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# Thyroid Dysfunction in South Indian Type 2 Diabetes: Prevalence, Clinical Correlates, and the Complex Interplay with Pharmacotherapy

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## Abstract

**Introduction:** Thyroid dysfunction (TD) is a common comorbidity in type 2 diabetes mellitus (T2DM), with bidirectional pathophysiological interactions. This study aimed to define its burden and correlates in a South Indian T2DM cohort.

**Methods:** This retrospective observational study analyzed 1,055 randomly selected patient records. TD was defined using standard criteria. Patients were stratified into groups based on thyroid status. Statistical analyses included chi-square tests, t-tests, calculation of odds ratios (OR), and multivariate logistic regression.

**Results:** The prevalence of TD was 14.7%, with clinical hypothyroidism (55.4% of TD cases) being predominant. Significant associations included female sex, family history of thyroid disease, BMI ≥25kg/$m^2$, advanced age, and anemia. Microvascular complications, especially diabetic retinopathy and erectile dysfunction, were strongly linked to TD, but not macrovascular events. Medication use analysis revealed that metformin and insulin were independently associated with overall TD and hypothyroidism after multivariate adjustment, and statin use was marginally linked with hypothyroidism. Simple prevalence associations for sulfonylureas, alpha-glucosidase inhibitors, and beta-blockers did not remain significant after adjustment.

**Conclusion:** TD is common in South Indian T2DM patients and linked to specific risk factors and microvascular complications. The associations of key medications with TD likely reflect underlying metabolic disease severity, underscoring the need for routine thyroid screening and rigorous statistical analysis.

**Keywords:** Thyroid Dysfunction; Type 2 Diabetes Mellitus; Hypothyroidism; Diabetes-Related Complications; Pharmacotherapy Associations

## Abbreviations

TD: Thyroid Dysfunction; DM: Diabetes Mellitus; T1DM: Type 1 Diabetes; T2DM: Type 2 Diabetes; SCH: Subclinical Hypothyroidism; ACE: Angiotensin Converting Enzyme; Arbs: Angiotensin Receptor Blockers; Tfts: Thyroid Function Tests; BMI: Body Mass Index; FBG: Fasting Blood Glucose; PPBG: Postprandial Glucose; Hba1c: Glycated Hemoglobin; TSH: Thyroid-Stimulating Hormone; T3: Triiodothyronine; HDL: High-Density Lipoproteins; LDL: Low-Density

Lipoproteins; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; EGFR: Estimated Glomerular Filtration Rate; DPN: Diabetic Peripheral Neuropathy; CAD: Coronary Artery Disease; CVD: Cerebrovascular Disease; PAD: Peripheral Artery Disease; ED: Erectile Dysfunction; ADA: American Diabetes Association; VPT: Vibration Perception Threshold; MI: Myocardial Infarction; ABI: Ankle-Brachial Index; OR: Odds Ratios.

## Introduction

Thyroid dysfunction (TD) is significantly more prevalent in individuals with diabetes mellitus (DM), affecting 10–15% of patients compared to 6% of the general population [1]. This comorbidity is driven by interconnected metabolic pathways between insulin and thyroid hormones, which can disrupt endocrine function and complicate clinical management. While autoimmune thyroiditis is well-documented in type 1 diabetes (T1DM), type 2 diabetes (T2DM) also shows a high and variable TD prevalence of 10–24% [2,3], rising to 31.4% in female subgroups [4].

Hypothyroidism (4.8–31.4%) is more common than hyperthyroidism (0.5–3.0%) within DM population [5]. Hyperthyroidism can worsen glycemic control and precipitate crises like diabetic ketoacidosis [6]. Conversely, overt and subclinical hypothyroidism (SCH) promote insulin resistance, exacerbating diabetes control and elevating the risk of cardiovascular disease, stroke, and microvascular complications [7,8]. Hypothyroidism and SCH have also been linked to increased risks for diabetic complications and erectile dysfunction in T2DM patients [9].

Medication interactions further complicate thyroid and diabetes management. Antidiabetic agents, such as metformin and insulin, can alter thyroid hormone concentrations and regulatory feedback [10,11]. Similarly, lipid-lowering [12] and antihypertensive drugs [13,14], including β-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), have variable effects on thyroid homeostasis and lipid metabolism, although the evidence remains inconsistent in euthyroid individuals.

Given these intricate relationships, profiling thyroid function, comorbidities, and medication use in T2DM is essential. This research is critical for developing effective screening and management strategies to improve outcomes in this high-burden population.

## Materials and Methods

This retrospective observational study analyzed 1,055 randomly selected patient records from a diabetes center in South India, following Institutional Ethics Committee approval. Based on a reported 17.5% TD prevalence in T2DM [15], a minimum sample of 262 participants was required. The final sample of 1,055 was selected to account for potential missing data and to enhance the robustness of the analysis. The study included T2DM patients aged ≥18 years with complete thyroid function tests (TFTs) and medical records. Exclusion criteria were incomplete data, age <18 years, pregnancy, T1DM, and use of drugs interfering with TFTs such as amiodarone, glucocorticoids, interferon, lithium, and iodide.

