ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

A study of the association of thyroid-stimulating hormone levels with microvascular complications in type 2 diabetes mellitus patients at a tertiary care center

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Submission: 20-12-2025 Revision: 30-01-2025 Publication: 01-03-2025

ABSTRACT

Background: Diabetes mellitus (DM) and hypothyroidism are two of the most common metabolic diseases worldwide. The prevalence of both conditions is drastically on the rise and if untreated is associated with long-term complications. Several studies have established the association between hypothyroidism and microvascular complications of diabetes. However, with the ever increasing diagnosis of sub-clinical hypothyroidism among diabetics, its association with the microvascular complications of DM needs to be studied. **Aims and Objectives:** The aims of this study were to study the association between thyroid-stimulating hormone (TSH) levels and microvascular complications of type 2 DM (T2 DM). DM is a metabolic disease which affects various organs of the body. The prevalence of T2 DM is on the rise much more rapidly, which is due to increasing obesity and reduced activity levels. Undiagnosed thyroid dysfunction may affect metabolic control and enhance cardiovascular and other chronic complication in diabetic patients. **Materials and Methods:** A total of 50 T2 DM patients were enrolled in this cross-sectional study. Subjects were evaluated for thyroid function, microvascular complications such as peripheral neuropathy, diabetic retinopathy, and diabetic kidney disease. TSH was divided into three levels: 0.27–2.49 mU/L, 2.5–4.2 mU/L, and >4.2 mU/L. The association between TSH levels and microvascular complications of T2 DM was studied. **Results:** Our study found a statistically positive association elevated TSH and microalbuminuria, macroalbuminuria, low GFR, and impaired vibration sense. Our study found no association between elevated TSH and retinopathy. **Conclusion:** It is ideal to screen all patients with T2 DM for thyroid dysfunction as elevated TSH levels in these patients can be an indicator of underlying microvascular complications.

Key words: Subclinical hypothyroidism; Diabetes mellitus; Microvascular complications; Retinopathy; Nephropathy; Neuropathy

Access this article online

Website: https://ajmsjournal.info/index.php/AJMS/index

DOI: 10.71152/ajms.v16i3.4368

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Type 2 diabetes mellitus (T2 DM) and hypothyroidism are two chronic non-communicable diseases which require lifelong follow-up and treatment. Both the diseases have lifelong effects on cardiovascular morbidity and mortality with increased risk pointing to the former. Hypothyroidism is associated with increased risk of coronary artery disease, with hypertension, dyslipidemia, and obesity being important contributory factors.[1] The prevalence of subclinical hypothyroidism in T2 DM is around 14.1% in an Indian population.[2] Subclinical hypothyroidism is associated with

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deterioration of endothelial dysfunction in patients with T2 DM.[3] Hypothyroidism increases the risk of microvascular complications in patients with T2 DM.[4-6] Even among T2 DM patients who are euthyroid, thyroid hormone levels have been associated with microvascular complications.[7] This study was conducted to determine the association between thyroid-stimulating hormone (TSH) levels and microvascular complications in T2 DM subjects in a tertiary care center.

Aims and objectives

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

MATERIALS AND METHODS

The present study was a single-center and cross-sectional study conducted on patients with T2 DM visiting the outpatient department or admitted in the wards of general medicine department of RajaRajeswari Medical College and Hospital, Bangalore, over a period of 1 year. Before initiation of the study, Ethical and Research Committee clearance was obtained from the Institutional Ethical Committee. The Institutional Ethical Committee meeting was held on October 16, 2019, where the study protocol was presented. After detailed deliberations, the committee's approval for the study was granted on October 19, 2019. During the present study, a total 86 patients with type 2 Diabetes were reviewed, among which 50 (58.13%) patients were enrolled into the study according to the inclusion criteria and 36 (41.80%) patients were excluded according to exclusion criteria.

Inclusion criteria

The inclusion criteria for the study were both male and female patients above 40 years of age diagnosed with T2 DM.

Exclusion criteria

The exclusion criteria were patients with T1 DM, past history of thyroid diseases, TSH> 10mIU/L, overt hypothyroidism, treatment with levothyroxine or anti-thyroid drugs, pregnancy, acute or chronic infection, malignancy, chronic kidney disease (CKD), patients on hemodialysis, age <40 years, and critically ill patients.

A detailed history was obtained from the study subjects and a thorough physical examination was performed for each subject. Thyroid function test was performed in all subjects by chemiluminescence assay using Beckman Coulter automated immunoassay analyzer, ACCESS 2 model. The study group was divided into three categories for further analysis according to the TSH levels: 0.27–2.49 mIU/L; 2.5–4.2 mIU/L; and >4.2 mIU/L. All subjects were assessed for microvascular complications of diabetes such as diabetic nephropathy, neuropathy, and retinopathy.

