

Unraveling the Relationship between Hypothyroidism and Type II Diabetes Mellitus

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ABSTRACT

Objective: To determine the frequency and association between hypothyroidism and Type II Diabetes Mellitus (DM) among patients at a tertiary care hospital.

Methodology: This cross-sectional study was conducted at the Federal Government Polyclinic Hospital, Islamabad from August 2023 to February 2024, enrolled 200 Type II DM patients through non-probability consecutive sampling. Samples for HbA1c and thyroid function tests were collected and analyzed. Data on demographics, clinical history, and laboratory results were statistically evaluated using SPSS 26.0, with significance determined at $p < 0.05$.

Results: In a study of 200 Type II DM patients, key findings include a slight male predominance (54%) and a middle-aged demographic with a mean age of 55.91 ± 9.55 years. The prevalence of hypothyroidism was 17.5%, with subclinical hypothyroidism at 14.5%. Hypothyroidism was significantly more prevalent among females (65.7%) and in the age group 56-65 years, indicating a notable association between age, gender, and thyroid dysfunction ($p < 0.001$). Obesity ($p = 0.018$) diabetes duration > 10 years (< 0.001) was associated with increased risk of hypothyroidism. There was positive correlation between HbA1c and TSH levels ($r = 0.176$), a weak negative correlation with fT3 levels ($r = -0.193$) and fT4 levels ($r = -0.135$).

Conclusion: This study found a significant association between Type II DM and thyroid dysfunction, with hypothyroidism more prevalent in older, obese females and linked to longer diabetes duration, suggesting a need for routine thyroid screening in diabetic patients to manage potential complications effectively.

Keywords: Diabetes Complications, Glycemic Control, Hyperthyroidism, Hypothyroidism, Metabolic Diseases, Subclinical Hypothyroidism, Thyroid Function Tests, Type II Diabetes.

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Introduction

Overt Hypothyroidism effect nearly effect 5% and Subclinical hypothyroidism 3-20% of the global population.^{1,2} In, Pakistan the prevalence of hypothyroidism ranges from 4.1 to 23.8% as reported by different epidemiological studies.^{3,4} Diabetes mellitus is the most common endocrine disorder effecting 10.5 % of adult population according to International Diabetes

Federation.⁵ Similar prevalence was reported in Pakistani population 11.77%, with male predominance.⁶ In addition, the Third National Health and Nutrition Examination Survey found an increased frequency of hypothyroidism in patients with diabetics compared to non-diabetics.⁷ Hypothyroidism and Type 2 Diabetes Mellitus (T2DM) have a bi-directional relationship, negatively impacting each other.

The pathogenesis linking Type II Diabetes Mellitus (DM) with thyroid dysfunction is complex, involving metabolic, immunological, and hormonal factors.^{8,9} Prolonged diabetes-induced hyperglycemia triggers oxidative stress, generating reactive oxygen species that damage thyroid cells and disrupt hormone synthesis, while also initiating autoimmune responses that worsen thyroid dysfunction.⁸ Insulin resistance, a characteristic of Type II DM, is linked to obesity and high BMI, with adipose tissue secreting adipokines and inflammatory cytokines like TNF- α and IL-6, which interfere with thyroid hormone signaling and contribute to insulin resistance, exacerbating both conditions. Studies have reported that correcting the thyroid functioning in hypothyroid patients with diabetes can improve glycemic regulation.^{9,10} Furthermore, diabetes-associated dysregulation of the hypothalamic-pituitary-thyroid axis affects thyroid hormone levels, with hyperinsulinemia altering the expression of thyroid hormone transporters and deiodinases, leading to changes in hormone availability and action.^{9,11} Several studies have demonstrated that patients with T2DM exhibit a higher prevalence of thyroid disorders, with hypothyroidism being the most common reported as 4.8% to 31.4%^{12,13}

This study addresses the significant gap in knowledge regarding hypothyroidism's prevalence and impact among Type II Diabetes Mellitus patients. Despite known links between thyroid dysfunction and diabetes, comprehensive data on hypothyroidism's frequency, its effect on glycemic control, and its role in microvascular complications are scarce. Routine thyroid evaluations are uncommon in diabetic care, possibly neglecting critical comorbidities. Our research aims to fill these voids by quantifying hypothyroidism prevalence in diabetic individuals, exploring its correlation with microvascular issues, and pinpointing risk factors, thereby guiding clinical practice towards potentially mandatory thyroid monitoring for better diabetes management.

