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# Thyroid hormonal variations: An overlooked factor in type 2 diabetes mellitus

Sadiya Sanjer [1], Sollapurappa Narayanaswamy Bhagyamma [2], Mohammed Abdul Majeed [3]*

1. Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Mangalgiri, Andhra Pradesh, India
2. Department of Biochemistry, Government Medical College, Anantapuramu, Andhra Pradesh, India
3. Department of Pharmacology, Government Medical College Paderu, Andhra Pradesh, India

* Correspondence: Mohammed Abdul Majeed. Department of Pharmacology, Government Medical College Paderu, Andhra Pradesh, India. Tel: +9700843778; Email: drmamajeed@yahoo.com

## Abstract

**Background:** Type 2 diabetes mellitus (T2DM) and thyroid dysfunction are recognized as two of the most widespread endocrine conditions in clinical settings. Untreated thyroid dysfunction can detrimentally affect the metabolic management of individuals with diabetes. Despite the significant metabolic interplay between these disorders, thyroid dysfunction frequently goes undetected in diabetic populations. Specifically, subclinical hypothyroidism has been linked to compromised glycemic control and an elevated risk of cardiovascular events. Consequently, this study is designed to assess the prevalence and specific profile of thyroid hormone alterations among T2DM patients. It also aims to investigate the relationship of these alterations with key clinical factors, including glycemic control (Glycated hemoglobin [HbA1c]), duration of diabetes, and patient demographics (Gender and age).

**Methods:** The current cross-sectional observational study was carried out at a tertiary care teaching hospital. In this study enrolled 200 participants. These individuals were systematically divided into two equally sized groups: A patient group comprising participants aged 30 to 70 years diagnosed with T2DM, and a control group consisting of healthy individuals precisely matched for both age and gender. An in-depth patient history was initially collected, succeeded by a clinical examination and a biochemical assessment. Comprehensive data encompassing demographic characteristics and biochemical markers were acquired and compiled.

**Results:** The research uncovered varying patterns of thyroid dysfunction among T2DM subjects, with subclinical hypothyroidism identified as the leading manifestation (24%). The occurrence rate of thyroid dysfunction was markedly elevated in the T2DM cohort relative to the non-diabetic reference group ($p < 0.001$). A strong, statistically significant positive association ($r = 0.76$, $p < 0.001$) emerged between increased TSH concentrations and inadequate glycemic control (HbA1c > 8%). Thyroid dysfunction demonstrated a higher frequency specifically in postmenopausal women and in patients whose duration of diabetes exceeded 5 years.

**Conclusion**: The result of study showed that the implementation of standardized, stratified thyroid screening protocols is recommended for all T2DM patients during their initial diagnostic evaluation. An annual follow-up is also advised, with particular emphasis on high-risk subsets. This proactive approach facilitates early identification of thyroid dysfunction, thereby mitigating associated diabetic complications and optimizing integrated endocrine management.

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## Highlights

**What is current knowledge?**

Current Practice of Thyroid Screening in T2DM: Routine clinical practice for thyroid evaluation in T2DM patients generally involves TSH screening only for euthyroid individuals who exhibit TSH concentrations exceeding 2.5 mU/L or possess detectable TPO antibodies. This approach signifies a lack of specific recommendations or a uniform protocol for systematic, routine TSH screening across the entire T2DM patient population.

**What is new here?**

This study offers insightful suggestions for the inclusion criteria of thyroid screening in T2DM, specifically advocating for the consideration of poor glycemic control (HbA1c > 8%), longer T2DM duration (Exceeding five years), and gender/age factors (Such as post-menopausal women). These proposed parameters can inform the development of a novel, universally stratified screening protocol for thyroid dysfunction, which would facilitate earlier detection, complication prevention, and ultimately improve integrated endocrine care.

