Original Research Paper

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Endocrinology

PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM AMONG TYPE 2 DIABETES MELLITUS PATIENTS ATTENDING THE DIABETES CLINIC IN A TERTIARY CARE MEDICAL COLLEGE AND HOSPITAL OF WEST BENGAL.

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ABSTRACT

BACKGROUND: It is seen that thyroid disorders and diabetes mellitus mutually influence each other. Diabetes mellitus influences thyroid function at the level of TSH release as well as conversion of T4 to T3 in the peripheral tissues. Numerous epidemiological studies have shown a higher prevalence of subclinical hypothyroidism among type 2 diabetes mellitus patients than in the normal subjects. Hence this study is done to elicit the prevalence of subclinical hypothyroidism among type 2 diabetes mellitus patients of West Bengal which may help in their further treatment.

METHODS: In this cross-sectional study, 100 consecutive type 2 diabetic patients without any clinical manifestations of thyroid disorders were assessed for hypothyroidism using serum free T4, T3 and TSH levels. They were then compared with 100 healthy individuals chosen as the control. The lipid profile and diabetic profile of the patients was also done.

RESULTS: In the above study, prevalence of subclinical hypothyroidism among Type-2 diabetes mellitus patients was found to be 16% showing an association between T2D and thyroid dysfunction. The prevalence is higher in women than men and increases with age (>65years). However, FT4 and TSH levels were not significantly different between the diabetic and control groups. There was also a significant positive correlation between serum cholesterol levels and serum TSH levels.

CONCLUSION: SCH was detected in 16% of type 2 diabetic patients and none had subclinical hyperthyroidism in our study. Elevated TPO antibody levels were present in 81.25% SCH patients. Diabetic retinopathy among SCH patients showed significant association with higher serum TSH levels. Patients with type 2 diabetes mellitus should be routinely screened for SCH to prevent complications and long-term mortality and morbidity.

KEYWORDS :

BACKGROUND:

According to WHO, subclinical hypothyroidism is defined as "serum thyroid stimulating hormone (TSH) above the defined upper limit of the reference range, with free serum thyroxin (T4) within the reference range."

Diabetes mellitus may be defined as a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas (type 1), or by the ineffectiveness of the insulin produced (type 2) as defined by ADA 2018.

On reviewing the epidemiology of type 2 diabetes mellitus (commonest) in India (according to NCBI), conclusions drawn are as follows:

1) 2.4% of the rural population and 11.6% of the urban population is affected by diabetes mellitus.
2) Subjects under 40 years of age have a higher prevalence of impaired glucose tolerance than diabetes.
3) Important risk factors for the development of type 2 diabetes mellitus are central obesity, insulin resistance, lifestyle changes, etc.

Thyroid disorders, on the other hand, are the commonest endocrine disorders in the world. Subclinical varieties of both hyper and hypothyroidism are very common. Subclinical hypothyroidism progresses to overt hypothyroidism in 2-5% of the cases per year. Select populations require treatment for hypothyroidism: pregnant women, patients with TSH>10mIU/L, those with infertility, goitre or individuals with elevated anti TPO antibody levels. It is prudent to avoid treatment in patients above 85 years of age.

It is seen that thyroid disorders and diabetes mellitus mutually influence each other. Diabetes mellitus influences thyroid function at the level of TSH release as well as conversion of T4 to T3 in the peripheral tissues[1]. Numerous epidemiological studies have shown a higher prevalence of subclinical hypothyroidism among type 2 diabetes mellitus patients (10%-24%)[2] than in the normal subjects (6.6%-13.4%)[3]. Generally subclinical hypothyroidism is asymptomatic but mild elevations in TSH (8-10mmol/L),along with free circulating thyroid hormone is observed[4].

Presently, controversy persists about indications for treatment of subclinical hypothyroidism and whether patients should be routinely screened for this dysfunction[5,6]. Till date not much data is available about the association of subclinical hypothyroidism with type 2 diabetes mellitus in population of West Bengal.

This study focuses on association of subclinical variety of hypothyroidism amongst the already diabetic patients in the population predominantly from West Bengal attending a tertiary care hospital for routine check up with age or gender and relationship with other related co-morbidities.

Hence keeping in mind the previous researches, this study seeks to elicit the prevalence of subclinical hypothyroidism among type 2 diabetes mellitus patients which may help in their further treatment.

OBJECTIVES:

The main objectives of this study are to determine the prevalence of subclinical hypothyroidism among type 2 diabetes mellitus patients, to assess the association of subclinical hypothyroidism in type 2 diabetes mellitus with gender and age, to compare the thyroid function tests in diabetic and normal patients and to investigate whether any diabetic complication (neuropathy, nephropathy, retinopathy, coronary artery disease, cerebrovascular disease, etc.) is more prevalent in subclinical hypothyroidism than euthyroid diabetic cases.

