

Relationship Between Free Thyroid Hormone Profile and Microalbumin Excretion in Patients with Type 2 Diabetes Mellitus: A Cross-Sectional Study

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ABSTRACT

Introduction: Diabetes mellitus (DM) is a major global health problem and a leading cause of microvascular complications, including diabetic nephropathy. Microalbuminuria represents the earliest clinically detectable marker of renal involvement in type 2 diabetes mellitus (T2DM). Thyroid hormones play an important role in glucose metabolism, endothelial function, and renal hemodynamics. Thyroid dysfunction, particularly hypothyroidism, is frequently associated with T2DM and may contribute to increased urinary albumin excretion. However, the relationship between free thyroid hormone levels and microalbuminuria remains underexplored.

Aim: To assess the relationship between free thyroid hormone profile (fT3, fT4, and TSH) and microalbumin excretion in patients with type 2 diabetes mellitus.

Materials and Methods: This hospital-based cross-sectional comparative study was conducted in the Department of Biochemistry at a tertiary care center. A total of 152 participants were included, comprising 76 patients with type 2 diabetes mellitus and hypothyroidism and 76 age- and sex-matched healthy controls. Fasting blood samples were analyzed for HbA1c, serum fT3, fT4, TSH, and creatinine. Spot urine samples were assessed for microalbumin and creatinine, and urine albumin-to-creatinine ratio (uACR) was calculated. Statistical analysis was performed using SPSS version 25. Group comparisons were done using unpaired t-test or Mann–Whitney U test, and correlations were assessed using Pearson’s correlation coefficient. A p-value <0.05 was considered statistically significant.

Results: Mean fT4 levels were significantly lower (11.89 ± 0.46 vs 16.46 ± 0.57 pmol/L; $p < 0.001$) and TSH levels significantly higher (5.15 ± 0.52 vs 2.35 ± 0.19 mIU/L; $p < 0.001$) in T2DM patients compared to controls, while fT3 levels were comparable. Mean urine ACR was significantly higher in T2DM patients (196.70 ± 82.35 vs 18.08 ± 16.20 mg/g; $p < 0.001$), with microalbuminuria present in 80.3% of cases. Urine ACR showed a significant negative correlation with fT3 ($r = -0.422$, $p < 0.001$) and fT4 ($r = -0.487$, $p < 0.001$), and a positive correlation with TSH ($r = 0.395$, $p < 0.001$).

Conclusion: Altered thyroid function, particularly elevated TSH and reduced free thyroid hormone levels, is significantly associated with increased microalbumin excretion in patients with type 2 diabetes mellitus. Routine assessment of thyroid profile along with microalbuminuria screening may help in early identification of diabetic patients at higher risk of nephropathy.

Keywords: Type 2 diabetes mellitus; Microalbuminuria; Free thyroxine; Free triiodothyronine; Thyroid-stimulating hormone; Diabetic nephropathy

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycaemia resulting from impaired insulin secretion, insulin action, or both. It has emerged as a major global public health challenge due to its increasing prevalence and its association with significant microvascular and macrovascular

complications [1]. The burden of DM is particularly high in developing countries such as India, where rapid urbanization, sedentary lifestyle, dietary changes, and psychosocial stress have contributed to a rising incidence of the disease [2]. Among the various complications of DM, diabetic nephropathy remains one

of the leading causes of chronic kidney disease and end-stage renal failure worldwide [3].

Microalbuminuria, defined as urinary albumin excretion between 30–300 mg/day or an elevated urine albumin-to-creatinine ratio (uACR), represents the earliest clinically detectable stage of diabetic nephropathy and reflects generalized endothelial dysfunction [4]. It is not only a marker of early renal damage but also an independent predictor of cardiovascular morbidity and mortality in patients with diabetes [5]. Early detection of microalbuminuria provides an opportunity for timely intervention to delay or prevent progression to overt nephropathy. However, microalbuminuria may develop even in patients with adequate glycaemic and blood pressure control, suggesting the involvement of additional pathophysiological factors [6].

Thyroid hormones play a critical role in regulating basal metabolic rate, lipid and carbohydrate metabolism, insulin sensitivity, and vascular function. The biologically active hormones, free triiodothyronine (fT3) and free thyroxine (fT4), influence hepatic glucose production, peripheral glucose uptake, and insulin resistance [7]. Thyroid dysfunction is frequently associated with diabetes mellitus due to shared autoimmune mechanisms, genetic predisposition, and metabolic interactions [8]. Several studies have reported a higher prevalence of overt and subclinical hypothyroidism in patients with type 2 diabetes mellitus (T2DM) compared to the general population [9].