## Introduction

Type 2 diabetes mellitus (T2DM) and thyroid dysfunction constitute significant endocrine disorders, sharing intricate clinical and metabolic overlaps. The systemic concentrations of circulating thyroid hormones influence various organs and cellular functions via nuclear receptor mechanisms. Specifically, thyroid hormones exert considerable control over the homeostasis of glucose, lipid, and protein metabolism. The thyroid, a key endocrine gland, is susceptible to compromise due to persistent states of hyperglycemia and the body's ongoing compensatory mechanisms aimed at addressing this chronic carbohydrate dysregulation. Multiple research studies have consistently documented minor fluctuations in the concentrations of thyroid hormones within individuals with diabetes (1-3). While the co-occurrence of T2DM and thyroid dysfunction might be coincidental, specific pathological links exist, involving conditions such as polyglandular autoimmune syndromes 1 and 2, multiple endocrine neoplasia (MEN) types 1 and 3, and various genetic or autoimmune factors. Although numerous etiologies underlie thyroid dysfunction, it is significant that hyperthyroidism actively detrimentally affects glycemic control in diabetic patients, whereas subclinical hypothyroidism shows a strong association with impaired blood glucose control and heightened

cardiovascular risk. The clinical importance of thyroid disorders in diabetic patients becomes much greater when thyroid function is impaired, as this can result in severe complications, such as frequent hypoglycemia in hypothyroidism and potentially life-threatening ketoacidosis in thyrotoxicosis, making diabetes management more challenging (4-6). While routine screening for dyslipidemia and nephropathy is common in T2DM, thyroid screening is not consistently prioritized. Therefore, diabetic patients should undergo annual thyroid screening to identify any asymptomatic thyroid dysfunction (7).

The current research is designed to assess the frequency and characteristic distribution of thyroid hormone alterations among individuals with T2DM. It will also examine the relationship between these alterations and glycemic control (Glycated hemoglobin [HbA1c), the duration of T2DM, and the patient's age and gender. Furthermore, the study aims to underscore the imperative for routine thyroid screening within T2DM management, proposing stratified protocols essential for comprehensive, integrated endocrine care.

## Methods

This observational, cross-sectional study was implemented over a 12-month period at a tertiary care teaching hospital in India. Prior to commencement, Institutional Ethics Committee approval was secured, and informed consent was obtained from all recruited participants. The study ultimately encompassed a total of 200 subjects. This cohort comprised two equally sized groups: A patient group, consisting of 100 diagnosed T2DM cases, aged 30 to 70 years and of both genders, and a control group, consisting of 100 non-diabetic individuals meticulously matched for both age and gender. A comprehensive clinical history was recorded, and participants underwent a thorough physical examination and complete biochemical evaluation. Individuals reporting a prior diagnosis of thyroid disease, those taking thyroid-altering medications, and pregnant women were systematically excluded. The final dataset was collected and organized to include demographic variables (Age and gender), the duration of T2DM, and specific biochemical parameters, including fasting blood sugar (FBS), postprandial blood sugar (PPBS), HbA1c, thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4). Anti-thyroid peroxidase (TPO) testing, although optional, was not performed because our study aimed to assess thyroid status and determine the necessity for treatment, rather than investigate the causes of thyroid dysfunction. Standard reference ranges were used to interpret the various biochemical parameters (Table 1) (8-10).

**Table 1.** Standard reference values for biochemical parameters

| Parameter | Normal reference range |
|---|---|
| FBS | 70 - 100 mg/dL |
| PPBS | < 140 mg/dL |
| HbA1c | < 5.7% (Normal) |
| TSH | 0.4 - 4.0 (µIU/mL) |
| FT3 | 2.0 - 4.4 pg/mL |
| FT4 | 0.8 - 2.0 ng/dL |

FBS: Fasting Blood Sugar, PPBS: Postprandial Blood Sugar, HbA1c: Glycated Hemoglobin, TSH: Thyroid Stimulating Hormone, FT3: Free Triiodothyronine, FT4: Free Thyroxine

The thyroid function status for every participant was assessed and then categorized according to standard classification guidelines (Table 2). This categorization yielded 5 distinct groups: Euthyroid, subclinical hypothyroidism, overt hypothyroidism, subclinical hyperthyroidism, and euthyroid sick syndrome, all based on the respective thyroid function test results.

**Table 2.** Thyroid status classification

| Classification | TSH (mIU/L) | FT4 (ng/dL) | FT3(pg/mL) |
|---|---|---|---|
| Euthyroid | Normal | Normal | Normal |
| Subclinical Hypothyroidism | ↑ | Normal | Normal |
| Overt Hypothyroidism | ↑ | ↓ | ↓ |
| Subclinical Hyperthyroidism | ↓ | Normal | Normal |
| Euthyroid Sick Syndrome | Normal/↓ | ↓ | ↓ |

TSH: Thyroid Stimulating Hormone, FT3: Free Triiodothyronine, FT4: Free Thyroxine

### Statistical analysis

Data analysis was conducted using SPSS software version 25.0. Continuous variables were reported as the mean ± standard deviation, while categorical variables were presented as percentages. Statistical relationships were assessed using Pearson's correlation for continuous data and the chi-square ($\chi^2$) test for categorical data.