Diabetic kidney disease (DKD) was defined as estimated glomerular filtration rate <60 mL/min/1.73 m2 (calculated by CKD-EPI formula) or presence of microalbuminuria/macroalbuminuria. Albumin creatinine ratio (ACR) was measured in spot urine sample to determine the presence of microalbuminuria (30–300 mg/g) or macroalbuminuria (>300 mg/g). Fundoscopy was done to detect diabetic retinopathy (DR). DR was defined on the basis of the international clinical DR severity scale.

Diabetic neuropathy was assessed by testing for vibration sense using 128Hz tuning fork. The tuning fork is struck and placed on bony points starting peripherally at the terminal phalanx, then over the medial or lateral malleoli, tibial tuberosity, anterior superior iliac spine, ribs or costal margins, lower end of radius, elbow, and clavicle. Vibration sense was compared on both sides and also with the sensation of the examiner at the same points. Reduction in vibration sense of the study subject compared to that of the examiner was considered as an indicator of diabetic neuropathy.

The sample size was calculated to be 50, as per the Yamane equation.

Yamane Equation: (for known population size) (Sample size) $n = N/1+N(e)^2$ Where

N=sample size, e=margin of error

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

Stages of diabetic retinopathy

Disease severity level	Findings observable on dilated ophthalmoscopy
No apparent retinopathy	No abnormalities
Mild non-proliferative diabetic retinopathy (NPDR)	Microaneurysms only
Moderate NPDR	More than just microaneurysms but less than severe NPDR
Severe NPDR	Any of the following: - More than 20 intraretinal hemorrhage each of four quadrants - Definitive venous beading in two or more quadrants - Prominent intraretinal microvascular abnormalities in one (or) more quadrant and no signs of PDR
Proliferative diabetic retinopathy (PDR)	One or more of the following: Neovascularization, vitreous hemorrhage, and photocoagulation scars.

n=56 (Population size is based on an average of these years hospital record on inclusion criteria) $n=56/1+(56\times0.05^2)=49.12\sim50$

The collected data were entered into Microsoft Excel Worksheet-2010 and data were 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. $P<0.05$ is considered significant.

RESULTS

The total number of subjects included in the study is 50, all in the age group of more than 40 years to 70 years. Two patients were aged between 41 and 45 years, seven patients between 46 and 50 years, 14 patients were aged between 51 and 55 years, 21 patients were between 56 and 60 years, and six patients were aged more than 60 years. Mean age of patients was 55.1 years. Mean age of the female patients was 55.34 years, while the mean age of male patient is 54.89 years. Age distribution showed majority of patients aged between 56 and 60 years.

The total number of subjects included in the study are 50, out of which 32 were male (64%) and 18 were female (36%). Male-to-female ratio was found to be 1.7:1. Out of 50 patients, 18 patients had TSH value between (0.27–2.49). Eighteen patients had TSH value between (2.5–4.20) and 13 of patients had TSH >4.2 (Table 1).

TSH levels were analyzed according to age distribution of the subjects. Among two patients in the age group of 41–45 years, one patient had TSH value in the range of (0.27–2.49) and one patient had TSH value in the range of (2.5–4.20). None of the patient had TSH >4.20. Among seven patients in the age group of 46–50 years, three of them had their TSH values in the range of (0.27–2.49), two patients had TSH value in the range of (2.5–4.2), and two patients had their TSH >4.2.

Among 14 patients in the age group of 51–55, four of them had their TSH value in the range of 0.27–2.49, six patients had TSH value in the range of 2.5–4.2, and four had their TSH >4.2. Among 21 patients in the age group of 56–60 years, seven patients had their TSH in the range of 0.27–2.49, eight patients had their TSH in the range of 2.5–4.20, and six patients had their TSH >4.2. Among six patients aged more than 60 years, three patients had their TSH between (0.27–2.49), two patients had their TSH (2.5–4.2), and one patient had TSH >4.2. There was no significant association between the age of the subjects and the TSH levels (P=0.23).

Table 1: TSH distribution in the study subjects

Sex	Frequency	Percentage
TSH (0.27–2.49)	18	36
TSH (2.50–4.20)	19	38
TSH (>4.20)	13	26
Total	50	100

TSH: Thyroid-stimulating hormone

TSH levels were analyzed according to the gender distribution of the study subjects. Among 32 males, 12 patients had TSH value between 0.27 and 2.49, 11 patients had TSH between 2.5 and 4.2, and nine patients had TSH >4.2. Among 18 females, six had TSH between 0.27 and 2.49, eight had TSH between 2.5 and 4.2, and four had TSH >4.2. No significant association was found between the gender distribution of the patients and TSH levels (P=0.08).