Data collection encompassed a wide range of parameters. Demographic and clinical data included sex, age, duration of diabetes, body mass index (BMI), blood pressure, family history of thyroid disease and diabetes, history of smoking, and the presence of dyslipidemia. Laboratory data included fasting blood glucose (FBG), 2-hour postprandial glucose (PPBG), glycated hemoglobin (HbA1c), and TFT - specifically thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3). Additional laboratory assessments consisted of the lipid profile [total cholesterol, triglycerides, high-density lipoproteins (HDL), low-density lipoproteins (LDL)], aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatinine, estimated glomerular filtration rate (eGFR), and uric acid. We systematically evaluated microvascular complications, including diabetic peripheral neuropathy (DPN), nephropathy, and retinopathy (DR); macrovascular complications, including coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral artery disease (PAD); and erectile dysfunction (ED).

Diagnostic criteria were rigorously defined. T2DM was diagnosed according to the American Diabetes Association (ADA) criteria [16]. TD was evaluated using established reference ranges: TSH (0.35–4.94 mIU/L), T4 (60-140 nmol/L), and T3 (1.1–2.7 nmol/L). Hyperthyroidism was diagnosed in the presence of low TSH with elevated T3 and T4, while hypothyroidism was identified by high TSH with low T3 and T4. Subclinical hyperthyroidism was defined as low TSH with normal T3 and T4, and SCH as elevated TSH with normal T3 and T4. Secondary hypothyroidism was diagnosed when T4 levels were low and TSH levels were low to normal. Autoimmune conditions were determined with reference to serum thyroid peroxidase antibody (TPO Ab) levels >5.61 kIU/L and/or thyroglobulin antibody levels >4.11 kIU/L. Individuals exhibiting any of these TFT abnormalities or with a documented history of thyroid disorders were classified as having TD.

DR was diagnosed by direct ophthalmoscopic examination after pupil dilation. DPN was confirmed using the Vibration Perception Threshold (VPT) test in patients with abnormal

ankle reflexes and/or an abnormal Monofilament Test or suggestive symptoms. CAD was diagnosed based on any of the following criteria: a documented history of myocardial infarction (MI); electrocardiogram (ECG findings indicative of ischemia or prior MI, as defined by Minnesota Code classification system (specifically codes 1.1–1.2, 4.1–4.3, and 5.1–5.3) [17], a positive stress test; echocardiographic evidence of a prior MI; coronary angiography demonstrating significant CAD (>70% stenosis in a major epicardial vessel or >50% left main stenosis); or a history of coronary revascularization. PAD was screened for using the Ankle-Brachial Index (ABI) test. Diabetic nephropathy was diagnosed in the presence of persistent albuminuria (urine albumin-to-creatinine ratio ≥3 mg/mmol on at least two of three occasions over 3–6 months) and/or an eGFR <60 mL/min/1.73 $m^2$, after excluding other primary causes of kidney damage. ED was diagnosed based on a single self-reported positive response to a direct inquiry by a physician. A stroke was defined by a documented history of stroke-related symptoms or treatments, or evidence of past ischemia or hemorrhage on radio-imaging techniques. Anemia was defined as a hemoglobin level of <120 g/L in females and <135 g/L in males.

Assessment of medication use included antidiabetic, antihypertensive, and antihyperlipidemic agents to evaluate their potential impact on thyroid function. The specific medications analyzed were second-generation sulfonylureas, metformin, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, insulin, and imeglimin for diabetes; second-generation β-blockers, ACE inhibitors, ARBs, calcium channel blockers, alpha-adrenergic blockers, and diuretics for hypertension; and statins and fibrates for hyperlipidemia. Glucagon-Like Peptide-1 Receptor Agonists and first-generation sulfonylureas and β-blockers were not included as none of the participants used them. In addition to comparing the prevalence of use, we analyzed the duration of use for each medication class.

For analytical purposes, patients were categorized into four groups based on thyroid function status: Group A (Any TD) included all patients with any thyroid disorder, including euthyroid goiter; Group B (Combined TD) comprised patients with combined hypothyroidism (clinical, subclinical, and secondary) and hyperthyroidism (clinical, subclinical, and secondary); Group C (Hypothyroidism) included patients with clinical and subclinical hypothyroidism; and Group D (Hyperthyroidism) consisted of patients with clinical and subclinical hyperthyroidism. All groups were individually compared with the no TD (NTD) group.

Statistical analysis was performed with categorical variables presented as percentages and continuous variables as mean ± standard deviation, with normality assessed. Group comparisons for baseline characteristics were performed using the student's t-test for continuous variables and the Chi-square test for categorical variables. Univariate logistic regression was used to evaluate associations between clinical factors and TD, with results expressed as odds ratios (OR) and 95% CI. The Chi-square test was applied to analyze associations of diabetes complications and medication use prevalence across study groups. To assess the relationship between medication duration and TD, multivariate logistic regression was employed, adjusting for age, gender, body mass index, and diabetes duration, with results reported as adjusted ORs (aOR) for the overall thyroid dysfunction group and its subgroups relative to the NTD group. A two-tailed P-value < 0.05 defined statistical significance.