Methodology

After getting approval from the institutional review board IRB#FGPC. 1/12/2023/Ethical Committee, a Cross-sectional observational study was conducted at department of Diabetes, Endocrinology and Metabolic Diseases, Federal Government Polyclinic Hospital, Islamabad over a period of 6 months from August 2023 to February 2024. Two hundred patients were enrolled in the study after taking informed consent. Sample size of 200 patients was calculated by assuming the prevalence of hypothyroidism as 24.8%, at confidence level of 95%

with 6% margin of error, using single proportion formula.¹⁴

All the patients presenting to OPD between age 35-75 years diagnosed with Type II DM (either having Fasting Blood sugar levels ≥ 126 or HbA1c level > 6.5) were enrolled in the study. Patients with type 1 diabetes mellitus, gestational diabetes, history of thyroid medication, surgery, or radioactive iodine treatment, those on medications known to affect thyroid function, such as amiodarone or lithium were excluded. Pregnant women, patients having acute diabetes complications e.g., ketoacidosis or hyperosmolar hyperglycemic state and severe comorbid conditions such as advanced malignancies, brain tumor, hypothalamic disorder, decompensated cardiac failure or sepsis were also excluded. Basic demographics and clinical history including age, gender, body mass index, duration of diabetes were documented for each patient. Patients were screened for diabetic nephropathy (diagnosed at albumin-to-creatinine ratio ≥ 30 mg/g on spot urinary protein), diabetic retinopathy (diagnosed by presence of retinal changes typical of diabetes identified through fundoscopic examination by a consultant ophthalmologist) and diabetic neuropathy (diagnosed by neurologist through clinical symptoms sensation or positive symptoms like numbness, prickling, burning or aching pain and/or electrophysiological testing examination using monofilament testing and vibration perception). Sample for HbA1c and Thyroid profile including Serum TSH, free T3 and free T4 was collected and sent to the hospital laboratory for tests. The quantification of HbA1c and Thyroid function tests was done using Roche Cobas c501/502 analyzers and automated immunoassay systems (Siemens ADVIA Centaur), respectively. The normal range of TSH was 0.5-5 mU/L. 3.1-6.8 pmol/L for free T3 and 10-22 pmol/L for free T4. Clinical hypothyroidism was defined as TSH > 5 mU/L, fT3 less than 3.1 pmol/L and fT4 < 10 pmol/L, Subclinical Hypothyroidism was defined as TSH > 5 mU/L with normal range fT3 and fT4, and Hyperthyroidism was defined as serum TSH < 0.5 and fT3 > 6.8 pmol/L and fT4 > 22 pmol/L.

Data was analyzed using SPSS version 26.0. Qualitative variables e.g., gender, age group, diabetes complications and thyroid status were presented as frequency and percentage. Quantitative variables age, body mass index, duration of diabetes, HbA1c and thyroid profile were calculated as mean and standard deviation. Chi-square was used to determine the association of gender, age

group, Body Mass Index (BMI) categories, diabetes complication and duration of diabetes with thyroid disorder status. Pearson's correlation was used to find correlation between HbA1c and thyroid function test. Quantitative variables were compared using Analysis of Variance (ANOVA). A p-value less than 0.05 was considered significant.

Results

Among 200 patients with Type II DM, 108 (54%) were males, while females made up 92 (46%) of the participants. The mean age of the patients was 55.91 ± 9.55 years, with 80 (40%) in the age group 56-65 years followed by 60 (30%) in the age group 45-55 years. The mean BMI of the patients was 26.54 ± 4.29 kg/m², most of the patients 75 (37.5%) had normal weight (BMI 18.5 - 24.9 kg/m²), followed by overweight (BMI 25.0 - 29.9 kg/m²) at 71 (35.5%). The mean duration of Diabetes and HbA_{1c} level was 6.77 ± 4.65 years and $8.49 \pm 1.38\%$ respectively. Among 200 patients, 55 (27.5%) were reported to be Hypertensive. In terms of diabetic complications, diabetic retinopathy was observed in 29 (14.5%), diabetic nephropathy in 35 (17.5%), and diabetic neuropathy in 32 (16.0%) of the patients. Dyslipidemia was reported in 26 (32.5%) of the cases.

