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ORIGINAL RESEARCH

Association of Sub Clinical Hypothyoidism with Microvascular Complications in Type2 Diabetes Mellitus Patients in A Tertiary Care Hospital

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ABSTRACT

Background: The incidence of Thyroid dysfunction in diabetics is higher than that of general population. Undiagnosed thyroid dysfunction may affect the metabolic control and enhance cardiovascular and other chronic complications in diabetic patients. Diabetes mellitus is one of the most common disease in the world and is acquiring epidemic Proportions in developed and developing countries. Indians are genetically more susceptible to diabetes. The prevalence of Type 2DM is on the rise much more rapidly, which is due to increasing obesity and reduced activity levels. Several studies have assessed the relationship between thyroid function and micro-vascular complications in patients with T2DM. Few studies have examined the relationship between subclinical hypothyroidism(SCH) and vascular complications in patients with Type 2 diabetes mellitus.

Objectives: To study the association between TSH levels and microvascular complications of Type 2 DM.

Materials and Methods: A total of 100 type 2 diabetes patients (40 males and 60females) were enrolled in this cross-sectional study. Subjects were evaluated for neuropathy, thyroid function, diabetic retinopathy, and diabetic kidney disease. TSH was divided into 3 levels: 0.27–2.49 mU/l, 2.5–4.2 mU/l and >4.2mU/l and <10 mU/l with normal FT4

Results: Our study found statistically positive association of elevated TSH and microalbuminuria, macroalbuminuria, low GFR and impaired vibration sensation. Our study found no association between elevated TSH and age, diabetes duration, HbA1c levels and retinopathy.

Conclusion: In our study we could not establish an association between TSH levels and diabetic Retinopathy. However, we found an association between elevated TSH levels and Diabetic Neuropathy and DKD. Hence it is ideal to screen all patients with Diabetes for Thyroid dysfunction, as elevated TSH levels in these patients can be an indicator of underlying micro-vascular complications. However, more research, involving more subjects is required with regard to the above.

Keywords: Type 2 Diabetes Mellitus, Hypothyoidism, microvascular complications, HbA1c, microalbuminuria.

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INTRODUCTION

Although SCH is an asymptomatic state, it almost affects every organ in the body. SCH is characterized by increased serum concentration of TSH but with normal serum thyroxine levels. Prevalence has been seen to vary between 4% & 10% in large screening surveys. Pathogenesis of vascular complications of SCH is related to hyperlipidemia, endothelial dysfunction, atherosclerosis which increases CVS disease. Association between SCH and CKD has been observed. Reported SCH levels in diabetes ranged from 2.2% - 17%. however, the relation of how SCH is related to DM related micro-vascular complications remains unclear[1,2]

OBJECTIVES OF THE STUDY

To study the association between TSH levels and microvascular complications of Type 2 Diabetes mellitus in a tertiary care hospital.

MATERIALS & METHODS

The present study was a single-center, cross sectional study conducted on patients admitted or visited with type2 Diabetes in the general medicine department of Rajarajeswari Medical College and Hospital, Bangalore from January 2020 to January 2021.Prior to initiation of the study. Ethical and Research Committee clearance from Rajarajeswari Medical College and Hospital, Bangalore was obtained. During present study a total of 150 type2 Diabetes Patients were reviewed in OPD, among which 100 (66.6%) patients were enrolled into the study and 50 (33.3%) patients were excluded according to inclusion, exclusion criteria.

Inclusion Criteria

Both male and female patients above 40 years of age diagnosed with type 2 DM.

Exclusion criteria

- Type 1 diabetes mellitus;
- Past history of thyroid diseases;
- TSH>10
- Overt hypothyroidism;
- Treatment with levothyroxine or anti-thyroid drugs;
- Pregnancy;
- Acute or chronic infection;
- Malignancy;
- Kidney disease other than diabetic kidney disease.
- Patients on hemodialysis
- Age < 40 years

Method of Collection of Data

Clinical examination and laboratory measurements

Clinical data including anthropometric measurements smoking and drinking status blood pressure Body mass index (BMI) previous history of hypertension and dyslipidemia and duration of diabetes were collected.