## Results

A total of 1,055 patients with T2DM were included in this study. The baseline characteristics of the study population are detailed in Table 1. The mean age of participants was 53.6 ± 11.6 years, and 63% were male. The cohort had a mean HbA1c of 8.6 ± 2.8% (70±31 mmol/mol) and an average diabetes duration of 9.96 ± 8.41 years. A family history of T2DM was common (87%), while 15.3% reported a family history of thyroid disease. The mean thyroid hormone levels were as follows: T3, 3.36 ± 12.79 nmol/L; T4, 102.3 ± 47.4 nmol/L; and TSH, 2.59 ± 3.84 mIU/L.

| Baseline characteristics | All samples (n=1055) | Diabetic subjects with TD (n=155) | Diabetic subjects without TD (n=900) | P value |
|---|---|---|---|---|
| Age (years) | 53.6 ± 11.6 | 54.34±11.84 | 53.49±11.56 | 0.405 |
| Female gender | 37% | 65% | 32% | <0.001 |
| Duration of DM (years) | 9.96±8.41 | 9.86±8.71 | 9.98 ± 8.37 | 0.869 |
| Family history of DM | 87% | 85% | 87% | 0.259 |
| Family history of TD | 15.30% | 32% | 18% | <0.001 |
| BMI (kg/m2) | 26.04 ± 4.3 | 27.2 ± 5.56 | 25.85 ±3.97 | <0.001 |
| Systolic BP (mm Hg) | 130.2 ± 18.7 | 128.05±17.34 | 131.74±19.14 | 0.242 |

| | | | | |
|---|---|---|---|---|
| HbA1c % (mmol/mol) | 8.6 ± 2.8 (70 ± 31) | 8.6 ± 2.1 (70 ± 23) | 8.6 ± 2.9 (71 ± 32) | 0.873 |
| Total cholesterol (mmol/L) | 4.84 ± 1.18 | 5.26 ± 1.25 | 4.75 ± 1.22 | 0.085 |
| Triglycerides (mmol/L) | 1.74 ± 0.94 | 1.75 ± 0.72 | 1.78 ± 1.02 | 0.917 |
| HDL (mmol/L) | 1.14 ± 0.24 | 1.21 ± 0.21 | 1.13 ± 0.28 | 0.337 |
| LDL (mmol/L) | 3.08 ± 1.10 | 3.58 ± 1.18 | 3.04 ± 1.10 | 0.082 |
| Hemoglobin (g/L) | 137 ± 17.7 | 130 ± 17.3 | 139 ± 17.6 | <0.001 |
| AST (µkat/L) | 0.48 ± 0.23 | 0.45 ± 0.19 | 0.48 ± 0.24 | 0.701 |
| ALT (µkat/L) | 0.65 ± 0.37 | 0.52 ± 0.21 | 0.67 ± 0.38 | 0.055 |
| T3 (nmol/L) | 3.36 ± 12.81 | 2.44 ± 2.66 | 1.66 ± 0.52 | 0.019 |
| T4 (nmol/L) | 102.3 ± 47.4 | 100.4 ± 55.7 | 109.6 ± 26.5 | 0.216 |
| TSH (mIU/L) | 2.59 ± 3.84 | 4.45 ± 6.51 | 1.9 ± 1.51 | <0.001 |
| Serum creatinine (µmol/L) | 85.7 ± 50.4 | 80.4 ± 29.2 | 86.6 ± 52.2 | 0.195 |
| e-GFR (mL/ min/1.73m$^2$) | 86.8±22.3 | 84.3±23.11 | 87.12±22.13 | 0.208 |

**Table 1:** Baseline characteristics of the study population stratified by thyroid dysfunction status.

**Legend:** Data are presented as mean ± standard deviation or percentage. P-values are derived from Student's t-test for continuous variables and Chi-square test for categorical variables. Abbreviations: TD, Thyroid Dysfunction; DM, Diabetes Mellitus; BMI, Body Mass Index; BP, Blood Pressure; HbA1c, Glycated Hemoglobin; HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; T3, Triiodothyronine; T4, Thyroxine; TSH, Thyroid-Stimulating Hormone; e-GFR, estimated Glomerular Filtration Rate. Bolded p-values indicate statistical significance (P<0.05).

TD was identified in 155 individuals, constituting a prevalence of 14.7% (Figure 1). Among the TD cases, clinical hypothyroidism was the most prevalent form (55.4%), followed by SCH (18.1%), clinical hyperthyroidism (5.8%), subclinical hyperthyroidism (1.3%), and secondary hypothyroidism (1.3%). Goiter was present in 18.1% of TD patients, with 7.7% of these having undergone thyroidectomy for indications including large benign nodules, multinodular goiter, or thyroid carcinoma. Data on autoimmune status were incomplete and were consequently excluded from the analysis.