There were 35 (17.5%) hypothyroid patients, 29 (14.5%) subclinical hypothyroid, 132 (66%) and 4 (2%) identified as hyperthyroid (Figure 1).

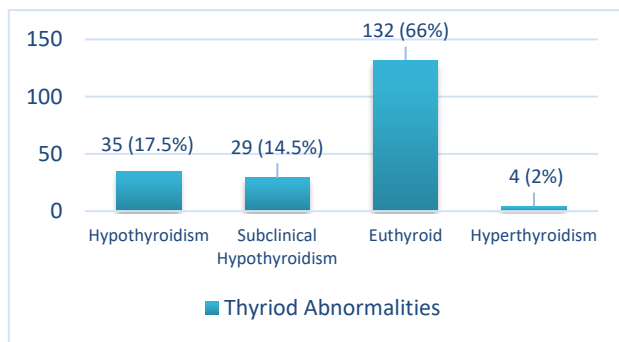


Figure 1. Thyroid abnormalities.

The analysis of baseline demographic and clinical details among different thyroid status revealed that hypothyroidism was more common among females 23/35 (65.7%), while subclinical hypothyroidism was more prevalent among males 17/29 (58.6%) compared to female 12/29 (41.4%) (p-value = 0.007). Both Hypothyroidism and subclinical hypothyroidism were more common in 56-65 years age group, reported as 16/35 (45.7%) and 14/29 (48.3%) respectively. A significant association between age and thyroid status

was observed ($p < 0.001$), with increasing age corresponding to a higher frequency of hypothyroidism. Notably, individuals with obesity had a hypothyroidism frequency of 34.3%, showing significant relationship between BMI and thyroid status (p-value=0.018). (Table I).

Out of 35 Hypothyroid patients, 20 (57.1%) were having T2DM for more than 10 years, whereas subclinical hypothyroidism was predominantly observed in 15/29 (51.7%) of patients with a history of type 2 diabetes mellitus for less than 5 years. The relationship between the duration of diabetes and thyroid dysfunction was statistically significant ($p < 0.001$) Table II

In the analysis of thyroid status relative to various clinical parameters, the ANOVA test yielded significant differences across groups for several measures. The mean age for hypothyroid patients being the highest at 59.83 ± 9.44 years ($p = 0.015$). The duration of diabetes also differed significantly ($p < 0.001$), with a notably longer duration in the hypothyroid group (10.66 ± 4.70 years) (Table III).

There was positive correlation between HbA_{1c} and TSH levels ($r = 0.176$), a weak negative correlation with fT3 levels ($r = -0.193$) and fT4 levels ($r = -0.135$).

Discussion

Diabetes mellitus and hypothyroidism are two common endocrine disorders that significantly impact patients' life. Their coexistence in patients can lead to complex clinical challenges, including the aggravation of metabolic abnormalities and increased risk of microvascular and macrovascular complication.

In this study, the demographic and clinical characteristics of 200 patients with Type II Diabetes Mellitus (DM) were explored, revealing a slight male predominance (54%) and a mean age of 55.91 years, indicating a middle-aged to older population predominance. Similarly, Talwalkar et al. reported 52.4% male.¹⁴ Contrarily several other studies reported female predominance 60%.^{15,16} Talwalkar et al. reported mean age of 52.4% and Nasim et al. 58.09 ± 10.95 years comparable to ours study.^{14,16} Singh et al. and reported slightly lower age range from 40-50 years.^{16,17}

Hypertension co-existed in 27.5% of the patients, underscoring the common interplay between diabetes and cardiovascular risk factors.