Thyroid function was confirmed by chemiluminescent immunometric assay.The subjects divided according to the TSH levels: 0.27–2.49 mU/l; 2.5–4.2 mU/l; and > 4.2 mU/l.

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Assessment of diabetic complications

Diabetic kidney disease (DKD) was defined as eGFR<60 mL/min/1.73 m2 (calculated by CKD-EPI formula) or presence of microalbuminuria/macroalbuminuria. A single morning urine sample for albumin measurement was done to detect microalbuminuria and macroalbuminuria. Fundoscopy was done to detect diabetic retinopathy. Diabetic neuropathy (DN) was assessed using tuning fork (128Hz) for vibration sense testing, tempetaure sense, pain perception, monofilament testing and examining reflexes. Diabetic retinopathy (DR) was defined on the basis of the international clinical DR severity scale.

Diabetic Retinopathy Scale

Disease Severity Level	
No apparent retinopathy	No abnormalities
Mild NPDR	Micro aneurysms only
Moderate NPDR	Multiple microaneurysms, dot and blot haemorrhages, venous bleeding, and/or cotton wool spots.
Severe NPDR	Any of the following - More than 20 intraretinal haemorrhage - Definitive venous beading in two or more quadrants - Prominent intra -retinal microvascular abnormalities in one (or) more quadrant and no signs of PDR
PDR	One or more of the following: Neovascularisation, photocoagulation scar Vitreous haemorrhage
NPDR : Non proliferative diabetic retinopathy.	

Informed Consent

All the patients fulfilled selection criteria and were explained about the details of the disease process, options of treatment, ultimate outcome, possible effects, complications and chances of recurrence in both procedure and a written informed consent was obtained before enrollment.

Data Collection

All the data was collected from the patients with type 2 diabetes mellitus who attended general medicine out-patient department and admitted in the wards with detailed history & thorough physical examinations. It included age, sex, nationality, complaints; duration of symptoms; predisposing factors and detailed address were collected for follow up.

Sample size estimation

Sample size

100

Sample size Calculation

Yamane Equation: (for known population size)

(Sample size) n = N

1+ Ne2

Where N = Population size e

= margin of error

(For 95% confidence level, margin error = 0.05)

Ref: An introductory analysis 2nd Edition New York, Harper & Row

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Statistical Analysis

The collected data was entered into Microsoft Excel Worksheet-2010 and data was taken into IBM SPSS Statistic for windows, version 24(IBM Corp., Armonk, N.Y., USA) software for calculation of frequency, percentage, mean, standard deviation and Probability value. P value <0.05 is considered significant.

RESULTS

Age Group	Frequency	Percentage
41-45	4	4
46-50	14	14
51-55	28	28
56-60	42	42
>60	12	12
Total	100	100

Table 1: Patients were distributed according Age group

The total number of subjects included in the study are 100, all in the age group of more than 40 years to 70 years. 4 patients were aged between 41-45 years, 14 patients between 46-50 years, 28 patients were aged between 51-55 years, 42 patients were between 56-60 years and 12 patients were aged more than 60 years.

Mean age of patients were 55.1±years. Mean age of the female patients were 55.34 ±years, while the mean age of male patient is 54.89±years. Age distribution showed majority of patients aged between 56-60 years.

The age distribution of patients showed no significant difference, P value 0.05.

Sex	Frequency	Percentage	Ratio
Male	40	40	**1.5 F/M**
Female	60	60	
Total	100	100	

Table 2: Patients were distributed according sex

The total number of subjects included in the study are 100, out of which 40 were male(40%) and 60 were female(60%). Female to male ratio was found to be 1.5:1. Indicating female preponderance.

