A Study of Prevalence of Subclinical Hypothyroidism in Patients of Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Type 2 diabetes mellitus characterized by hyperglycemia that resulting from the combination of resistance to insulin action, insufficient insulin secretion, and excessive or inappropriate glucagon secretion. Study aimed to see the prevalence of subclinical thyroid disorders in patients with type 2 diabetes mellitus.

Material and methods: It is study for a period of 2years, a total of 100 patients (50 male and 50 female patients). Patients were examined for signs of hypothyroidism and hyperthyroidism. All patients were subjected to following investigations.FBS, PPBS, HbA1C, Serum freeT3, freeT4, TSH, fasting lipid profile, ECG, 2D Echocardiography, Ophthalmological evaluation.

Results: Difference observed between the two groups in duration of diabetes mellitus and serum TSH level is statistically significant, but not in serum HbA1C level. Diabetic neuropathy was present in 15.4% of SCH patients. Both of the 2 patients had bilateral lower limb sensory - motor polyneuropathy. All the 4 patients with LV diastolic dysfunction on 2D echocardiography, were known cases of systemic hypertension on treatment. Thyroid autoimmunity is present in 85% of SCH patients with type 2 DM, with higher frequency in women than in men.

Conclusion: In this study, the percentage of subclinical hypothyroidism in type 2 DM patients is 13%, whereas the percentage of subclinical hyperthyroidism is 0. Female patients are more frequently affected by SCH than male patients.

Keywords: Diabetic mellitus, hypothyroidism, Subclinical thyroid disorders.

INTRODUCTION

There is a deep underlying relation between diabetes mellitus and thyroid dysfunction.[1,2] A plethora of studies have evidenced an array of complex intertwining biochemical, genetic, and hormonal malfunctions mirroring this pathophysiological association.[2,3] 5′ adenosine monophosphate-activated protein kinase (AMPK) is a central target for modulation of insulin sensitivity and feedback of thyroid hormones associated with appetite and energy expenditure.[3]

Hypothyroidism is a common endocrine disorder resulting from deficiency of thyroid hormone. Throid dysfunctions increasingly found in the T2DM patients and prevalence is around 13.4%. The presence of thyroid dysfunction may affect DM control and plasma lipid metabolism, increases risk of CV disease and atherosclerosis.

Subclinical hypothyroidism is an asymptomatic state in which reduction of thyroid activity is compensated by elevated TSH to maintain euthyroid state. The studies have clearly shown that patients with SCH have impaired LV diastolic dysfunction at rest and systolic dysfunction during activity.

Early detection in conjuction with adequate treatment, prevents the progression of the disease, which if not detected in time, can cause progressive and disabling consequences of the disease.

Diagnostic criteria by the American Diabetes Association (ADA) include the following 4:

- A fasting plasma glucose (FPG) level of 126 mg/dL (7.0 mmol/L) or higher, *or*
- A 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75-g oral glucose tolerance test (OGTT), *or*
- A random plasma glucose of 200 mg/dL (11.1 mmol/L) or higher in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

Whether a hemoglobin A1c (HbA1c) level of 6.5% or higher should be a primary diagnostic criterion or an optional criterion remains a point of controversy.

Nowhere is the diabetes epidemic more pronounced than in India as the World Health Organization (WHO) reports show that 32 million people had diabetes in the year 2000.[5] The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025.[6,7]

Third-generation thyroid-stimulating hormone (TSH) assays are generally the most sensitive screening tool for primary hypothyroidism[1] If TSH levels are above the reference range, the next step is to measure free thyroxine (T4) or the free thyroxine index (FTI), which serves as a surrogate of the free hormone level. Routine measurement of triiodothyronine (T3) is not recommended.

Results in patients with hypothyroidism are as Elevated TSH with decreased T4 or FTI, Elevated TSH (usually 4.5-10.0 mIU/L) with normal free T4 or FTI is considered mild or subclinical hypothyroidism. Study aimed to see the prevalence of subclinical thyroid disorders in patients with type 2 diabetes mellitus.

MATERIAL AND METHODS

This was a descriptive study for a period of 2 years, a total of 100 patients (50 male and 50 female patients). Method of collection of data was by evaluation, which were done by taking detailed history, clinical examination and laboratory investigations using proforma designed for this study. Patients were examined for

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signs of hypothyroidism and hyperthyroidism.