Table I: Comparison of baseline characteristics of participants between thyroid disorders. (n=200)					
Baseline Characteristics	Hypothyroidism	Subclinical Hypothyroidism	Euthyroid	Hyperthyroidism	Chi square (p-value)
Gender					
Male	12 (34.3%)	17 (58.6%)	79 (59.8%)	0 (0.0%)	0.007
Female	23 (65.7%)	12 (41.4%)	53 (40.2%)	4 (100.0%)	
Age Group					
< 45 years	3 (8.6%)	11 (37.9%)	18 (13.6%)	0 (0.0%)	<0.001
45-55 years	6 (17.1%)	2 (6.9%)	48 (36.4%)	4 (100.0%)	
56-65 years	16 (45.7%)	14 (48.3%)	50 (37.9%)	0 (0.0%)	
66-75 years	10 (28.6%)	2 (6.9%)	16 (12.1%)	0 (0.0%)	
BMI Category					
Underweight	0 (0.0%)	0 (0.0%)	3 (2.3%)	0 (0.0%)	0.018
Normal weight	9 (25.7%)	8 (27.6%)	57 (43.2%)	1 (25.0%)	
Overweight	14 (40.0%)	18 (62.1%)	36 (27.3%)	3 (75.0%)	
Obesity	12 (34.3%)	3 (10.3%)	36 (27.3%)	0 (0.0%)	
Duration of Diabetes					
< 5 years	2 (5.7%)	15 (51.7%)	61 (46.2%)	1 (25.0%)	<0.001
5-10 years	13 (37.1%)	8 (27.6%)	51 (38.6%)	1 (25.0%)	
> 10 years	20 (57.1%)	6 (20.7%)	20 (15.2%)	2 (50.0%)	

Table II: Comparison of Diabetic complications with thyroid disorders. (n=200)					
Variable	Hypothyroidism n=35	Subclinical Hypothyroidism n=29	Euthyroid n=132	Hyperthyroidism (n=4)	Chi-Square (p-value)
Diabetic Retinopathy (n=29)	10 (28.6%)	4 (13.8%)	15 (11.4%)	0 (2.9%)	0.062
Diabetic Nephropathy n=35)	8 (22.9%)	5 (17.2%)	18 (13.6%)	4 (100.0%)	<0.001
Diabetic Neuropathy (n=32)	10 (28.6%)	8 (27.6%)	14 (10.6%)	0 (0.0%)	0.014
Dyslipidemia (n=26)	26 (74.3%)	19 (65.5%)	20 (15.2%)	0 (0.0%)	<0.001

Table III: Comparison of Descriptive statistics among patients with different thyroid status.					
Outcomes	Hypothyroidism	Subclinical Hypothyroidism	Euthyroid	Hyperthyroidism	ANOVA (p-value)
Age (Years)	59.83 ± 9.44	53.00 ± 11.02	55.70 ± 9.05	49.75 ± 4.11	0.015
Duration of Diabetes (Years)	10.66 ± 4.70	5.69 ± 4.19	5.92 ± 4.18	8.75 ± 5.56	<0.001
HbA1c (%)	9.10 ± 1.36	8.19 ± 1.35	8.42 ± 1.38	7.90 ± .29	.025
TSH Level (mIU/L)	20.55 ± 3.05	12.86 ± 2.11	2.60 ± 1.33	0.18 ± 0.10	<0.001

Nephropathy found to be the most prevalent microvascular complication 17.5% followed by retinopathy (14.5%), nephropathy (17.5%), and neuropathy (16.0%). Most microvascular complications were observed in the same patients, with a higher proportion in those who had diabetes for more than 10 years and HbA1c levels above 8%. Hussein *et al.*, reported higher but similar trends of microvascular complications with 38.8% diabetic nephropathy, 23.9% having diabetic retinopathy, and 22.5% diabetic neuropathy.¹⁸ The consistency in the results suggests that nephropathy tends to develop earlier compared to microvascular complications. Chen *et al.* that found sub-clinical hypothyroidism to be a risk factor for nephropathy and cardiovascular disease among type 2

diabetic patients.¹⁹ In contrast, Mehalingam *et al.* reported no correlation between thyroid dysfunction and diabetic complications in patients¹³

Additionally, the reported dyslipidemia in 32.5% of the patients aligns with the recognized risk of lipid abnormalities in the diabetic population. These findings suggest the complex relationship between T2DM, its management, and the risk of both complications, highlighting the need for comprehensive and multidisciplinary approaches to care.

