Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/yf5v2756

PREVALENCE OF SUBCLINICAL HYPOTHYROIDISM AND ITS ASSOCIATION WITH TYPE 2 DIABETES MELLITUS IN PATIENTS: A CASE-CONTROL STUDY

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Abstract

Objective: To determine the prevalence of subclinical hypothyroidism (SCH) and its association with type 2 diabetes mellitus (T2DM) in patients.

Study Design: Case-control study.

Place and Duration: The study was carried out from September 2024 to September 2025 at Jinnah Postgraduate Medical Centre/SMC Karachi

Methods: A total of 126 participants, including 63 patients with established T2DM (age >40 years, diabetes duration ≥2 years) and 63 sex and age-matched non-diabetic controls were included. Fasting venous samples were submitted for TSH, free T3, and free T4 level analysis by chemiluminescence immunoassay methods. A TSH concentration higher than 4.5 mIU/mL with normal free T3 and free T4 levels was defined as SCH.

Results: T2DM patients' prevalence of subclinical hypothyroidism was 38 (60.3%), normal thyroid function was 24 (38.1%), and subclinical hyperthyroidism was 1 (1.6%). Mean serum TSH was significantly higher in diabetic patients (5.1 ± 2.8 µIU/mL) than in controls (2.4 ± 1.2 µIU/mL; $p < 0.001$), while free T3 (3.1 ± 0.6 pg/mL) and free T4 (1.3 ± 0.35 ng/dL) remained normal. Thyroid dysfunction was not significantly associated with age group (p=0.78), gender (p=0.48), education level (p=0.39), married status (p=0.64), or frequent exercise (p=0.45).

Conclusion: Subclinical hypothyroidism is surprisingly common in T2DM patients and is closely linked to elevated levels of TSH in the face of normal levels of thyroid hormone. The absence of

demographic predictors argues for routine screening for thyroid function in all T2DM patients regardless of age, gender, or lifestyle factors.

Keywords: Subclinical hypothyroidism, Type 2 diabetes mellitus, TSH, Thyroid dysfunction, Prevalence.

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by insulin resistance and progressive beta cell dysfunction, which predisposes to neurological, cardiovascular, and renal complications and chronic hyperglycemia [1]. It was estimated that 537 million individuals (aged 20-79) had diabetes in 2021 and by 2045, this is expected to reach 783 million, indicating that the disorder had reached epidemic proportions [2]. Thyroid axis dysfunction frequently interacts with metabolic diseases, as thyroid hormones are crucial for glucose metabolism, energy expenditure, and insulin sensitivity regulation [3].

In type 2 diabetics, the most common kind of thyroid dysfunction is subclinical hypothyroidism (SCH), which is defined by elevated thyroid-stimulating hormone (TSH) levels but normal levels of free thyroxine (FT4) and free triiodothyronine (FT3) [3, 4]. So far, the evidence indicates a two-way causality between SCH and T2DM. On one hand, dysfunction in the hypothalamic-pituitary-thyroid axis and peripheral T4 to T3 conversion may result from persistently high blood sugar and insulin resistance [3, 5]. On the other hand, SCH itself drives insulin resistance, dyslipidemia, and systemic inflammation, which may aggravate glycemic control and hasten diabetic complications [5]. Many studies have shown that type 2 diabetics are twice as likely as the general population to have thyroid dysfunction, namely hypothyroidism and SCH [5, 6].

Subclinical hypothyroidism is about twice as common among people with T2DM than in the general population, with a combined incidence of 10.2% internationally [5]. In Pakistan, 17.4% of prevalence has been reported in hospital-based studies [7]. The higher prevalence in women, older age groups, and those with longer diabetes duration or poorer glycemic control has been repeatedly documented [7]. The presence of SCH in diabetic patients is clinically relevant because it is associated with higher HbA1c levels, increased insulin requirements, greater risk of diabetic nephropathy, retinopathy, peripheral neuropathy, and cardiovascular events [5, 8].

The mechanisms linking the two conditions include chronic low-grade inflammation, altered thyroid hormone receptor expression in liver and adipose tissue, impaired cellular uptake of T4, and autoimmune overlap, as both conditions frequently involve anti-thyroid antibodies [6]. Diabetes patients with SCH are at a higher risk of cardiovascular complications due to endothelial dysfunction, dyslipidemia, and obesity [3]. Despite these associations, controversy remains regarding whether routine screening for SCH and treatment with levothyroxine are associated with better long-term outcomes in T2DM patients without overt symptoms [6, 8].