## Results

The study cohort comprised 58% female and 42% male participants (Mean age = 52.4 ± 10.2 years), with a mean duration of T2DM exceeding 7 years (7.1 ± 3.5 years). T2DM patients demonstrated an elevated mean HbA1c value of 8.2 ± 1.3 overall. Female predominance was specifically noted within the patient population (Table 3).

**Table 3.** Patient demographics

| Variable | Mean ± Standard Deviation |
|---|---|
| Age (Years) | 52.4 ± 10.2 |
| Mean duration of T2DM (Years) | 7.1 ± 3.5 |
| Mean HbA1c (%) | 8.2 ± 1.3 |

T2DM: Type 2 Diabetes Mellitus, HbA1c: Glycated Hemoglobin

Within the cohort of T2DM patients (n = 100), hypothyroidism was identified in 34% of subjects, encompassing both subclinical and overt hypothyroidism. The most frequently observed thyroid condition in the T2DM group was subclinical hypothyroidism (24%), followed sequentially by overt hypothyroidism (10%), subclinical hyperthyroidism (8%), and euthyroid sick syndrome (6%) (Table 4).

**Table 4.** Prevalence of thyroid dysfunction in type 2 diabetes mellitus (T2DM)

| Thyroid Dysfunction | N =100 |
|---|---|
| Subclinical Hypothyroidism | 24 (24%) |
| Overt Hypothyroidism | 10 (10%) |
| Subclinical Hyperthyroidism | 8 (8%) |
| Euthyroid Sick Syndrome | 6 (6%) |
| Euthyroid | 52 (52%) |

The thyroid status of all participants underwent rigorous analysis. The prevalence of thyroid dysfunction was significantly elevated in individuals diagnosed with T2DM compared to the non-diabetic control group (64% versus 16%; $p < 0.001$). Among subjects exhibiting abnormal thyroid function, hypothyroidism was identified as the predominant abnormality observed, contrasting with the euthyroid status (Figure 1).

T2DM patients were evaluated for thyroid function across various durations of their diabetes. It was found that the incidence of subclinical hypothyroidism raised as the duration of diabetes increased. Overt hypothyroidism and euthyroid sick syndrome were more frequently seen in individuals with diabetes lasting longer than 5 years. Overall, thyroid dysfunction of any type was significantly more prevalent in patients with T2DM lasting longer than 5 years. Subclinical hypothyroidism was the most commonly observed condition across all duration groups (Table 5).

The scatter plot depicts the interrelationship between HbA1c (A biomarker for long-term glycemic control) and TSH (A biomarker of thyroid function) in 100 individuals diagnosed with T2DM. A discernible positive correlation is evident between HbA1c percentages and TSH concentrations (µIU/mL). As elevated HbA1c values signify inadequate glycemic control, TSH levels generally demonstrate a corresponding increase, suggesting a likely link between suboptimal glycemic control and thyroid dysfunction. Notably, a statistically robust positive association ($r = 0.76$, $p < 0.001$) was established linking elevated TSH levels with poor glycemic control (HbA1c > 8%) (Figure 2).

The thyroid status of all T2DM patients was assessed based on gender. A female predominance in overall thyroid dysfunction was identified across the entire patient cohort. A statistically significant relationship was noted between thyroid function and gender (Chi-square [$\chi^2$] = 10.2, $p = 0.03$), with the prevalence of hypothyroidism being higher among females. Specifically, subclinical hypothyroidism represented the most frequent thyroid abnormality observed in females diagnosed with T2DM (Figure 3).