MATERIALS AND METHODS:

It is an epidemiological descriptive type of observational hospital based cross sectional study done in Medical College Kolkata, Dept.of Endocrinology and OPD Biochemistry Laboratory. The duration of this study was 2 months.

100 type 2 diabetes mellitus patients >18 yrs attending the diabetes clinic in Endocrine OPD of Medical College and Hospital Kolkata were screened and included as the study population and another 100 healthy normal volunteers were included as control group.

All known type 2 diabetes mellitus patients without any clinical symptoms of hypothyroidism (fatigue, dry skin, enlarged thyroid, unexplained weight gain, hair loss, cold sensitivity, etc.) were included whereas patients with type 1 diabetes mellitus and patients with known hyperthyroidism/ hypothyroidism were excluded from the study.

Tools required for the study are syringe, tourniquet and blood vials (fluoride vial for fasting blood sugar, EDTA vial for thyroid hormone

estimation and clot vials).

METHODOLOGY-

Subjects are first interrogated using a questionnaire prepared beforehand for obtaining information which may be correlated with the prevalence of the entity in question. All the study subjects are explained about the study procedure in detail and informed consent is taken from them. 5ml venous blood from the anterior cubital vein is collected after overnight fasting using a syringe and tourniquet from the patients with type 2 diabetes mellitus for estimation of fasting blood glucose and other parameters. Blood is then transferred in respective vials and sent for biochemical investigations. Biochemical parameters included are-

(a) Diabetic profile (fasting blood sugar, HbA1c)
(b) Thyroid profile (FT4, TSH and Anti-TPO)
(c) Lipid profile (cholesterol, triglyceride, LDL, HDL)

Blood glucose is estimated using Glucose oxidase peroxidise method. TSH and T4 were estimated by immunochemiluminiscence assay. HbA1c was assessed by direct enzymatic assay method. Total cholesterol was estimated by cholesterol oxidase method, HDL by direct immune-inhibition method, LDL by direct measurement.

PREVALENCE IS THEN CALCULATED AS THE NO. OF CASES WITH SUBCLINICAL HYPOTHYROIDISM IN TYPE 2 DIABETES MELLITUS DIVIDED BY THE TOTAL NO. OF PATIENTS WITH TYPE 2 DIABETES MELLITUS.

ETHICAL ISSUES-

(i) Informed consent from both study and control subjects was taken before the process.
(ii) Pretested and prefixed questionnaire was used.
(iii) Approval by Institutional Ethics Committee was obtained before the study.

FUNDING/SPONSOR:

All the tests were done free of cost for the patients from the OPD Biochemistry Laboratory after taking prior permission from Medical Superintendant and Vice Principal of Medical College and Hospital, Kolkata.

There are no conflicts of interest in this study.

RESULTS:

After careful analysis of the data collected during the study period based on the biochemical values, it was determined that out of the 100 patients, 84 were euthyroid (serum TSH and FT4 levels within normal limits) and 16 patients had subclinical hypothyroidism (serum TSH>4mIU/L and normal free T4 levels). There were no subjects with overt hypothyroidism. None of them had subclinical or overt hyperthyroidism.

Table 1: Distribution of study population according to age and presence of subclinical hypothyroidism (n=100)

Age in years	Subclinical hypothyroidism		Total
	Present	Absent	
30-39	0	12(100%)	12(100%)
40-49	4(14.29%)	24(85.71%)	28(100%)
50-59	8(20%)	32(80%)	40(100%)
60-69	4(33.33%)	8(66.67%)	12(100%)
70-79	0	8(100%)	8(100%)
Total	**16(16%)**	**84(84%)**	**100**

It is seen that majority (40%) of the study population belonged to the age group of 50-59 years and prevalence of subclinical hypothyroidism was seen in 20% of the patients belonging to this age group. However the prevalence of subclinical hypothyroidism is found to be maximum (33.3%) in the age group 60-69 years.

The mean age of the SCH subjects was 55.5 ± 9.83 years, whereas the mean age in euthyroid patients was 51.5 ± 7.49 years, the difference was not statistically significant.

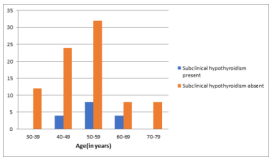

Figure 1: Bar diagram showing distribution of study population according to age and presence of subclinical hypothyroidism.