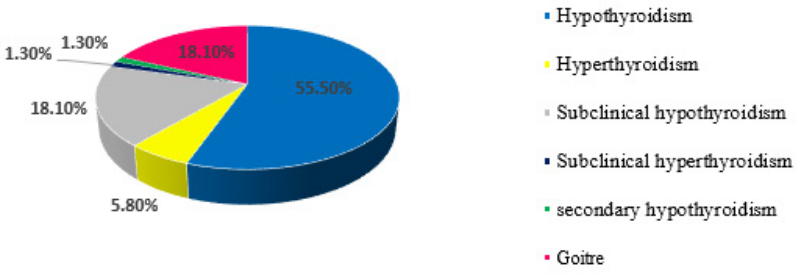


**Figure 1:** Prevalence of Thyroid Dysfunction in a South Indian Type 2 Diabetes Cohort.
**Legend:** Pie chart showing the proportion of patients with and without thyroid dysfunction (TD). The analysis included 1,055 individuals with type 2 diabetes mellitus (T2DM), of which 155 (14.7%) were found to have TD.

A comparison of clinical and demographic factors between the TD and NTD groups revealed several significant associations (Table 2). In Group A, a family history of thyroid disease (OR = 2.17; 95% CI: 1.49-3.16; P<0.001), female sex (OR = 3.82; 95% CI: 2.67-5.47; P<0.001), BMI ≥25 kg/m$^2$ (OR = 1.5; 95% CI: 1.05-2.14; P=0.026), and the presence of anemia (OR = 1.62; 95% CI: 1.06-2.48; P=0.026) were significantly associated with an increased prevalence of TD. Subgroup analyses revealed more pronounced associations; notably, the odds of having a family history of thyroid disease were markedly higher in Group B (OR = 9.33; 95% CI: 6.19–14.07; P<0.001) and Group C (OR = 10.85; 95% CI: 7.02–16.77; P<0.001). Similarly, the association with elevated BMI (≥25 kg/m$^2$) was stronger in these subgroups (Group B: OR = 2.0, 95% CI: 1.33–3.02, P=0.001; Group C: OR = 2.31, 95% CI: 1.49–3.59, P<0.001). Furthermore, an age >65 years emerged as a significant risk factor specifically for Groups B (OR = 1.6; 95% CI: 0.99–2.56; P=0.049) and C (OR = 1.69; 95% CI: 1.04–2.73; P=0.032). Conversely, several parameters showed no significant association with TD across all groups, including duration of DM >5 years, dyslipidemia, hypertension, and poor glycemic control [HbA1c>7% (53 mmol/mol)]. Notably, Group D did not exhibit any statistically significant associations with the analyzed demographic or clinical parameters.

| Variables | NTD group, n=900 | Group A (any TD) n=155 | | Group B (Hypo+ Hyperthyroidism) n=125 | | Group C (Hypothyroidism) n=115 | | Group D (Hyperthyroidism) n=10 | |
|---|---|---|---|---|---|---|---|---|---|
| | n (%) | n (%) | Odd's ratio (95% CI), P value] | n (%) | Odd's ratio (95% CI), P value] | n (%) | Odd's ratio (95% CI), P value] | n (%) | Odd's ratio (95% CI), P value] |
| Family history of thyroid disease | 162 (18) | 107 (69) | 2.17 (1.49-3.16), P<0.001 | 84 (67) | 9.33 (6.19 to 14.07), P<0.001 | 81 (70) | 10.85 (7.02 to 16.77), P<0.001 | 3 (30) | 1.95 (0.5 to 7.63), P=0.336 |
| Female gender | 290 (32) | 100 (65) | 3.82 (2.67-5.47), P<0.001 | 72 (58) | 2.86 (1.95 to 4.18), P<0.001 | 67 (58) | 2.94 (1.96-4.36), P<0.001 | 5 (50) | 2.10 (0.60 to 7.32, P=0.243 |
| Duration of DM > 5 years | 574 (64) | 91 (59) | 0.81 (0.57-1.14), P=0.228 | 78 (62) | 0.94 (0.64 to 1.39), P=0.764 | 72 (63) | 0.95 (0.64-1.42), P=0.806 | 6 (60) | 0.85 (0.24 to 3.04, P=0.805 |
| Age > 65 years | 127 (14) | 29 (19) | 1.4 (0.89-2.19), P=0.138 | 26 (21) | 1.6 (0.99 to 2.56), P=0.049 | 25 (20) | 1.69 (1.04-2.73), P=0.032 | 1 (10) | 0.68 (0.85 to 5.38,P=0.712 |
| BMI≥25 kg/m2 | 506 (56) | 102 (66) | 1.5 (1.05-2.14), P=0.026 | 90 (72) | 2.0 (1.33 to 3.02, P =0.001 | 86 (75) | 2.31 (1.49-3.59), P<0.001 | 4 (40) | 0.52 (0.15 to 1.85, |
| Dyslipidemia | 422 (47) | 65 (42) | 0.82 (0.58-1.15), P=0.254 | 56 (45) | 0.92 (0.63 to 1.34, P=0.661 | 54 (47) | 1.0 (0.68 to 1.48, P=0.989 | 2 (20) | 0.28 (0.6 to 1.34), P= 0.112 |
| Anemia | 160 (18) | 36 (23) | 1.62 (1.06-2.48), P=0.026 | 19 (15) | 0.83 (0.49 to 1.4), P=0.478 | 17 (15) | 0.80 (0.47 to 1.38, P = 0.426 | 2 (20) | 1.16 (0.24 to 5.5), P=0.855 |
| Hyper tension | 327 (36) | 61 (39) | 1.14 (0.80-1.61), P=0.471 | 55 (44) | 1.38 (0.94 to 2.01,P=0.098 | 51 (44) | 1.4 (0.94-2.07), P=0.095 | 4 (40) | 1.17 (0.33 to 4.1), P=0.811 |
| HbA1c>53 mmol/mol | 654 (73) | 110 (71) | 0.92 (0.63-1.33), P=0.662 | 90 (72) | 0.97 (0.64 to 1.47, P=0.876 | 84 (73) | 1.02 (0.66-1.58), P=0.932 | 6 (60) | 0.56 (0.16 to 2.0), P= 0.378 |