In Pakistan, both T2DM and thyroid disorders are common, but routine thyroid screening is not routinely performed in diabetic clinics [7]. Healthcare avoidance and delayed routine screening became widely prevalent during and after the COVID-19 pandemic, as demonstrated in regional studies showing significant fear-based reduction in clinical visits. [9] Such behavioral patterns are particularly relevant to chronic diseases such as type 2 diabetes mellitus, where thyroid screening is often postponed despite high SCH prevalence."

Local data suggest that knowledge and screening rates are low, and many people remain undiagnosed until complications arise. This study aims to determine the prevalence and strength of association of SCH in patients with T2DM.

Methodology

A total of 126 individuals were recruited, including 63 patients with confirmed T2DM and 63 non-diabetic controls matched for age and sex. Patients were selected from the diabetes outpatient clinic, whereas controls were healthy individuals accompanying patients or hospital staff with no history of

diabetes. Inclusion criteria for cases were age above 40 years, confirmed diagnosis of type 2 diabetes for at least two years, and treatment with oral hypoglycemic drugs, insulin, or both. The diagnosis for diabetes was established based on the American Diabetes Association, which included HbA1c levels greater than 6.5%, or random blood glucose levels greater than 200 mg/Dl, or fasting blood glucose levels of 126 mg/dL or more. This study did not include people who had type 1 diabetes, were pregnant, had chronic liver or renal illness, had uncontrolled hypertension, or were using drugs that impair thyroid function, such as lithium or amiodarone.

A detailed history was taken, and physical examination was performed for every participant. A calibrated mercury sphygmomanometer was used to take the patient's blood pressure while they were seated after ten minutes of rest. Following an overnight fast, venous blood samples were taken. HbA1c and glucose levels were tested using the Roche Cobas 501 chemistry analyzer while fasting and at random. Using the Abbott Architect i1000SR analyzer, thyroid function tests (free T4, free T3, and TSH) were conducted using chemiluminescence technique. TSH was 0.4–4.5 μIU/mL, free T4 was 0.8-1.8 ng/dL, and free T3 was 2.0-4.4 pg/mL.

TSH >4.5 μIU/mL with normal free T3 and free T4 levels was considered subclinical hypothyroidism. Overt hypothyroidism was diagnosed when TSH was elevated along with low free T4 and/or free T3. Overt hyperthyroidism and subclinical hyperthyroidism were distinguished by high free T3 and free T4, respectively, and suppressed TSH (<0.4 μIU/mL).

IBM SPSS version 23.0 was used to input and analyze the data. Categorical variables were compared with the Fisher's test and Chi-Square test, which were represented as frequencies and percentages. For statistical significance, a p-value of less than 0.05 was used.

Results

Among the 126 participants, cases (type 2 diabetic patients) were more likely to be male (36, 57.1%) than controls (20, 31.7%), while females predominated in the control group (43, 68.3%). Diabetic patients were slightly older (mean age 52.8 ± 10.4 years) compared to controls (48.9 ± 7.6 years). Nearly all participants were married in both groups (controls: 61, 96.8%; cases: 60, 95.2%). Regular exercise was reported by 23 (36.5%) diabetic patients versus 14 (22.2%) controls. All diabetic participants had a family history of diabetes (63, 100%) and diabetes duration of at least two years, and all were receiving oral hypoglycemic agents (63, 100%). None had hypertension at enrollment (Table 1).

Table 1. Clinical and demographic characteristics of participants (N=126)

Characteristics		**Control (n=63)**	**Cases (n=63)**
Gender	Male	20 (31.7%)	36 (57.1%)
	Female	43 (68.3%)	27 (42.9%)
Age (years)	Mean ± SD	48.9 ± 7.6	52.8 ± 10.4
Marital status	Single	2 (3.2%)	1 (1.6%)
	Married	61 (96.8%)	60 (95.2%)
	Widowed	0 (0.0%)	2 (3.2%)
Education level	Primary	8 (12.7%)	13 (20.6%)
	Secondary	27 (42.9%)	35 (55.6%)
	Graduate	26 (41.3%)	12 (19.0%)
	Masters	2 (3.2%)	3 (4.8%)
Regular exercise	Yes	14 (22.2%)	23 (36.5%)
	No	49 (77.8%)	40 (63.5%)

Family history of diabetes	Yes	0 (0.0%)	63 (100.0%)
	No	63 (100.0%)	0 (0.0%)
Duration of diabetes	≥2 years	-	63 (100.0%)
Hypertension	Yes	0 (0.0%)	0 (0.0%)
	No	63 (100.0%)	63 (100.0%)
On oral hypoglycemic agents	Yes	-	63 (100.0%)

Among the type 2 diabetic patients (n=63), thyroid function assessment revealed that 60.3% had subclinical hypothyroidism, 1.6% had subclinical hyperthyroidism, and 38.1% had normal thyroid function (Table 2).