Table 2: Distribution of study population according to gender and prevalence of subclinical hypothyroidism (n=100)

Gender	Subclinical hypothyroidism		Total
	Present	Absent	
Males	12(20%)	48(80%)	60(100%)
Females	4(10%)	36(90%)	40(100%)
Total	**16(16%)**	**84(84%)**	**100**

Out of the 100 study subjects, 60 were males and 40 were females. Out of the males, 20% of them had subclinical hypothyroidism while only 10% of the females showed prevalence of subclinical hypothyroidism.

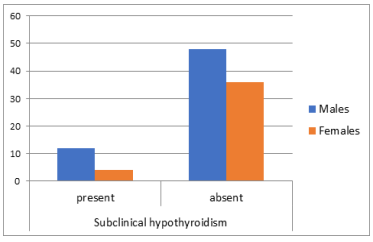

Figure 2: Bar diagram showing prevalence of subclinical hypothyroidism among male and female type 2 diabetic patients.

Table 3: Distribution of study population according to duration of diabetes mellitus type 2 and subclinical hypothyroidism (n=100)

Duration (in years)	Total no. of patients	No. of patients with subclinical hypothyroidism	Percentage
0-5	28	3	10.71%
6-10	35	4	11.42%
11-15	21	1	4.76%
16-20	11	6	54.55%
>20	5	2	40%

Majority (35%) of the study population had been suffering from type 2 diabetes mellitus for 6-10 years of which only 4 (11.42%) had subclinical hypothyroidism. Out of the 11 subjects having diabetes mellitus for 16-20 years, 6 (54.55%) had subclinical hypothyroidism

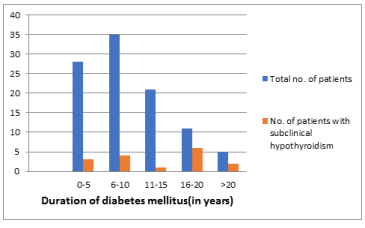

Figure 3: Bar diagram showing distribution of study population according to duration of type 2 diabetes mellitus (in years) and prevalence of subclinical hypothyroidism.

Table 4: Distribution of study population showing association of subclinical hypothyroidism with hypercholesterolemia (n=100)

Total cholesterol level(in mg/dl)*	Total no. of patients	No. of patients with TSH>4 (mIU / L) with normal FT4 levels	Percentage
<200 (normal)	78	12	15.38%
200-240 (borderline high)	16	3	18.75%
>240 (high)	6	1	16.67%

*according to reference levels of total cholesterol by NIH: National institute of Heart, Lung and Blood institute.

78% of the subjects were found to have normal levels of serum cholesterol while the rest showed borderline high or high serum cholesterol levels. 18.75% of the patients having borderline cholesterol levels (200-240mg/dL) have subclinical hypothyroidism as compared to 15.38% and 16.67% of patients with normal and high total cholesterol levels respectively.

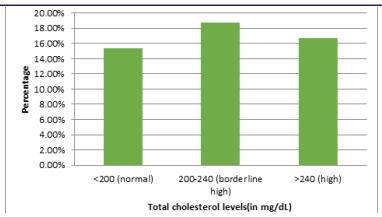

Figure 4: Bar diagram showing association of subclinical hypothyroidism with hypercholesterolemia.

Table 5: Distribution of study population showing relationship between levels of HbA1c and subclinical hypothyroidism (n=100)

HbA1c level (in %)*	Total frequency	No. of patients with TSH>4 (mIU /L) and normal FT4 levels	Percentage
<7.5 (well controlled)	42	5	11.9%
≥7.5 (poorly controlled)	58	11	18.96%

*as per new ADA guidelines treatment target and treatment criteria of our institution.

42% of the study population showed well controlled levels of HbA1c and 58% showed poorly controlled levels. Only 11.9% of the well controlled(7.5% of HbA1c) subjects showed prevalence of subclinical hypothyroidism as compared to 18.96% of the subjects with poorly controlled levels (≥7.5% of HbA1c).

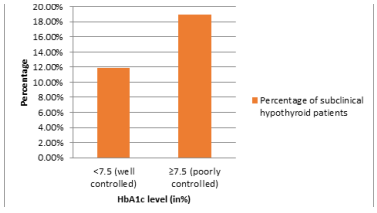

Figure 5: Bar diagram showing relationship between levels of HbA1c and subclinical hypothyroidism.

Table 6: Relation between thyroid dysfunction and high LDL-CH levels

LDL-CH levels (in mg/dL) *	Diabetics with subclinical hypothyroidism	Diabetics without subclinical hypothyroidism
>100	13(81.25%)	61(72.62%)
<100	3(18.75%)	23(27.38%)

*according to ADA guidelines.