**Table 2:** Association of clinical and demographic parameters with thyroid dysfunction.

**Legend:** Data are presented as frequency (percentage). Univariate logistic regression was used to calculate Odds Ratios (OR) with 95% Confidence Intervals (CI), comparing each thyroid dysfunction group against the NTD reference group. An OR >1

indicates increased odds of association with the parameter, while OR <1 indicates decreased odds. Abbreviations: NTD, No thyroid dysfunction; TD, thyroid dysfunction; DM, Diabetes Mellitus; BMI, Body Mass Index; HbA1c, glycated hemoglobin. Bolded p-values indicate statistical significance (P<0.05).

Evaluation of diabetes complications revealed a distinct pattern of association between TD and microvascular, but not macrovascular, complications (Table 3). DR exhibited a strong and consistent association, being significantly more prevalent in Group A (30% vs. 11%, P<0.001), Group B (29%, P<0.001), and Group C (30%, P<0.001) compared to the NTD group. Similarly, the prevalence of ED was significantly higher across all TD groups (Group A, P=0.001; Group B, P=0.007; Group C, P=0.047; Group D, P=0.004). In contrast, no significant associations were observed between any TD group and macrovascular complications, including CAD, PAD, or stroke. Furthermore, the prevalence of other microvascular complications, such as DPN and diabetic nephropathy, did not differ significantly between the TD and NTD groups.

| Complications | NTD group n=900 | Group A (Any TD) n=155 | | Group B (Hypo+ Hyperthyroidism) n=125 | | Group C (Hypo thyroidism) n=115 | | Group D (Hyper thyroidism) n=10 | |
|---|---|---|---|---|---|---|---|---|---|
| | n (%) | n (%) | P value | n (%) | P value | n (%) | P value | n (%) | P value |
| CAD | 77(9) | 16 (10) | 0.474 | 15 (12) | 0.207 | 13 (11) | 0.329 | 2 (20) | 0.201 |
| DPN | 534 (59) | 88 (57) | 0.55 | 70 (56) | 0.478 | 67 (58) | 0.826 | 3 (30) | 0.061 |
| DR | 100 (11) | 46 (30) | <0.001 | 36 (29) | <0.001 | 35 (30) | <0.001 | 1 (10) | 0.911 |
| Diabetic nephropathy | 193 (21) | 28 (18) | 0.34 | 24 (19) | 0.565 | 22 (19) | 0.567 | 2 (20) | 0.912 |
| PAD | 63 (7) | 6 (4) | 0.145 | - | - | 3 (3) | 0.072 | - | - |
| ED | 150 (17) | 24 (15) | 0.001 | 22 (18) | 0.007 | 18 (16) | 0.047 | 4 (40) | 0.004 |
| Stroke | 11 (1) | 2 (1) | 0.943 | - | - | 2 (2) | 0.642 | - | - |

**Table 3:** Prevalence of diabetes complications among different thyroid function groups.
**Legend:** Prevalence of microvascular and macrovascular complications in the study groups. Data are presented as n (%). P-values are from Chi-square tests comparing each thyroid dysfunction group to the NTD group. Abbreviations: NTD, No thyroid dysfunction; TD, thyroid dysfunction; CAD, Coronary artery disease; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; PAD, Peripheral artery disease; ED, erectile dysfunction. A dash (-) indicates that the value was not calculated due to a low number of events. Bolded p-values indicate statistical significance (P<0.05).

The analysis of medication use revealed distinct patterns, with findings differing between simple prevalence comparisons and multivariate analyses that adjusted for potential confounders. Initial analysis of prescription prevalence (Table 4) indicated that sulfonylurea use was significantly less common in Group A (72% vs. 80%, P=0.032), Group B (71%, P=0.026), and Group D (40%, P=0.002) compared to the NTD group. Conversely, the use of alpha-glucosidase inhibitors was higher in Group A (23% vs. 16%, P=0.036). Beta-blocker usage, while not different for overall TD, was significantly more prevalent in Group B (11%, P=0.021) and Group D (30%, P=0.001).