Table 2. Thyroid function status among T2DM patients (n=63)

Thyroid function status	n	Percentage (%)
Normal	24	38.1
Subclinical hypothyroidism	38	60.3
Subclinical hyperthyroidism	1	1.6
Total	**63**	**100.0**

Compared to the control group, individuals with type 2 diabetes had a significantly higher mean blood TSH level. Diabetic individuals had an average TSH of 5.1 ± 2.8 µIU/mL, significantly higher than the control group's 2.4 ± 1.2 µIU/mL ($p < 0.001$). The average TSH level in the patients was noticeably greater than in the controls ($p < 0.01$), as shown in Table 3.

Table 3. Comparison of thyroid function tests between study groups (N=126)

Variable	Controls (n=63)		Cases (n=63)		p-value
	Mean	SD	Mean	SD	
Free T4 (ng/dL)	-	-	1.3	0.35	N.A
Free T3 (pg/mL)	-	-	3.1	0.6	N.A
TSH (µIU/mL)	2.4	1.2	5.1	2.8	<0.001*

Among the type 2 diabetic patients, subclinical hypothyroidism was present in 38 (60.3%), normal thyroid function in 24 (38.1%), and subclinical hyperthyroidism in 1 (1.6%). Age group (p=0.78), gender (p=0.48), married status (p=0.64), education level (p=0.39), or frequent exercise (p=0.45) did not significantly correlate with thyroid dysfunction. Nearly all patients used oral hypoglycemic medications (n = 63, 100%) and had a positive family history of diabetes (n = 61, 96.8%) and diabetes for more than two years (n = 63, 100%) (Table 4).

Table 4. Thyroid dysfunction patterns by demographic and clinical characteristics in patients diagnosed with T2DM

Variables	Normal thyroid function (n=24)	Subclinical hypothyroidism (n=38)	Subclinical hyperthyroidism (n=1)	p-value
Age group				0.78
<45 years	9 (37.5%)	12 (31.6%)	0 (0.0%)	
46–55 years	8 (33.3%)	11 (28.9%)	1 (100.0%)	
56–65 years	4 (16.7%)	10 (26.3%)	0 (0.0%)	
>65 years	3 (12.5%)	5 (13.2%)	0 (0.0%)	

Gender				0.48
Male	13 (54.2%)	23 (60.5%)	0 (0.0%)	
Female	11 (45.8%)	15 (39.5%)	1 (100.0%)	
Marital status				0.64
Single	0 (0.0%)	1 (2.6%)	0 (0.0%)	
Married	24 (100.0%)	35 (92.1%)	1 (100.0%)	
Widowed	0 (0.0%)	2 (5.3%)	0 (0.0%)	
Education level				0.39
Primary	6 (25.0%)	6 (15.8%)	1 (100.0%)	
Secondary	13 (54.2%)	22 (57.9%)	0 (0.0%)	
Graduate	3 (12.5%)	8 (21.1%)	0 (0.0%)	
Masters	2 (8.3%)	2 (5.3%)	0 (0.0%)	
Regular exercise				0.45
Yes	10 (41.7%)	13 (34.2%)	0 (0.0%)	
No	14 (58.3%)	25 (65.8%)	1 (100.0%)	
Family history of diabetes				0.98
Yes	23 (95.8%)	37 (97.4%)	1 (100.0%)	
No	1 (4.2%)	1 (2.6%)	0 (0.0%)	
Hypertension				N.A
Yes	0 (0.0%)	0 (0.0%)	0 (0.0%)	
No	24 (100.0%)	38 (100.0%)	1 (100.0%)	
Duration of diabetes ≥2 years	24 (100.0%)	38 (100.0%)	1 (100.0%)	N.A
On oral hypoglycemic agents	24 (100.0%)	38 (100.0%)	1 (100.0%)	N.A

Discussion

This study aimed to assess the prevalence and association of SCH among T2DM patients, revealing a notably high rate of 60.3% SCH alongside elevated TSH levels) compared to controls. Such findings indicate a robust association between T2DM and thyroid dysregulation, in line with worldwide patterns of thyroid hormone effects on insulin sensitivity and glucose metabolism [8, 10]. Globally, the demographic patterns in our study are consistent with known patterns: T2DM cases are older and predominantly male, which are known to increase the risk of SCH. A study by Singh et al. confirmed higher SCH odds in T2DM patients over 60 and in females overall, yet our male predominance in cases may reflect local healthcare-seeking behaviors among diabetic men [5]. The universal family history of diabetes (100%) in cases supports bidirectional links, as a study in Qatar found SCH associated with a 2.82-fold odds (95% CI: 1.13–7.02) for T2DM after confounder adjustment, emphasizing shared autoimmune and metabolic pathways [8]. However, our low subclinical hyperthyroidism rate (1.6%) contrasts with a figures of 2.49% from the meta-analysis by Hadgu et al. [11]. This possibly indicates under-detection in our controls or protective glycemic effects in non-diabetics.