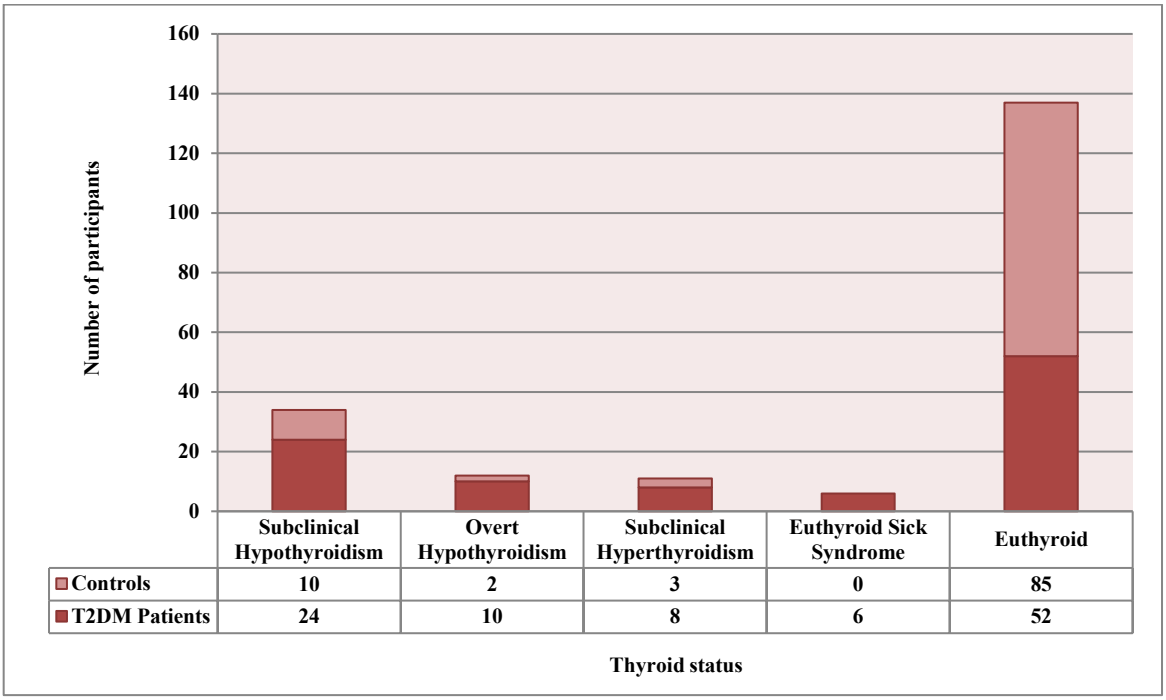


**Figure 1.** Thyroid dysfunction in type 2 diabetes mellitus (T2DM) patients versus controls

**Table 5.** Duration of type 2 diabetes mellitus (T2DM) versus thyroid dysfunction status in type 2 diabetes mellitus (T2DM) patients

| Duration of T2DM | Total patients | Euthyroid | Subclinical Hypothyroid | Overt Hypothyroid | Subclinical Hyperthyroid | Euthyroid Sick Syndrome |
|---|---|---|---|---|---|---|
| < 5 years | 30 | 21 | 6 | 2 | 2 | 1 |
| 5-10 years | 35 | 14 | 8 | 3 | 4 | 3 |
| > 10 years | 35 | 17 | 10 | 5 | 2 | 2 |
| Total | 100 | 52 | 24 | 10 | 8 | 6 |