13 (81.25%) of the subclinical hypothyroid patients had LDL-CH levels >100 mg/dL and 3 (18.75%) had LDL-CH levels <100mg/dL. In the subjects without subclinical hypothyroidism, 61 (72.62%) had LDL-CH levels >100mg/dL and 23 (27.38%) had LDL-CH levels <100mg/dL.

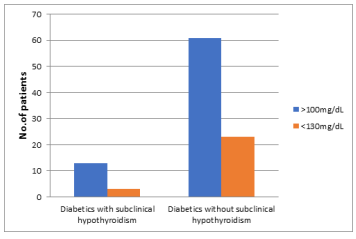

Figure 6: Bar diagram showing relation between thyroid dysfunction and high LDL-CH levels.

Table 7: Relation between thyroid dysfunction and HDL-CH levels

HDL-CH levels (in mg/dL) *	Diabetics with subclinical hypothyroidism	Diabetics without subclinical hypothyroidism
<40	5(31.25%)	26(29.54%)
>40	11(68.75%)	62(70.45%)

*according to ADA guidelines

5 (31.25%) of the subclinical hypothyroid patients had HDL-CH levels <40 mg/dL and 11 (68.75%) had HDL-CH levels >40mg/dL. In the subjects without subclinical hypothyroidism, 26 (29.54%) had HDL-CH levels <40mg/dL and 62 (70.45%) had HDL-CH levels >40mg/dL.

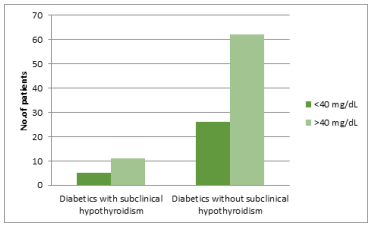

Figure 6: Bar diagram showing relation between thyroid dysfunction and HDL-CH levels.

ANTI-DIABETIC MEDICATIONS-

Out of the 16 SCH subjects, 2 (12.5%) were found to be on regular insulin therapy along with oral hypoglycemic agents, 5 (31.25%) patients were on more than 2 classes of OHA and the remaining 9 (56.25%) were on upto 2 classes of oral hypoglycemic drugs.

CLINICAL PROFILE OF SUBCLINICAL HYPOTHYROID PATIENTS-

Out of the 16 SCH patients detected in the study, 3 (18.75%) had clinical features suggestive of hypothyroidism. Goitre was detected in 2 (12.5%) patients with SCH **(Table 8)**

Table 8: Clinical profile of diabetic patients with subclinical hypothyroidism.

Clinical features	%of SCH patients with the symptom
Symptom of hypothyroidism	
Weakness/Lethargy	23
Poor memory	15.4
Muscle ache	23
Cold intolerance	7.7
Constipation	7.7
Clinical signs of hypothyroidism	
Dry coarse skin	23
Cool peripheral extremities	7.7

CHRONIC COMPLICATIONS OF DIABETES MELLITUS-MACRO VASCULAR COMPLICATIONS

Among the 16 subclinical hypothyroid patients, 3 (18.75%) were found to have associated **macro vascular complication** (Coronary artery disease) with a positive history of ischaemic heart disease. There was no clinical evidence of Peripheral artery disease or Cerebrovascular disease in any of the 16 SCH patients in the study.

MICRO VASCULAR COMPLICATIONS

9 (56.25%) of 16 SCH patients had one or more **micro vascular complications** (nephropathy, retinopathy, neuropathy) as per previous reports of diagnostic tests. 9 (56.25%) of SCH patients had diabetic retinopathy, 3 (18.75%) SCH patients had diabetic nephropathy, 2 (12.5%) had diabetic neuropathy.

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 5.21 ± 1.34 mIU/L, mean serum HbA1c of 6.81 ± 2.15% and mean duration of DM being 7.83 ± 2.54 years. SCH patients without retinopathy had a mean serum TSH value of 2.90 ± 0.55 mIU/L, mean serum HbA1c of 7.24 ± 21.58% and mean duration of DM being 2.85 ± 1.80 years. Statistically significant difference between the two groups was observed.

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 ± 1.77mIU/L, 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 ± 1.17mIU/L, 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.

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 ± 1.60mIU/L, 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 ± 1.21mIU/L, 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.

SERUM LEVELS OF ANTI-TPO ANTIBODIES-

Among the 16 SCH patients, serum level of anti-TPO antibodies was elevated in 13 patients (81.25% of SCH patients). 11 SCH patients with elevated anti-TPO antibody were male, 2 were female. The remaining 3 SCH patients had serum levels of anti-TPO antibodies within normal limits. Therefore, serum anti-TPO antibody levels were elevated in 91.67 % of male SCH patients and in 50% of female SCH patients.