Sex	Frequency	Percentage
TSH (0.27-2.49)	36	36
TSH (2.50-4.20)	38	38
TSH (>4.20)	26	26
Total	100	100

Table 3: Patients were distributed according TSH levels

Out of 100 patients, 36 patients had TSH value between [0.27 – 2.49]. 38 patients had TSH value between [2.5 – 4.20] and 26 of patients had TSH > 4.2

Patients distribution according to TSH levels showed no significant difference statistically. P value 0.15.

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Age Group	TSH (0.27-2.49)	TSH (2.50-4.20)	TSH (>4.20)	P-Value
41-45	2 (5.55%)	2 (5.26%)	0 (0.00%)	
46-50	6 (16.66%)	4 (10.52%)	4 (15.38%)	
51-55	8 (22.22%)	12 (31.57%)	8 (30.76%)	
56-60	14 (38.88%)	16 (42.10%)	12 (46.15%)	**0.23**
>60	6 (16.66%)	4 (10.52%)	2 (7.69%)	
Total	**36**	**38**	**26**	
Table 4: Patients were distributed according Age group Vs TSH Levels				

Among 4 patients in the age group of 41-45 years. 2 patient had TSH value in the range of (0.27 – 2.49) and 2 patient had TSH value in the range of [2.5 – 4.20]. None of the patient had TSH >4.20.

Among 14 patients in the age group of 46 – 50 years. 6 of them had their TSH values in the range of (0.27 – 2.49). 4 patients had TSH value in the range of (2.5 – 4.2) and 4 patients had their TSH > 4.2.

Among 28 patients in the age group of 51- 55 . 8 of them had their TSH value in the range of [0.27 – 2.49]. 12 patients had TSH value in the range of [2.5 – 4.2] and 8 had their TSH > 4.2.

Among 42 patients in the age group of 56- 60 years , 14 patients had their TSH between [0.27 -2.49]. 8 patients had their TSH (2.5 – 4.20) and 12 patients had their TSH > 4.2

Among 12 patients aged more than 60 years, 6 patients had their TSH between [0.27 – 2.49], 4 patients had their TSH [2.5 – 4.2] and 2 patients had TSH > 4.2.

The age distribution of the participants had no significant difference statistically P value 0.23.

Sex	TSH (0.27-2.49)	TSH (2.50-4.20)	TSH (>4.20)	P-Value
Female	24 (66.67%)	22 (57.89%)	9 (69.23%)	
Male	12 (33.33%)	16 (42.10%)	4 (30.76%)	**0.08**
Total	**38**	**38**	**26**	
Table 5: Patients were distributed according Sex Vs TSH Levels				

Among 40 males, 14patients had TSH value between [0.27–2.49]. 15 patients had TSH between [2.5–4.2] and 11 patients had TSH > 4.2. Among 60 females 24 had TSH between (0.27 – 2.49), 28 had TSH between (2.5 – 4.2) and 8 had TSH > 4.2

SEX V/S TSH level showed no significant difference statistically P value 0.08.

DM Duration	TSH (0.27-2.49)	TSH (2.50-4.20)	TSH (>4.20)	P-Value
5-6	10 (27.77%)	12 (31.57%)	8 (30.76%)	
7-8	16 (44.44%)	14 (36.84%)	10 (38.46%)	
8-9	6 (16.66%)	8 (21.05%)	8 (30.76%)	
≥10	4 (11.11%)	4 (10.52%)	0 (00.00%)	**0.14**
Total	**36**	**38**	**26**	
Table 6: Patients were distributed according Diabetes duration Vs TSH Levels				

Among patients with duration of diabetes 5-6 years. 10 patients had TSH value between (0.27 -2.49), 12 patients had TSH between (2.5 – 4.2) and 8 had TSH > 4.2.