Our findings of 60.3 of SCH align closely with a Pakistani study showing 61.1% SCH in 72 T2DM patients [12]. Another study by Akhtar et al. reported 55.1% thyroid dysfunction in T2DM, supporting the comorbidity but with lower SCH specificity [13]. The study by Abbas and Khan further supports our TSH findings, linking hypothyroidism to an increased risk of T2DM through beta-cell dysfunction. However, case-control designs such as ours limit causal inference compared with longitudinal data [14]. Comparatively, Haider et al. reported thyroid dysfunction in 23.8% of T2DM, with hypothyroidism predominant and correlations with longer disease duration and BMI, in

line with our exclusion of overt thyroid cases but contrasting with our higher yield, likely due to their euthyroid-dominant cohort compared to our dysfunction-heavy group [15]. These alignments support SCH's advocacy of dyslipidemia and endothelial dysfunction in T2DM, as our elevated TSH levels replicate meta-analytic odds ratios for complications such as nephropathy (OR 1.74) [10].

Our findings revealed a significantly elevated mean serum TSH level of 5.1 ± 2.8 μIU/mL in T2DM patients versus 2.4 ± 1.2 μIU/mL in controls ($p < 0.001$), with normal FT3 (3.1 ± 0.6 pg/mL) and FT4 (1.3 ± 0.35 ng/dL) in cases, indicative of thyroid axis dysregulation in this population. This aligns with Rong et al., establishing high TSH as a T2DM risk factor, where each 1 mIU/L increase correlates with an 11.4% heightened incidence, often exceeding 5.0 mIU/L in affected cohorts [16]. Similarly, Azeez et al. reported significantly higher TSH (mean 3.14 ± 4.26 μIU/mL) compared to controls (1.91 ± 1.10 μIU/mL, $p < 0.001$) [17]. An Indian study of 200 T2DM cases found higher TSH levels in hypothyroid subgroups vs. controls [18].

In our study, no associations emerged between SCH and age group, gender, marital status, education level, or exercise habits, despite near-universal family history of diabetes (96.8%) and all cases on oral agents with ≥2-year duration. Our lack of age association contrasts with a study by Fakhroo et al., which found SCH significantly tied to age 50–85 years (OR=29.52, $p<0.001$), though overall SCH rate was low at 4.6% [8]. Similarly, Haider et al. reported thyroid dysfunction associated with age >60 years ($p=0.032$), with SCH at 14.9% [15]. However, our non-significant $p=0.78$ aligns with a narrative review on SCH in obesity and metabolic syndrome, where no clear age-specific SCH-MetS ties emerged beyond general TSH decline with aging [19]. Regarding gender, our neutral finding ($p=0.48$) diverges from female predominance in the study of Noor et al., which showed SCH (61.1%) more common in females, though not statistically detailed [12].

For education and marital status, scant global data exists, but our null links ($p=0.39$, $p=0.64$) contrast indirect socioeconomic influences; the Qatari study adjusted for education without SCH specificity [8]. On exercise, our $p=0.45$ aligns with an NHANES analysis showing vigorous occupational activity inversely associated with SCH (OR=0.83 per session/week), though not T2DM-specific [20]. The absence of demographic associations implies SCH screening in T2DM should be universal, not targeted by age or gender, to address hidden risks in diverse groups [11]. Moreover, promoting exercise as a modifiable factor could mediate SCH, warranting lifestyle integration in diabetes protocols.

The small sample size and single-hospital representation may have restricted the extent to which the results can be generalized. Additionally, detailed information on glycemic control, body mass index, and anti-thyroid antibodies was not collected.

Conclusion

This study shows a strong association of T2DM and subclinical hypothyroidism in our setting. Thyroid dysfunction was common among diabetic patients, but it was not significantly different based on age, gender, education, or exercise habits. The findings underscore the importance of routine thyroid screening, especially in individuals with T2DM without classic risk factors. Early identification of subtle changes in the thyroid may help to improve diabetes control and prevent some long-term complications. Routine checks could become a worthwhile but simple part of diabetes care in everyday medical practice.

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