HISTORY OF SURGICAL PROCEDURES OR SPECIAL TREATMENTS-

None of the subjects under study had undergone any recent surgical procedures or special treatments (corticosteroids/chemotherapy/blood products).

Table 9: Comparison of the thyroid function tests in diabetic and normal patients.

Parameter	Diabetic (n=100)	Non-diabetic (n=100)
TSH (mIU/L)	1.69 ± 1.22	1.47 ± 0.78
FT4(pmol/L)	13.67 ± 2.98	13.14 ± 2.54

Normal range of FT4 is9.14-23.81 pmol/L, TSH is 0.47-4.64 mIU/L. All values are in mean ± SD.

The mean serum levels of FT4 and TSH were similar between the two groups.

DISCUSSION:

In the above study, prevalence of subclinical hypothyroidism among Type-2 diabetes mellitus patients was found to be 16%. The above results are in agreement with previous studies showing an association between T2D and thyroid dysfunction. SCH or mild thyroid failure is a common problem, with a prevalence of 3-8% in the population without known thyroid disease[13,14].

The prevalence is higher in women than men[8] and increases with age[9] (>65years) From Table nos. 1 and 2 of our study, it can be clearly seen that maximum prevalence of subclinical hypothyroidism (33.33%) was found in the sixth decade of life but it was found to be higher in males as compared to females which is not in confirmation to previous study reports. This difference in the prevalence of thyroid dysfunction may be due to the varying number of subjects included in each age and gender groups. After the sixth decade of life, the prevalence in men approaches that of women, with a combined prevalence of 10% as per previous studies.

Dyslipidemia[15] is a reported complication of hypothyroidism in non-diabetic and diabetic subjects as seen in various studies done by *Elder J et al.*[16] and *Gray RS et al*.[17] From Table no.6 of our study, it can be clearly stated that out of the 16 subjects of hypothyroidism, it was found that 13(81.25%) had LDL- cholesterol levels >100mg/dl and 3 (18.75%) had LDL-Cholesterol levels <100mg/dl. In the subjects without hypothyroidism 61 (72.62%) had LDL-CH >100mg/dl whereas 23 (27.38%) had levels <100mg/dl. A greater percentage of diabetics with hypothyroidism had high serum LDL-CH levels when compared to those without hypothyroidism.

Similarly, from Table no.7 of our study, it can be clearly stated that out of the 16 subjects of hypothyroidism, it was found that 5 (31.25%) had HDL-Cholesterol levels <40 mg/dL and 11 (68.75%) had HDL-Cholesterol levels >40mg/dL. In the subjects without subclinical hypothyroidism, 26 (29.54%) had HDL-CH levels <40mg/dL whereas 62 (70.45%) had HDL-CH levels >40mg/dL. Thus, a greater percentage of diabetics without hypothyroidism had high serum HDL-CH levels when compared to those with hypothyroidism.

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[18]. *Celani et al.*[19] found that prevalence of thyroid disease in type 2 diabetics was 31.4%, out of which SCH was most commonform (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 hadhigh levels of anti-TPO antibodies.

In the present study, serum TPO antibody elevation was seen in 13 (81.25%) of SCH patients, indicating thyroid disease of autoimmune etiology. In a study by *Celani et al.*[19], it was observed that 61.3% SCH patients with T2DM had elevated serum anti-TPO antibody levels. *Celani et al*.[19] 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.

Several recent meta-analyses of observational studies found an association between SCH and coronary artery disease[20,21,22].

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 euthyroidcounterparts[23]. Both SCH and hyperthyroidism have been linkedto increased cardiovascular risk.

Altered thyroid hormone levels have been previously reported in insulin requiring diabetic patients before and after treatment (*Saunders et al, 1978)*[24] where FT4 and TSH levels were significantly different in the diabetic and the control study subjects. From Table no. 9 of our study, it is clearly seen that the FT4 and TSH levels were not significantly different between the diabetic and control groups.

CONCLUSION:

From the study, a number of significant conclusions can be arrived at. SCH is common among type 2 diabetic patients, especially in the age group 60-69 years. This study justifies the view that all diabetic patients should be screened for hypothyroidism.

SCH is most commonly secondary to autoimmune thyroid disease. Micro vascular 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.

The coexistence of subclinical hypothyroidism with diabetes mellitus leads to high serum cholesterol levels. The ability to diagnose and treat unsuspected hypothyroidism in diabetics may result in prevention of longterm morbidity and mortality.

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