T2DM: Type 2 Diabetes Mellitus

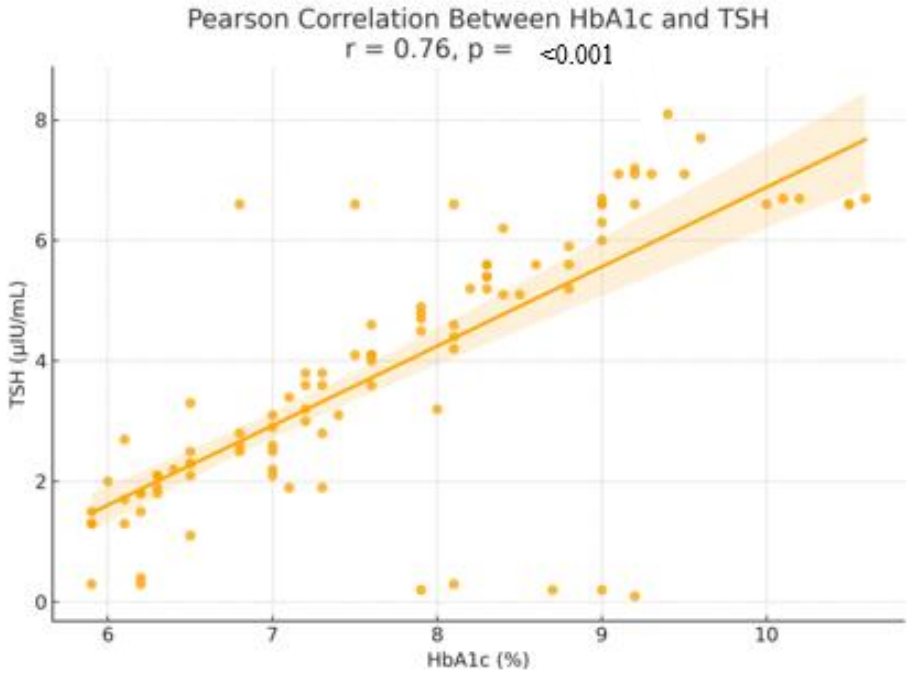


**Figure 2.** Correlation between glycated hemoglobin (HbA1c) and thyroid stimulating hormone (TSH) levels in type 2 diabetes mellitus patients

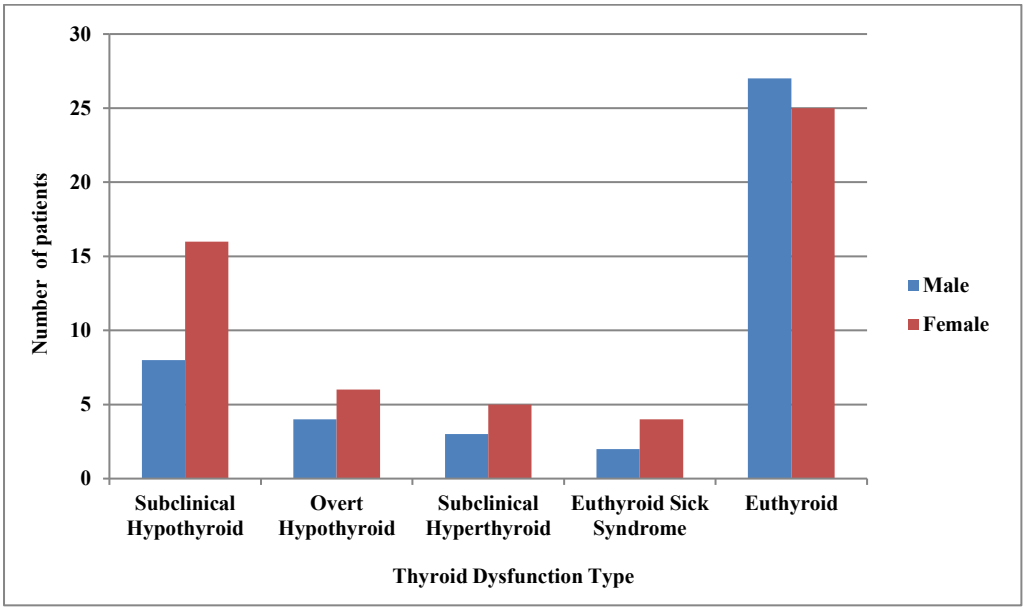


**Figure 3.** Gender-wise thyroid dysfunction in type 2 diabetes mellitus (T2DM)

## Discussion

The current study demonstrated thyroid dysfunction in T2DM patients, with subclinical hypothyroidism identified as the most prevalent form (24%). In contrast, the non-diabetic cohort exhibited a minimal prevalence of thyroid disorders. These findings align with prior research, which has established a significantly increased risk of thyroid dysfunction among diabetic individuals (1-4). The high frequency of subclinical hypothyroidism specifically underscores a strong clinical link between T2DM and altered thyroid function, supporting established literature and emphasizing the need for routine thyroid screening in all diabetic patients (7-16).

In individuals with long-term T2DM, a greater frequency of both overt hypothyroidism and euthyroid sick syndrome was observed, indicating progressive endocrine-metabolic dysregulation associated with the chronic nature of the disease. The prevalence of thyroid dysfunction demonstrated a direct relationship with the duration of T2DM. This elevated incidence of hypothyroidism is consistent with progressive dysregulation, underscoring the necessity of screening thyroid hormone levels in patients with long-standing T2DM (13,14). Persistent hyperglycemia and insulin resistance are known to compromise the function of the hypothalamic-pituitary axis. Elevated plasma glucose concentrations potentially inhibit the hypothalamic release of thyrotropin-releasing hormone (TRH). This action disrupts the normal feedback loop, which could then lead to increased TSH levels through an effect on hypothalamic neurons. This mechanism may also reduce sensitivity to circulating thyroid hormones. Prior research supports this hypothesis, demonstrating both disrupted circadian TSH secretion and altered TRH-TSH axis responsiveness in patients with uncontrolled T2DM. Insulin and its associated downstream signaling cascade elements are principally situated within the cortical and hippocampal brain regions. Key molecular components implicated in compromised insulin signaling encompass the insulin receptor substrate (IRS), phosphatidylinositol 3-kinase (PI3K), protein kinase B (Akt), and glycogen synthase kinase-3 beta (GSK-3β). The aberrant functioning of these core molecules, whether through enhanced or reduced phosphorylation-leading to activation or inactivation-is central to the development of insulin signaling defects or insulin resistance (3-15).