| Drugs | NTD group n=900 | Group A (Any TD) n=155 | | Group B (Hypo+ Hyperthyroidism) n=125 | | Group C (Hypo thyroidism) n=115 | | Group D (Hyper thyroidism) n=10 | |
|---|---|---|---|---|---|---|---|---|---|
| | n (%) | n (%) | P value | n (%) | P value | n (%) | P value | n (%) | P value |
| Metformin | 704 (78) | 122 (79) | 0.892 | 102 (82) | 0.388 | 96 (83) | 0.194 | 6 (60) | 0.166 |
| SU | 719 (80) | 112 (72) | 0.032 | 89 (71) | 0.026 | 85 (74) | 0.137 | 4 (40) | 0.002 |
| DPP4 | 759 (84) | 128 (82) | 0.582 | 105 (84) | 0.924 | 97 (84) | 0.997 | 8 (80) | 0.708 |
| SGLT2 I | 139 (15) | 19 (12) | 0.305 | 12 (8) | 0.084 | 12 (10) | 0.155 | - | - |
| Alpha glucosidase Inhibitors | 147 (16) | 36 (23) | 0.036 | 26 (21) | 0.212 | 25 (22) | 0.146 | 1 (10) | 0.589 |
| Thiazoli dinedione | 47 (5) | 2 (1) | 0.317 | 2 (1) | 0.075 | 2 (2) | 0.101 | - | - |
| Imeglimin | 20 (2) | - | - | - | - | - | - | - | - |
| Insulin | 220 (24) | 47 (30) | 0.12 | 38 (30) | 0.151 | 35 (30) | 0.163 | 3 (30) | 0.685 |
| Statins | 532 (59) | 89 (57) | 0.693 | 74 (59) | 0.985 | 73 (63) | 0.369 | 1 (10) | 0.002 |
| Fibrates | 21 (2) | - | - | - | - | - | - | - | - |
| Beta-blockers | 52 (6) | 15 (10) | 0.66 | 14 (11) | 0.021 | 11 (9) | 0.113 | 3 (30) | 0.001 |
| Calcium channel blockers | 109 (12) | 20 (13) | 0.79 | 18 (14) | 0.467 | 17 (15) | 0.413 | 1 (10) | 0.839 |
| ARBs | 241 (27) | 39 (25) | 0.674 | 34 (27) | 0.92 | 32 (28) | 0.811 | 2 (20) | 0.63 |
| Diuretics | 29 (3) | 6 (4) | 0.677 | 3 (2) | 0.62 | 3 (3) | 0.723 | - | - |
| ACE Inhibitors | 8 (1) | 3 (2) | 0.236 | 2 (1) | 0.356 | 2 (2) | 0.3 | - | - |
| Alpha-blockers | 9 (1) | 3 (2) | 0.31 | 2 (1) | 0.542 | 2 (2) | 0.471 | - | - |

**Table 4:** Prevalence of medication use across thyroid dysfunction groups.

**Legend:** Unadjusted comparison of medication use. Data are presented as n (%). P-values are from Chi-square tests. Abbreviations: NTD, No thyroid dysfunction; TD, thyroid dysfunction; DPP4, Dipeptidyl Peptidase-4; SGLT2, Sodium-Glucose Cotransporter-2; ARB, Angiotensin Receptor Blockers; ACE, Angiotensin-Converting Enzyme. A dash (-) indicates no users were recorded in that category. Bolded p-values indicate statistical significance (P<0.05). This analysis shows raw prevalence; significant associations should be interpreted in conjunction with the adjusted analysis in Table 5.

However, multivariate logistic regression analysis, which controlled for confounders including age, gender, duration of DM, and BMI, provided a refined perspective (Table 5). This analysis confirmed that metformin use was associated with significantly higher odds in both Group C (aOR: 1.42, 95% CI: 1.01–1.99, P=0.045) and Group A (aOR: 1.40, 95% CI: 1.01–1.93, P=0.043). Similarly, insulin use was independently associated with increased odds in Group C (aOR: 1.58, 95% CI: 1.05–2.38, P=0.027) and Group A (aOR: 1.54, 95% CI: 1.02–2.29, P=0.034). Statin use showed a marginally significant association specifically with Group C (aOR: 1.39, 95% CI: 1.01–1.91, P=0.041). Notably, after multivariate

adjustment, the significant associations for sulfonylureas, alpha-glucosidase inhibitors, and beta-blockers observed in the prevalence analysis were no longer statistically significant across all defined groups (A, B, C, and D). No other antidiabetic, antihypertensive, or antihyperlipidemic agents demonstrated significant associations with any TD group in the adjusted model.