Among patients with duration of diabetes of 7-8 years. 16 had their TSH between (0.27 – 2.49), 7 patients had TSH (2.5 – 4.2) and 10 patients had TSH > 4.2

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Among patients with duration of diabetes 8-9 years, 6 patients had their TSH between (0.27 2.49), 8 patients had their TSH (2.5 – 4.2) and 8 patients had TSH >4.2
Among patients with duration of diabetes > 10years, 4 had their TSH between [0.27 – 2.49] 4 patients had their TSH (2.5 -4.2) and none had their TSH > 4.2.
Diabetes duration Vs TSH Levels showed no significant difference statistically P value of 0.14.

HbA1c	TSH (0.27-2.49)	TSH (2.50-4.20)	TSH (>4.20)	P-Value
7-8	2 (5.55%)	4 (10.50%)	0 (00.00%)	**0.09**
8-9	8 (22.22%)	10 (26.31%)	6 (23.07%)	
10-11	14 (38.88%)	14 (36.84%)	12 (46.15%)	
≥12	12 (33.33%)	10 (26.31%)	8 (30.76%)	
Total	**36**	**38**	**26**	

Table 7: Patients were distributed according HbA1c Vs. TSH Levels

Among patients with their HbA1c values between 7-8%. 2 had their TSH (0.27 – 2.49). 4 had their TSH (2.5 – 4.2) and none had TSH > 4.2
Among patients with their HbA1c values between 8-9%, 8 had their TSH [0.27 – 2.49], 10 had their TSH [2.5 – 4.2] and 6 had TSH > 4.2
Among patients with their HbA1c value of 10 -11%, 14 had their TSH (0.27 – 2.49), 14 had their TSH (2.5 – 4.2) and 12 had their TSH > 4.2
Among patients with their HbA1c value of >12%, 12 had their TSH value between (0.27 – 2.49), 5 patients had their TSH value between (2.5 – 4.2) and 8 patients had their TSH >4.2.
HbA1c Vs TSH Levels showed no significant difference statistically P value 0.09

Retinopathy	TSH (0.27-2.49)	TSH (2.50-4.20)	TSH (>4.20)	P-Value
Yes	16 (44.44%)	18 (47.36%)	14 (53.84%)	**0.15**
No	20 (55.55%)	20 (52.63%)	12 (46.15%)	
Total	**36**	**38**	**26**	

Table 8: Patients were distributed according Retinopathy Vs TSH Levels

Among 16 patients with TSH value (0.27 – 2.49), 18 patients with TSH (2.5- 4.2) and 14 patients with TSH > 4.2 had retinopathy.
Among 20 patients with TSH (0.27 – 2.49), 20 patients with TSH (2.5 – 4.2) and 6 patients with TSH > 4.2 had no retinopathy.
This table showed that there is no association betweenRetinopathy Vs TSH Levels (P value 0.15).

Microalbuminuria	TSH (0.27-2.49)	TSH (2.50-4.20)	TSH (>4.20)	P-Value
Yes	6 (16.66%)	6 (15.78%)	8 (30.76%)	**0.01**
No	30 (83.33%)	32 (84.21%)	18 (69.23%)	
Total	**36**	**38**	**26**	

Table 9: Patients were distributed according Micro-albuminuria Vs TSH Levels

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Among 3 patients with TSH (0.27 – 2.49), 6 patients with TSH (2.5 – 4.2) and 8 patients with TSH > 4.2 had microalbuminuria.
Among 30 patients with TSH (0.27 – 2.49), 32 patients with TSH (2.5 – 4.2) and 18 with TSH (2.5 – 4.2) had no microalbuminuria.
This table showed that there is an association betweenSCHand microalbuminuria with statistically significant P value 0.01.

Vibration sense	**TSH (0.27-2.49)**	**TSH (2.50-4.20)**	**TSH (>4.20)**	**P-Value**
Normal	22 (61.11%)	20 (52.63%)	10 (38.46%)	**0.02**
Abnormal	14 (38.88%)	18 (47.36%)	16 (61.53%)	
Total	**36**	**38**	**26**	
Table 11: Patients were distributed according Vibration sense Vs TSH Levels				

Among 22 patients TSH value [0.27 – 2.49] and 20 patients with TSH value (2.5 – 4.2) and 10 patients with TSH > 4.2 had normal (VPT) vibration sense.
Among 14 patients with TSH value (0.27 – 2.49) and 18 patients with TSH value (2.5 – 4.2) and 16 patients with TSH > 4.2 had abnormal (VPT) vibration sense.