Significantly higher TSH concentrations demonstrated a strong positive correlation with suboptimal glycemic control, specifically measured by HbA1c ($r = 0.76$, $p < 0.001$). This observed association suggests that deteriorating glucose regulation relates to either an increased incidence or greater severity of thyroid gland impairment, notably subclinical or overt hypothyroidism. Such thyroid dysfunction could potentially exacerbate insulin resistance or, alternatively, manifest as a result of chronic metabolic stress, thereby confirming its likely contribution to the worsening of insulin resistance (10,11). Persistent hyperglycemia triggers a cascade involving oxidative stress, the release of cytokines, and microvascular injury within endocrine organs, including the thyroid gland. The resulting accumulation of advanced glycation end-products (AGEs) in thyroid tissue, along with concurrent local inflammation, may disrupt TSH receptor signaling or the process of iodide uptake. This ultimately compromises thyrocyte function, culminating in the development of hypothyroidism and elevated levels of TSH (17-19).

Thyroid dysfunction was observed more frequently among female patients, particularly those who were postmenopausal, and in individuals suffering from diabetes for longer than 5 years. This highlights the critical necessity for proactive screening for thyroid dysfunction, specifically targeting postmenopausal women and patients with chronic diabetes (12,13).

## Conclusion

A considerable proportion of T2DM patients present with undiagnosed thyroid dysfunction, which can negatively affect their glycemic control. Crucially, the prevalent subclinical thyroid dysfunction should not be overlooked; regular screening is essential to mitigate diabetes-related complications and achieve optimal glycemic control. A significant number of individuals with long-standing diabetes who fail to meet their glycemic targets, despite sufficient therapeutic intervention, are often found to exhibit abnormal TSH concentrations. Diabetic women experiencing menopause frequently and asymptomatically exhibit elevated serum TSH levels. These observations collectively underscore the imperative for TSH screening both during the initial diagnostic workup and throughout the annual follow-up of all T2DM individuals. It is therefore recommended to develop innovative, risk-stratified protocols for thyroid screening in T2DM. These protocols should consider specific high-risk factors: Female post-menopausal status, a history of chronically poor glycemic control (HbA1c > 8%), and a longer duration of T2DM (> 5 years). This approach will enable earlier detection and foster improved integrated endocrine management. A limitation of the current research is its inability to fully characterize the etiology of thyroid dysfunction among T2DM patients, a factor that could directly impact their metabolic status. Furthermore, to effectively establish thyroid screening protocols within T2DM management, there is a clear requirement for meta-analyses and longitudinal, multi-center studies. These efforts are necessary to validate the efficacy of specific biochemical parameter ranges-such as HbA1c thresholds indicating poor glycemic control-alongside gender, age, and duration of T2DM.

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## Ethical statement

This study received formal approval from the Institutional Ethics Committee of GMC Anantapuramu, Andhra Pradesh, India (Project code: 10-D/2021), which was sanctioned on October 1st, 2021. Prior to their involvement, informed consent was meticulously obtained from all participants before they were officially enrolled in the study.

## Conflicts of interest

No conflict of interest.

## Author contributions

Dr. Sadiya Sanjer: Major contributor to data collection, interpretation of patient data results, and drawing all final conclusions regarding the prevalence and patterns of thyroid dysfunction in T2DM. Dr. SN Bhagyamma: Overall proofreading and collecting relevant literature. Dr. Mohammed Abdul Majeed: Supporting in all aspects, including excluding patients on drugs influencing thyroid, statistical tools, and organizing data into tables and figures. All authors have read and approved the final manuscript.

## Data availability statement

All data is confidential and safely maintained on a drive by the authors.

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