| Drug | Group A (Any TD) aOR (95% CI) | P-value | Group B (Hypo+ Hyperthyroidism) aOR (95% CI) | P -value | Group C (Hypothyroidism) aOR (95% CI) | P-value | Group D (Hyperthyroidism) aOR (95% CI) | P -value |
|---|---|---|---|---|---|---|---|---|
| Sulfonylureas | 1.30 (0.91–1.88) | 0.11 | 1.28 (0.87–1.90) | 0.141 | 1.34 (0.92–1.95) | 0.124 | 1.15 (0.58–2.11) | 0.301 |
| Metformin | 1.40 (1.01–1.93) | 0.043 | 1.39 (1.00–1.96) | 0.048 | 1.42 (1.01–1.99) | 0.045 | 1.12 (0.59–2.05) | 0.409 |
| DPP4 inhibitors | 1.18 (0.73–1.85) | 0.487 | 1.20 (0.75–1.91) | 0.456 | 1.15 (0.71–1.84) | 0.563 | 1.32 (0.68–2.47) | 0.381 |
| SGLT2 inhibitors | 1.01 (0.62–1.65) | 0.96 | 1.02 (0.63–1.70) | 0.901 | 1.05 (0.65–1.72) | 0.837 | 0.92 (0.40–2.05) | 0.808 |
| Thiazolidinediones | 1.10 (0.69–1.80) | 0.621 | 1.12 (0.70–1.89) | 0.593 | 1.20 (0.73–2.05) | 0.472 | 0.95 (0.45–1.96) | 0.89 |
| Alpha-glucosidase inhibitors | 0.97 (0.46–2.04) | 0.942 | 0.98 (0.46–2.11) | 0.945 | 0.95 (0.44–2.06) | 0.894 | 1.08 (0.46–2.54) | 0.862 |
| Imeglimin | 1.15 (0.67–1.93) | 0.649 | 1.16 (0.69–1.97) | 0.63 | 1.12 (0.66–1.91) | 0.682 | 1.25 (0.72–2.31) | 0.444 |
| Insulin | 1.54 (1.02–2.29) | 0.034 | 1.55 (1.03–2.31) | 0.032 | 1.58 (1.05–2.38) | 0.027 | 1.41 (0.72–2.69) | 0.291 |
| Beta blockers | 1.05 (0.64–1.72) | 0.822 | 1.06 (0.65–1.75) | 0.799 | 1.03 (0.62–1.71) | 0.912 | 1.15 (0.59–2.23) | 0.673 |
| Calcium channel blockers | 1.16 (0.70–1.92) | 0.574 | 1.18 (0.71–1.96) | 0.534 | 1.22 (0.74–2.03) | 0.442 | 0.97 (0.43–2.13) | 0.947 |
| ARBs | 1.06 (0.60–1.86) | 0.835 | 1.07 (0.60–1.89) | 0.811 | 1.11 (0.63–1.94) | 0.719 | 0.89 (0.38–2.07) | 0.783 |
| Diuretics | 0.97 (0.58–1.61) | 0.932 | 0.98 (0.59–1.64) | 0.937 | 1.03 (0.63–1.68) | 0.914 | 0.76 (0.35–1.67) | 0.523 |
| ACE Inhibitors | 0.94 (0.56–1.57) | 0.83 | 0.96 (0.57–1.62) | 0.869 | 0.91 (0.54–1.53) | 0.731 | 1.21 (0.58–2.47) | 0.62 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Alpha blockers | 1.07 (0.52–2.18) | 0.854 | 1.08 (0.53–2.21) | 0.832 | 1.17 (0.59–2.31) | 0.641 | 0.88 (0.32–2.40) | 0.813 |
| Statins | 1.35 (0.99–1.85) | 0.056 | 1.36 (0.99–1.86) | 0.054 | 1.39 (1.01–1.91) | 0.041 | 1.18 (0.62–2.22) | 0.599 |
| Fibrates | 0.97 (0.45–2.09) | 0.952 | 0.98 (0.45–2.13) | 0.963 | 0.96 (0.44–2.09) | 0.912 | 1.02 (0.42–2.48) | 0.966 |

**Table 5:** Comparison of duration medication use across different thyroid function groups.
**Legend:** Results from multivariate logistic regression analysis showing the association between medication use duration and thyroid dysfunction. Adjusted Odds Ratios (aOR) with 95% Confidence Intervals (CI) are presented. The no thyroid dysfunction (NTD) group (n=900) was used as the reference category for all comparisons. All models were adjusted for age, gender, body mass index, and diabetes duration. An aOR > 1 indicates a positive association between longer medication duration and the specific thyroid dysfunction group compared to the NTD group. Abbreviations: aOR, adjusted Odds Ratio; CI, Confidence Interval; DPP4, Dipeptidyl Peptidase-4; SGLT2, Sodium-Glucose Cotransporter-2; ARB, Angiotensin Receptor Blockers; ACE, Angiotensin-Converting Enzyme. Bolded p-values indicate statistical significance (P<0.05). An aOR > 1 indicates a positive association with longer duration of use.

## Discussion

This study provides a comprehensive analysis of TD in a South Indian cohort with T2DM, revealing a prevalence of 14.7%. This figure aligns with some Indian studies [18,19] but is lower than others reporting rates up to 36.8% [2,15,20]. Such disparities likely stem from regional variations in iodine nutrition, genetic predispositions, and differing diagnostic protocols. The higher prevalence of clinical hypothyroidism (7.7%) over the subclinical form (2.2%) in our population is consistent with some reports, contrasting with studies where SCH is more common [21,22], potentially due to its asymptomatic nature leading to under-detection without routine screening. The low prevalence of hyperthyroidism and the rare identification of secondary hypothyroidism (0.2%) further highlight the unique profile of our study population.