Inclusion criteria: Patients who have been detected with diabetes mellitus after 40 years of age.

Exclusion criteria: Known cases of thyroid disease. Patients have diabetes mellitus before 40 years of age, patients on drugs which alter thyroid hormonal levels, seriously ill patients. Diabetic patients who are previously diagnosed with chronic conditions known to alter thyroid function, like hepatic dysfunction and psychiatric illness, Pregnant women with DM, Patients refusing to give informed consent for the study.

In all cases, a detail clinical history was taken. Emphasis was given to symptoms of hypothyroidism and hyperthyroidism.

Clinical examination was done in detail. General physical and systemic examination was done in all patients. Patients were examined for signs of hypothyroidism and hyperthyroidism.

All patients were subjected to following investigations.FBS, PPBS, HbA1C, Serum freeT3, freeT4, TSH, fasting lipid profile, ECG, 2D Echocardiography. Anti-TPO antibodies were measured by immunoenzymatic assay using 0.5ml of patient's serum sample. Values > 9.0 IU/ml were interpreted as elevated.

Subclinical hypothyroidism was defined as serum TSH > 4.2 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).

Age group in years	Total number of patients	Sub clinical hypothyroidism
<51 years	19	1(5.3%)
51-60 years	48	7(14.6%)
>60 years	33	5(15.1%)

Table-1: Demographic distribution

Thyroid function	No. of patients	Percentage
Euthyroidism	84	84
Subclinical hypothyroidism	13	13
Subclinical hyperthyroidism	0	0
Overt hypothyroidism	3	3
Overt hyperthyroidism	0	0
Total	100	100

Table-2: Division according to thyroid function tests

STATISTICAL ANALYSIS

In the present study, the data collected 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 are compared using student's t test for independent samples and the difference is considered statistically significant when the p value <0.05.

RESULTS

Study consist of total 100 patients of type 2 Diabetes Mellitus underwent thyroid function test including serum free T3, free T4, and TSH Division of study sample based on thyroid function.

SCH was present in 5.3% of patients of age below 51 years, 14.6% of patients of age 51 to 60 years, and 15.1% of patients of age above 60 years.

The mean age of SCH patients was 58.62 (SD ±5.47) years, whereas the meanage in euthyroid patients was 56.98 (SD ±7.49) years, the difference not being statistically significant (p value: 0.304).

Euthyroid patients are 84% most common group and followed by sub clinical hypothyroidism 13%.

Statistically significant difference was observed between the two groups in duration of DM (p value =<0.05), serum TSH level (p value-=<0.05), but not in serum HbA1C level

Macrovascular complications of DM

There was no evidence of peripheral arterial disease or

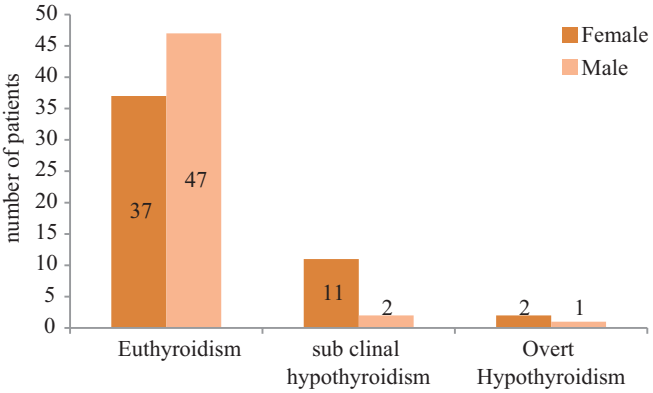

Figure-1: Gender distribution of thyroid dysfunction.