This table shows that there is an association between SCH and impaired Vibration sense with significant P value 0.02.

GFR	**TSH (0.27-2.49)**	**TSH (2.50-4.20)**	**TSH (>4.20)**	**P-Value**
>60 mL/min/1.73 m^2	34 (94.44%)	36 (94.73%)	20(76.92%)	**0.001**
<60 mL/min/1.73 m^2	2 (5.55%)	2 (5.26%)	6 (23.07%)	
Total	**36**	**38**	**26**	
Table 12: Patients were distributed according GFR Vs TSH Levels				

34 patients with TSH (0.27 – 2.49), 36 patients with TSH (2.5 – 4.2) and 20 patients with TSH > 4.2 had GFR > 60ml/min/1.73m^2
2 patients with TSH (0.27-2.49), 2 patients with TSH (2.5-4.2) and 6 patients with TSH > 4.2 had GFR < 60ml/min/1. 73m^2
This table showed an association between SCH and low GFRwith significant P value 0.001.

Diabetic kidney disease	**TSH (0.27-2.49)**	**TSH (2.50-4.20)**	**TSH (>4.20)**	**P-Value**
Yes	6 (16.66%)	8 (21.05%)	12 (46.15%)	**0.001**
No	30 (83.33%)	30 (78.94%)	14 (53.84%)	
Total	**36**	**38**	**26**	
Table 13: Patients were distributed according Diabetic kidney disease Vs. TSH Levels				

6 patients with TSH (0.27 – 2.49), 8 patients with TSH (2.5 – 4.2) and 12 patients with TSH >4.2 had Diabetic kidney disease.
30 patients with TSH (0.27 – 2.49), 30 patients with TSH (2.5 – 4.2) and 14 patients with TSH >4.2 had no Diabetic kidney disease.
This table showed an association betweenSCH and DKD with significant P value 0.001.

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DISCUSSION

The present study was a single-center, cross sectional study conducted on patients admitted or visited with type2 Diabetes in the general medicine department of Rajarajeswari Medical College and Hospital, Bangalore from January 2020 to January 2021. Sub clinical hypothyroidism denotes mild form of thyroid dysfunction. The prevalence of SCH in general population is around 5 to 15%[3]. Worldwide prevalence of SCH is found to be 7.5-8.5% in women and 2.8 - 4.4% in men. According to Indian epidemiological study, prevalence of SCH is 8.73% in females and 7.17% in males[4]. The SCH is more common in women than men. Patients with SCH are mostly asymptomatic or may have minimal symptoms. Thus, SCH is solely a laboratory diagnosis[5].

Several studies have assessed the relationship between thyroid function and microvascular complications in patients with T2DM, but the results were controversial. In a study conducted by Feng Gao, et al.in 2019. Association among subclinical hypothyrodism, TSH levels and microvascular complications in Type 2 diabetic patients was studied.

Yang JK et al study showed that SCH was associated with DR[6,7], while Ramis JN et al and Chen HS et al could not find any relationship between SCH and DR[8,9]. Kim et al. failed to show a relationship between SCH and DR[10]. our study could not find an association between SCH and DR.

Weijing Zhao et al study showed that a high thyroid stimulating hormone level is associated with diabetic peripheral neuropathy in type 2 diabetic patients[11], our study showed an association between SCH and impaired vibration sense.

Asvold BO et al demonstrated an association between TSH and eGFR in the general population[12,13]. However, studies in patients with diabetes mellitus are still lacking. Rodacki et al. reported that there was a significant interrelationship between thyroid function and a lower GFR in subjects with type 1diabetes[14]. Furukawa et al. found that eGFR was higher in the euthyroid group than that in the SCH group among patients with T2DM[15]. In our study we found that there was a statistical significant association between SCH and low GFR.