The association between the duration of diabetes and TSH levels was studied. Among patients with duration of diabetes 5–6 years, five patients had TSH value between (0.27 and 2.49), six patients had TSH between (2.5 and 4.2), and four had TSH >4.2. Among patients with duration of diabetes of 7–8 years, eight had their TSH between (0.27 and 2.49), seven patients had TSH (2.5–4.2), and five patients had TSH >4.2. Among patients with duration of diabetes 8–9 years, three patients had their TSH between (0.27 and 2.49), four patients had their TSH in the range of (2.5–4.2), and four patients had TSH >4.2. Among patients with duration of diabetes >10 years, two had their TSH between 0.27–2.49, four patients had their TSH in the range of 2.5–4.2, and none had their TSH >4.2. There was no significant association between duration of diabetes and TSH levels (P=0.14).

The association of TSH levels with Hba1c was studied. Among patients with their HbA1c values between 7 and 8%, one had their TSH between 0.27–2.49, two had their TSH in the range of 2.5–4.2, and none had TSH >4.2. Among patients with their hemoglobin A1c (HbA1c) values between 8 and 9%, four had their TSH between 0.27 and 2.49, five had their TSH between 2.5 and 4.2, and three had TSH >4.2. Among patients with their HbA1c value of 10–11%, seven had their TSH in the range of 0.27–2.49, seven had their TSH between 2.5 and 4.2, and six had their TSH >4.2. Among patients with their HbA1c value of >12%, six had their TSH value between 0.27 and 2.49, five patients had their TSH value between 2.5 and 4.2, and four patients had their TSH >4.2. No significant association was found between TSH level and Hba1c (P=0.09) (Table 2).

The association between TSH levels and retinopathy was studied. Retinopathy was present in eight patients with TSH between 0.27 and 2.49, nine patients with TSH between

2.5 and 4.2, and in seven patients with TSH >4.2. No significant association was found between TSH levels and retinopathy (P=0.15) (Table 3).

Microalbuminuria was present in three patients with TSH between 0.27 and 2.49, three patients with TSH between 2.5 and 4.2, and in four patients with TSH >4.2. A statistically significant association was found between higher TSH levels and presence of microalbuminuria (P=0.01) (Table 4).

Macroalbuminuria was present in two patients among those with TSH between 0.27 and 2.49, in two patients among those with TSH between 2.5 to 4.2, and in four patients among those with TSH>4.2.A significant association was found between higher TSH levels and macroalbuminuria with P=0.01 (Table 5).

Seventeen patients with TSH 0.27–2.49, 18 patients with TSH 2.5–4.2, and ten patients with TSH >4.2 had GFR >60 mL/min/1.73m^2. One patient with TSH 0.27–2.49, one patient with TSH 2.5–4.2, and three patients with TSH >4.2 had GFR <60 mL/min/1.73m^2 (Table 6). A significant association was found between higher TSH levels and low GFR with P=0.001.

The association between TSH levels and DKD was studied. DKD was present in three patients with TSH between 0.27 and 2.49, in four patients with TSH 2.5–4.2, and six patients with TSH >4.2. Table 7 shows the association between DKD and TSH levels. A significant association was found between higher TSH levels and DKD (P=0.001).

Table 2: Association between Hba1c and TSH level

HbA1c	TSH (0.27-2.49) (%)	TSH (2.50-4.20) (%)	TSH (>4.20) (%)	P-value
7–8	1 (5.55)	2 (10.50)	0 (00.00)	0.09
8–9	4 (22.22)	5 (26.31)	3 (23.07)	
10–11	7 (38.88)	7 (36.84)	6 (46.15)	
≥12	6 (33.33)	5 (26.31)	4 (30.76)	
Total	18	19	13	

HbA1c: Hemoglobin A1c, TSH: Thyroid-stimulating hormone

Table 3: Association between TSH levels and retinopathy

Retinopathy	TSH (0.27-2.49)	TSH (2.50-4.20)	TSH (>4.20)	P-value
Yes	8 (44.44)	9 (47.36)	7 (53.84)	0.15
No	10 (55.55)	10 (52.63)	6 (46.15)	
Total	18	19	13	

TSH: Thyroid-stimulating hormone

Table 4: Association between TSH levels and microalbuminuria

Microalbuminuria	TSH (0.27-2.49) (%)	TSH (2.50-4.20) (%)	TSH (>4.20) (%)	P-value
Yes	3 (16.66)	3 (15.78)	4 (30.76)	0.01
No	15 (83.33)	16 (84.21)	9 (69.23)	
Total	18	19	13	

TSH: Thyroid-stimulating hormone

Table 5: Association between macroalbuminuria and TSH Levels

Macroalbuminuria	TSH (0.27-2.49) (%)	TSH (2.50-4.20) (%)	TSH (>4.20) (%)	P-value
Yes	2 (11.11)	2 (10.52)	3 (23.07)	0.01
No	16 (88.88)	17 (89.47)	10 (76.92)	
Total	18	19	13	