Study Variable	SCH patients	Mean Value	Standard Deviation	P value
Duration of DM	with microvascular complication	8.75 yrs	±2.54	0.002*
	without microvascular	3.45yrs	±1.80	
Serum HbA_{1C}	with microvascular complication	7.59 %	±2.15	0.929
	without microvascular complication	7.12 %	±1.58	
Serum TSH	with microvascular complication	7.54 µIU/ml	±1.34	0.004*
	without microvascular complication	4.81 µIU/ml	±0.55	
*p value=<0.05 is significant				

Table-3: Microvascular complications of Diabetes Mellitus

2D echocardiography	Number of patients	Percentage
Within normal limits	9	69.2%
LV diastolic dysfunction	2	15.4%
LV diastolic dysfunction + Concentric LV hypertrophy	2	15.4%

Table-4: Cardiac imaging of SCH patients

Study variable	Patients	No. of patients	Mean value	Standard Deviation	P value
FBS(mg%)	SCH	13	148.23	±37.77	0.123
	Euthyroid	84	157.04	±60.27	
PLBS(mg%)	SCH	13	240.30	±65.06	0.154
	Euthyroid	84	242.09	±67.8	
HbA1C (%)	SCH	13	7.84	±1.07	0.178
	Euthyroid	84	8.09	±2.15	
Serum Total cholesterol	SCH	13	175.69	±28.05	0.188
	Euthyroid	84	164.35	±32.73	
Serum LDL (mg%)	SCH	13	102.30	±27.3	0.352
	Euthyroid	84	94.64	±28.87	
Serum HDL (mg%)	SCH	13	38.14	±4.12	0.142
	Euthyroid	84	40.06	±6.94	
Serum TG (mg%)	SCH	13	178.0	±66.03	0.185
	Euthyroid	84	151.10	±77.03	

Table-5: Biochemical parameters in the study.

Variable	Number of patients	Female	Males
serum level of anti – TPO antibodies was elevated	11	10(84.6%)	1(15.4%)
serum levels of anti – TPO antibodies within normal limits.	2	1(50%)	1(50%)

Table-6: Serum levels of anti – TPO antibodies

cerebrovascular disease clinically in any of the thirteen SCH patients in the study.

All the 4 patients with LV diastolic dysfunction on 2D echocardiography, were known cases of systemic hypertension on treatment. No other abnormalities like pericardial effusion, asymmetric septal hypertrophy were recorded in any of SCH patients.

Statistically significant difference was not observed in study parameters between the two groups, although SCH patients had low mean values of FBS, PPBS, and serum HbA1C, compared to euthyroid subjects relatively. Although SCH patients hadhigher mean values ofserum total cholesterol, LDL,TG, and lower mean value of serum HDL, compared to euthyroid subjects, the difference was not statistically significant.

Therefore, serum anti – TPO antibody levels were elevated in 91% of female SCH patients and in 50% of male SCH patients.

DISCUSSION

In this study, the percentage of subclinical thyroid disorders among type 2 diabetic patients was Subclinical hypothyroidism – 13% Subclinical hyperthyroidism – 0%

In a study conducted by Diez JJ et al[8], among type 2 DM patients in Spain, prevalence of SCH and subclinical hyperthyroidism was 10.7% and 3.1% respectively. Celani MF et al[9], in their study, found the prevalence of SCH and subclinical hyperthyroidism to be 15% and 7.5% respectively among type 2 DM patients.

Gender–wise prevalence: In this study, SCH was present in 22% of female and 4% of male patients. In a study in 420 adult females with type 2 DM selected in the Fremantle Diabetes Study (Australia) prevalence of SCH was 8.6%. A study by Chen HS et al[10] (Taiwan) revealed that the prevalence of SCH was 5.2% in males and 8.4% in females.

Age: In this study, the mean age of euthyroid subjects was 56.98 (SD ±7.49) years, whereas the mean age of SCH patients was 58.77 (SD±5.47) years, the difference was not statistically significant. In the study by Kim et al[11], the mean age of euthyroid patients of type 2 DM was 57.8 (SD ±11.8) years and the mean age of type 2 diabetics with SCH was 61.7 (SD ±9.8) years (p value 0.014) indicating that SCH in type 2 DM was associated with increasing age. The above difference can be due to the difference in the mean age of SCH patients in the three studies: 58.77 years in the present study vs. 61.7 years in the study by Kim et al[11] vs. 61.0 years in the study by Yang et al.[12] Symptoms of hypothyroidism in SCH patients in the present study in comparison with the Colorado Thyroid disease prevalence study.