Yasuda et al in their study found an association between SCH and albuminuria in patients with type 2 DM[16]. In our study we found an association between SCH and albuminuria in patients with type 2 DM. Shinya Furukawa et al performed a study that demonstrated an association between SCH and DKD in patients with type 2 DM[15].

In our study we found a significant association between SCH and DKD.The present study revealed that serum TSH levels were associated with diabetic kidney disease, but not with diabetic retinopathy. The multivariate analysis demonstrated the higher frequency of DKD with higher TSH levels. Thyroid function was an independent factor for DKD in subjects with T2DM after adjustment for several other factors. Our results were consistent with those of Chen et al[9], showing that SCH was associated with DN, but differed from those of Kim et al[10], who reported an association between SCH and an increased risk of severe diabetic retinopathy, but not with diabetic nephropathy.

Currently, the reasons for this discrepancy remain unanswered. They may be related to differences in demographic and clinical characteristics, ethnicity, and research design. The duration of diabetes and poor glycemic control are risk factor for microvascular complications in type 2 diabetes. Our study had younger participants (the mean age 55.06 years) with poorer glycaemic control (HbA1c 9.53±2.16%) than did that of Kim et al[10]. Furthermore, in our and other studies[10], the duration of T2DM was shorter than those other previous studies[6,10]. Moreover, the sample size of other previous studies[6,10] was smaller than the present study. In addition, our hospital is a specialized hospital for the prevention and treatment of diabetes and its complications. Thus, the number of subjects with severe diabetic retinopathy was small in this study, which was different from the studies conducted in Beijing Tongren Hospital[6,7].

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In our study the overall prevalence of SCH was 26%. The prevalence of SCH in males was 22% among type 2 DM. The prevalence of SCH in females was 28% among type 2 DM indicating no significant difference between two groups.

Several mechanisms may be involved in the relationship between thyroid dysfunction and microvascular complications in diabetes. Firstly, it has been demonstrated that insulin resistance is associated with clinical and subclinical hypothyroidism[17].

A correlation between insulin resistance and microalbuminuria has been reported[18]. A possible mechanism could be defective fibrinolysis[19] or impaired vasodilation[20] associated with insulin resistance, and SCH decreased paraoxonase and arylesterase activities[21], meaning that the antioxidative capacity of SCH decreased significantly. However, oxidative stress plays an important role in the pathogenesis of diabetes-related complications; lipid levels may be responsible for the association. Disordered lipid metabolism was observed in patients with subclinical hypothyroidism[22,23]. As is well known, dyslipidemia plays an important role in the pathogenesis of diabetic complications[24]. SCH is often complicated with endothelial dysfunction, manifested by thickening of the capillary basement membrane[25,26]. It has been reported that endothelial dysfunction can affect the pathogenesis of diabetic complication[7]. Lastly, thyroid hormone influences kidney growth, kidney structure, and many of its functions[27]. Overt and subclinical hypothyroidism affects kidney function as a result of cardiac dysfunction, peripheral vascular resistance, endothelial dysfunction, and renal hemodynamics.

CONCLUSION

In conclusion, we could demonstrate an association between SCH and microalbuminuria, macroalbuminuria, low GFR, DKD and impaired vibration sense. However, we could not find any association between age distribution and sex of the patients and TSH levels between duration of diabetes and HbA1c levels and TSH levels and also, between retinopathy and TSH levels.

Our study was a cross sectional study, conducted in a tertiary care centre. Our study has demonstrated the association between elevated TSH and microvascular complications of type2 DM.

Considering the above facts, all patients with diabetes mellitus should be screened for thyroid dysfunction and microvascular complications. It is also important to know whether appropriate thyroid replacement therapy is beneficial for type 2DM patients with high normal TSH levels.

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