This study reported hypothyroidism in 17.5% of patients, with subclinical hypothyroidism in 14.5%, Euthyroidism in 66%, and hyperthyroidism in 2%. Similarly, Nasim *et al.* reported overt hypothyroidism in 17.8%, subclinical

hypothyroidism 10.5%, Singh et al. reported 6.5% hypothyroidism, Swamy et al. reported higher prevalence of subclinical hypothyroidism 31% followed by 12% clinical hypothyroid and Vamshidhar et al. reported comparably low prevalence of hypothyroidism and subclinical hypothyroidism compared to these studies 6% and 8% respectively.^{15,16,20,21} Al-Geffari et al. demonstrated the prevalence of hypothyroidism as 25.3%.²²

In another study, 23.8% were identified as having hypothyroidism, 12.8% were found to have hyperthyroidism, and 35.4% were diagnosed with subclinical hypothyroidism, whereas 28% of the participants were determined to be euthyroid. Statistical analysis revealed a significant correlation between the prevalence of thyroid disorders and age ($P < 0.001$), yet the relationship between thyroid conditions and gender was not statistically significant ($P = 0.351$).³ A notable gender disparity was observed, with hypothyroidism more prevalent in females (65.7%) and subclinical hypothyroidism more common in males (58.6%), suggesting a potential influence of gender on thyroid dysfunction in Type 2 Diabetes Mellitus (T2DM) patients. Similar predominance female gender was reported by previous studies^{4,16,20}. While Singh et al. reported that there was no significant difference in incidence of hypothyroidism among gender.¹⁵

The age group of 56-65 years exhibited a higher incidence of both hypothyroidism (45.7%) and subclinical hypothyroidism (48.3%), indicating a significant association between age and thyroid status ($p < 0.001$). The mean age for hypothyroid patients being the highest at 59.83 ± 9.44 years ($p = 0.015$). Consistent with other studies showing that prevalence of Hypothyroidism increases with advancing age.^{8,13,21}

Chauhan et al. found that Hypothyroidism was more common in age group 70-79 years (66.7%).²³ In contrast, Nasim et al and Javed reported that higher prevalence with mean age 35 years and 41.93 years respectively, showing that there was statistically significant difference between age and thyroid disease. Additionally, a substantial relationship between Body Mass Index (BMI) and thyroid status was evident, with obesity linked to a higher frequency of hypothyroidism (34.3%, p -value=0.018). The duration of diabetes also showed a significant correlation with thyroid dysfunction. Among hypothyroid patients, 57.1% had T2DM for more than 10 years, while subclinical hypothyroidism was predominantly observed in patients with a shorter

duration of T2DM (less than 5 years, 51.7%). This suggests that the longer the duration of diabetes, the greater the likelihood of developing hypothyroidism, highlighting the importance of monitoring thyroid function in patients with prolonged T2DM. This study demonstrates the association between higher BMI and hypothyroidism, aligning from previous literature.^{9,11,24} This correlation may be due complex metabolic relationships among central obesity, glycemic control, and thyroid hormone, affecting each other.

Alsolami et al. reported HbA1c levels of $8.0 \pm 1.7\%$ in hypothyroid patients compared to $7.4 \pm 1.7\%$ in controls.²⁵ Ardekani et al. observed significantly higher HbA1c levels in diabetic patients with thyroid disorders, consistent with our findings.²⁶ There was positive correlation between HbA1c and TSH levels ($r = 0.176$), a weak negative correlation with fT3 levels ($r = -0.193$) and fT4 levels ($r = -0.135$). Similarly, Bazrafshan et al. found a significant correlation between HbA1c and TSH levels.²⁷ This might suggest that in individuals with poorly controlled glucose levels, as indicated by higher HbA1c, there may be a tendency towards hypothyroidism, as TSH is the hormone responsible for stimulating thyroid activity.

This study's strengths include detailed comprehensive analysis of multiple factors related to Type II DM and Thyroid disorder. Limitations include smaller sample size, missing of control group that harbors its broader applicability. Future studies with inclusion of control group and multicenter approach are recommended to get a clearer picture.

Conclusion

Among Type II DM patients, this study identified a clear link between diabetes duration, age, BMI, and thyroid dysfunction, notably hypothyroidism, which was more prevalent in older, obese females and those with longer diabetes history. These findings underscore the importance of regular thyroid function screening, particularly in patients with longstanding diabetes, to detect and manage hypothyroidism early. The correlation between HbA1c and thyroid hormone levels further highlights the complex interplay between glucose control and thyroid health, necessitating a comprehensive approach to patient care.

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