Blood Pressure: Mean SBP and DBP of SCH patients in the present study was 137.38 (SD ± 11.59) mm Hg and 79.69 (SD ± 8.40) mm Hg respectively. In the study by Kim et al[11], the mean SBP and DBP among SCH patients was 142 (SD ± 21) mm Hg and 81 (SD ±13).

Glycemic profile: In the present study, no statistically significant difference was found in mean serum HbA1C, mean FBS, mean PPBS levels between SCH patients and euthyroid subjects, although SCH patients had relatively lower mean values of the above study variables, compared to euthyroid subjects. The above findings were similar to that observed in the study by Kim et al.[11]

Lipid profile: In the present study, among SCH patients, the mean values of serum TC, LDL, and TG were relatively higher than the respective mean values in euthyroid subjects, whereas mean serum HDL was relatively lower in SCH patients than euthyroid subjects. But no statistically significant difference was found in any of the above study variables between the two groups.

In a study by Kim et al[11], SCH patients had relatively higher mean values of serum TC, LDL, HDL, compared to euthyroid subjects and relatively lower mean TG compared to euthyroid counterparts; but none of the above parameters showed any statistically significant difference between the two groups.

Studies have also been done to determine the effect of treatment of SCH on serum lipids. In a study by Ineck et al[13] in USA, it

was shown that levothyroxine therapy in SCH reduces serum TC and serum LDL levels. Diabetic retinopathy**:** In the present study, 46% SCH patients had NPDR, and none of the 13 SCH patients had PDR. However, in other studies consisting of larger population of SCH patients with type 2 DM, Kim et al[11] found NPDR in 39% of SCH patients, and PDR in 18% SCH patients; Yang et al[12] found NPDR in 39% SCH patients and PDR in 16.5% SCH patients; indicating that SCH was associated with PDR in type 2 DM.

Diabetic nephropathy**:** In the present study, 23% SCH patients had nephropathy in form of microalbuminuria. None of SCH patients had macroalbuminuria or deranged blood urea / serum creatinine levels.

In previous studies involving large number of SCH patients, Kim et al[11] observed that 13.6% SCH patients had diabetic nephropathy in form of microalbuminuria, and 6.7% SCH patients had macroalbuminuria.

Coronary artery disease: In the present study, CAD was present in 1 (7.7%) SCH patient, as ascertained by history and 2D echocardiography.In previous studies by Hak et al[14], Chen et al[10], SCH has been associated with a greater prevalence of aortic atherosclerosis and MI. In the present study 2D echocardiography at rest, showed LV diastolic dysfunction among 30.8% SCH patients. In a study by Biondi et al[15] in Italy, it was observed that SCH was significantly associated with LV diastolic dysfunction which was reversible on levothyroxine therapy.

Serum anti-TPO antibody: 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[9], it was observed that 61.3% SCH patients with type 2 DM had elevated serum anti-TPO antibody levels. Celani et al[4] also observed that the 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. In the present study, mean serum HbA1C of SCH patients who were TPO antibody negative, was 8.95%. Therefore, it would be appropriate to retest these patients for serum TSH after adequate treatment for DM.

CONCLUSION

In this study, the percentage of subclinical hypothyroidism in type 2 DM patients is 13%, whereas the percentage of subclinical hyperthyroidism is 0. Female patients are more frequently affected by SCH than male patients. Difference of age is not significant between SCH and euthyroid patients, as per the present study. SCH patients with clinical features of hypothyroidism have significantly higher serum TSH and lower serum freeT3, freeT4 levels compared to SCH patients without clinical features of hypothyroidism.

Difference in BMI is not significant between SCH and euthyroid patients. Among SCH patients, diabetic retinopathy is significantly associated with higher serum TSH level. Diabetic neuropathy and nephropathy are not associated with higher serum TSH levels, among SCH patients. LV diastolic dysfunction is a common 2D echocardiography finding among SCH patients. The difference in blood sugar levels is not significant between SCH patients and euthyroid subjects, with type 2 DM. The difference in fasting lipid profile is not significant between SCH patients and euthyroid subjects, with type 2 DM. Thyroid autoimmunity is present in 85% of SCH patients with type 2 DM, with higher frequency in women than in men.

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