TSH: Thyroid-stimulating hormone

Table 6: Association between GFR and TSH Levels

GFR	TSH (0.27-2.49) (%)	TSH (2.50-4.20) (%)	TSH (>4.20) (%)	P-value
>60 mL/min/1.73 m^2	17 (94.44)	18 (94.73)	10 (76.92)	0.001
<60 mL/min/1.73 m^2	1 (5.55)	1 (5.26)	3 (23.07)	
Total	18	19	13	

TSH: Thyroid-stimulating hormone, GFR: Glomerular filtration rate

Table 7. Association between diabetic kidney disease and TSH levels

Diabetic kidney disease	TSH (0.27-2.49) (%)	TSH (2.50-4.20) (%)	TSH (>4.20) (%)	P-value
Present	3 (16.66)	4 (21.05)	6 (46.15)	0.001
Absent	15 (83.33)	15 (78.94)	7 (53.84)	
Total	18	19	13	

TSH: Thyroid-stimulating hormone

Table 8: Association between vibration sense and TSH levels

Vibration sense	TSH (0.27-2.49) (%)	TSH (2.50-4.20) (%)	TSH (>4.20) (%)	P-value
Normal	11 (61.11)	10 (52.63)	5 (38.46)	0.02
Abnormal	7 (38.88)	9 (47.36)	8 (61.53)	
Total	18	19	13	

TSH: TSH: Thyroid-stimulating hormone

Eleven patients with TSH value 0.27–2.49, ten patients with TSH value 2.5–4.2, and five patients with TSH >4.2 had normal vibration sense, whereas seven patients with TSH value 0.27–2.49, nine patients with TSH value 2.5–4.2, and eight patients with TSH >4.2 had abnormal vibration sense. Table 8 shows the association between vibration sense and TSH levels. A significant association was found between higher TSH levels and impaired vibration sense with P=0.02.

DISCUSSION

The present study is a cross-sectional study conducted at a tertiary care hospital over a period of 1 year on patients with T2 DM attending the outpatient department or admitted as inpatients, fulfilling the inclusion/exclusion criteria. The study was conducted to determine the association between TSH levels and microvascular complications of diabetes. The present study showed a significant association between high TSH levels and low GFR. Similarly in a study conducted by Yang et al.,[8] a negative correlation was found between TSH levels and GFR. Chen et al.,[9] also found a significant association between high TSH levels and low GFR.

A significant association was found between albuminuria and higher TSH levels in the present study. This finding is consistent with the result of the study conducted by Gao et al.,[10] where a positive correlation was found between TSH and UACR. Similarly, Najmaldin et al.,[11] also concluded that T2 DM patients with SCH patients had a higher rate of albuminuria as compared to euthyroid patients and increasing TSH values were associated with increasing urine ACR. DKD was significantly associated with higher TSH levels in the present study. Similar findings were stated in a study conducted by Gao et al.,[10] where increased TSH was associated with DKD in type 2 diabetes patients. In a study conducted by Al-Majedy et al.,[12] SCH was independently associated with CKD in T2 DM.

The present study found a significant association between TSH levels and diabetic peripheral neuropathy. In a study conducted by Allam et al.,[6] SCH was found to be highly prevalent in diabetic peripheral neuropathy and independently related with its severity. Furthermore, Hu et al.,[7] also found a significant positive association between TSH levels and diabetic peripheral neuropathy. Reshdat et al.,[13] also concluded that the severity of neuropathy in diabetic patients is related to subclinical hypothyroidism.

Our study did not find an association between TSH levels and DR. Similarly, in a study conducted by Kassawneh et al.,[14] no significant association was found between thyroid dysfunction and DR. Even Zou et al.,[15] did not find any association between TSH levels and DR. However, in a study conducted by Hejrat et al.,[16] an association was found between DR and elevated TSH levels.

Limitations of the study

The study had a few limitations like a small sample size and single centre study.

CONCLUSION

This study was conducted to determine the association between TSH levels and microvascular complications of T2 DM. This study found a significant association between elevated TSH levels and microalbuminuria, macroalbuminuria, low GFR, DKD, and diabetic peripheral neuropathy. However, no association was found between TSH levels and DR. Hence, an association was demonstrated between TSH levels and microvascular complications of T2 DM.

ACKNOWLEDGMENT

We would like to express our gratitude to all the patients for their consent and co-operation to participate in the

study. We are also thankful to the faculty members for their guidance.

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Authors' Contributions:
SB- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **PS-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **MP-** Design of study, statistical analysis, and interpretation.

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Source of Support: Nil, **Conflicts of Interest:** None declared.