duration of type 2 DM is 62 months (just more than 5 years). It is found that 139 (68.8%) are euthyroid, 33 (16.3%) have subclinical hypothyroidism, 23 (11.4%) have clinical hypothyroidism, 4 (2%) have subclinical hyperthyroidism and 3 (1.5%) are hyperthyroidism cases. This study showed prevalence of 31.2% thyroid dysfunction in type 2 diabetes [21]. Gurjeet Singh et al in their study found 30% thyroid dysfunction among type 2 diabetes. Hypothyroidism was present in 23.75%, (15% subclinical hypothyroidism and 8.75% Primary hypothyroidism) and hyperthyroidism was present in 6.25% (all primary hyperthyroidism) of diabetic subjects [22]. Athanasia papazafiropoulou et al, in their study showed that the prevalence of thyroid dysfunction among Greek diabetic patients attending an outpatient clinic was 12.3%. Diabetic women were more frequently affected than men [23].

Table-8: Comparison of different studies regarding prevalence of thyroid dysfunction in Indian type 2 diabetes patients.

Study	Thyroid dysfunction	Subclinical hypothyroidism	Overt hypothyroidism	Hyperthyroidism
Ashok khurana et al	16	7.5	4.5	2.5
Navneet Agrawal	27.8	15.2	10.6	2
Laloo demitrost	31.2	16.3	11.4	1.5
Gurjeet Singh et al	30	15	8.75	6.25
Present study	24	11.25	12	0.75

We have compared the present study with other studies in the table 8 and the prevalence of thyroid dysfunction is almost similar. Overt and subclinical hypothyroidism is more common in type 2 diabetes patients. The present study reports the prevalence of thyroid dysfunction in 24%, out of which subclinical hypothyroidism in 11.25%, overt hypothyroidism in 12% and hyperthyroidism in 0.75% of 400 type 2 diabetes subjects studied.

Thyroid dysfunction was present in 13% of non diabetic controls, out of which Subclinical hypothyroidism was present in 7%, overt hypothyroidism in 5% and hyperthyroidism 1% of 200 non diabetic controls. This corresponds to the prevalence data reported in the above quoted studies. This highlights the fact that all diabetic population should be screened for thyroid dysfunction.

Conclusions

Hypothyroidism and subclinical hypothyroidism are more common in South Indian type 2 diabetes individuals and so it is necessary to investigate for thyroid dysfunction in type 2 diabetes subjects. Failure to recognize the presence of abnormal thyroid hormone level in type 2 diabetes may be a primary cause of poor

management often encountered in some treated type 2 diabetics. There is therefore need for the routine assay of thyroid hormones in type 2 diabetics.

Abbreviations

DM- Diabetes mellitus.

BMI- Body mass index

TSH- Thyroid stimulating hormone.

HDL- high density lipoprotein

LDL- Low density lipoprotein

VLDL- Very low density lipoprotein

FPG- Fasting plasma glucose

PPPG- Postprandial plasma glucose

HBA1C- Glycosylated hemoglobin

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