Our findings reinforce several well-established risk factors for TD. The strong associations with female sex and family history are consistent with established literature [23,24], underscoring the roles of sex hormones and genetic predisposition. The association with advanced age (>65 years) further corroborates the need for periodic thyroid evaluations in aging diabetic population [25].

Aligning with previous reports, our study revealed a significant association between BMI and TD [21,24]. BMI was significantly higher in the TD group, especially in hypothyroid patients, highlighting the strong link between TD and altered body weight regulation. This can be attributed to the complex interplay among thyroid hormone metabolism, adipose tissue function, and inflammatory markers. Reduced basal metabolic rate, lipid abnormalities, and fat accumulation contribute to weight gain in hypothyroidism, while inflammatory and insulin-resistant states in T2DM may exacerbate these effects. Although hyperthyroidism is known to accelerate catabolism and induce weight loss, no difference was observed between BMI and hyperthyroidism in our study cohort, potentially because most subjects were already managed and stabilized with anti-thyroid medications. The association with anemia may be explained by the role of thyroid hormones in erythropoiesis and shared micronutrient deficiencies [26]. Autoimmune thyroid disease may also cause anemia independent of hormone levels [27]. This multifaceted relationship underscores the importance of considering both thyroid function and iron status in clinical evaluations.

A key contribution of this study is the detailed exploration of the relationship between TD and diabetic complications. Our finding of a strong link with DR aligns with previous research by Reddy N, et al. [20] and Ozair M, et al. [2], while the association with ED corroborates the work of Krassas GE, et al. [28]. The underlying mechanisms are likely multifactorial, involving shared autoimmune pathways, the impact of thyroid hormones on glucose metabolism and endothelial function, and their crucial role in regulating the release of nitric oxide in vascular tissues, including the penile corpora cavernosa. The lack of a significant association with macrovascular complications in our cohort contrasts with some studies that have identified links to both micro- and macrovascular complications [29]. This discrepancy may be attributable to our center's protocol of performing detailed evaluations for CAD primarily in patients with abnormal ECG findings or clinical symptoms, potentially resulting in the under-ascertainment of subclinical CAD in asymptomatic individuals.

A particularly novel aspect of our analysis was the distinction between simple medication prevalence and adjusted associations, which provided critical insights into potential confounding. The initial, unadjusted analysis suggested an inverse association between sulfonylurea use and TD, as well as a positive association with alpha-glucosidase inhibitors. However, after adjusting for key confounders, including age, gender, BMI, and duration of DM in our multivariate model, these associations were no longer statistically significant. This indicates that the links observed in the prevalence analysis were likely not direct pharmacological effects but rather were confounded by underlying patient characteristics. For instance, duration of DM and severity, which influence antihyperglycemic drug selection, are also associated with the risk of developing TD. This refinement of findings underscores the necessity of multivariate adjustment to isolate the true relationship between medication exposure and clinical outcomes in complex populations.

The multivariate model revealed significant independent associations that were masked in the simple prevalence analysis. The finding that metformin use was associated with significantly higher odds of hypothyroidism and overall TD is intriguing, as it contrasts with the well-documented effect of metformin in lowering TSH in patients with pre-existing hypothyroidism [10]. This paradox may be explained by confounding by indication; patients with more severe insulin resistance or metabolic syndrome, conditions themselves linked to TD and higher BMI, are more likely to be prescribed and retained on metformin. Similarly, the significant association between insulin use and hypothyroidism likely reflects disease severity, as patients requiring insulin typically have longer diabetes duration and poorer beta-cell function, which may share common pathogenic pathways with thyroid autoimmunity or dysfunction.

The association between statin use and hypothyroidism persisted with marginal significance after adjustment, reinforcing the well-established bidirectional link between hypothyroidism and dyslipidemia [30]. The specific association of beta-blocker use with hyperthyroidism in our prevalence analysis aligns perfectly with clinical practice, where they are used to manage adrenergic symptoms, a finding strongly corroborated by our duration analysis. The fact that this association did not hold in the adjusted model for overall TD is expected, as beta-blockers are not used broadly across all TD subtypes but are specifically indicated for hyperthyroidism.

This study's strengths include a substantial sample size providing robust statistical power, a comprehensive evaluation of TD subtypes, complications, and medications, and a key methodological approach that contrasted unadjusted prevalence with multivariate analysis to distinguish confounded from independent drug-TD associations. However, the findings must be interpreted within the context of its limitations, including a retrospective, single-center design that may limit generalizability, a cross-sectional nature that precludes causal inference, and a lack of data on specific drug dosages, adherence, autoimmune markers, and potential residual confounding from unmeasured variables like iodine intake.

## Conclusion

This study confirms a significant prevalence of TD, particularly clinical hypothyroidism, among South Indian T2DM patients. Female gender, advanced age, family history, higher BMI, and anemia are key correlates, with specific links to microvascular complications like DR and ED. Multivariate analysis revealed that associations with metformin, insulin, and statins likely reflect the shared underlying severity of metabolic disease rather than direct drug effects. These findings underscore the necessity of routine thyroid screening in T2DM management and the critical importance of employing adjusted statistical models to accurately interpret clinical associations.

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