Thyroid hormones exert significant effects on renal physiology by modulating renal blood flow, glomerular filtration rate (GFR), tubular function, and sodium–water balance [10]. Hypothyroidism is associated with reduced cardiac output, decreased renal plasma flow, and lowered GFR, whereas hyperthyroidism leads to increased renal perfusion and hyperfiltration [11]. These alterations in renal hemodynamics may influence urinary albumin excretion, particularly in patients with underlying diabetic microvascular damage.

Emerging evidence suggests that even subtle alterations in free thyroid hormone levels within the reference range may contribute to renal dysfunction in diabetic patients. Previous studies have demonstrated associations between lower fT3 and fT4 levels and increased prevalence of microalbuminuria and diabetic nephropathy [12,13]. Wang et al. reported that reduced fT3 and fT4 levels were independently associated with diabetic kidney disease in euthyroid patients with T2DM [14]. Similarly, Zhao et al. observed a significant correlation between the fT4/fT3 ratio and urinary albumin excretion, highlighting the role of thyroid hormone metabolism in renal injury [15].

Despite growing evidence linking thyroid dysfunction and diabetic nephropathy, data evaluating the independent relationship between free thyroid hormone profile and microalbuminuria remain limited, particularly in the Indian population. Most available studies have focused primarily on thyroid-stimulating hormone (TSH) or overt thyroid disease, with relatively few exploring the role of fT3 and fT4 in early renal involvement. Understanding this relationship may aid in identifying high-risk diabetic patients and facilitate early preventive strategies.

Therefore, the present study was undertaken to evaluate the relationship between free thyroid hormone profile (fT3, fT4, and TSH) and microalbumin excretion in patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

Study Design and Participants

This hospital-based cross-sectional comparative study was conducted in the Department of Biochemistry at Santosh Medical College and Hospital, Ghaziabad, after obtaining approval from the Institutional Ethics Committee. A total of 152 participants were enrolled and divided into two groups: Group I consisted of 76 patients with type 2 diabetes mellitus (T2DM) and hypothyroidism, and Group II included 76 age- and sex-matched healthy controls.

Patients aged more than 35 years with a known history of T2DM for at least five years and HbA1c $\geq 6.5\%$ were included in the study group. The control group comprised apparently healthy individuals with HbA1c $< 6.5\%$. Participants of both genders who provided written informed consent and had complete medical records were included.

Patients with known thyroid disorders receiving treatment, chronic kidney disease unrelated to diabetes, severe cardiovascular disease, active systemic infections, inflammatory conditions, or incomplete medical records were excluded from the study.

Sample Collection and Biochemical Analysis

After an overnight fast of 8–10 hours, approximately 10 mL of venous blood was collected from each participant under aseptic conditions. Two milliliters of blood were collected in EDTA vials for estimation of HbA1c, which was measured using turbidimetric method. The remaining blood was collected in plain vacutainer tubes, centrifuged at 3000 rpm for 15 minutes, and serum was separated for biochemical analysis.

Serum free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) were estimated using electrochemiluminescence immunoassay (ECLIA). Serum creatinine was measured using Jaffe's kinetic method. Spot urine samples were collected for estimation of urinary microalbumin by turbidimetric

method and urinary creatinine. Urine albumin-to-creatinine ratio (uACR) was calculated and expressed in mg/g. Hypothyroidism was defined based on elevated serum TSH levels with reduced or normal free thyroxine levels according to laboratory reference ranges.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) version 25. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Normality of data distribution was assessed using the Kolmogorov–Smirnov test. Comparisons between groups were performed using unpaired Student’s t-test for normally distributed variables and Mann–Whitney U test for non-normally distributed variables. Associations between categorical variables were analyzed using Chi-square test or Fisher’s exact test, as appropriate. Correlation between quantitative

variables was assessed using Pearson’s correlation coefficient. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 152 participants were included in the study, comprising 76 patients with type 2 diabetes mellitus (T2DM) with hypothyroidism (Group I) and 76 age- and sex-matched healthy controls (Group II).

The mean age of participants in Group I was 52.62 ± 9.90 years and in Group II was 50.54 ± 13.28 years. The age distribution between the two groups was comparable, with no statistically significant difference (p=0.27). Females constituted 60.5% of the study group and 56.6% of the control group, with no significant gender difference between groups (p=0.62). Glycaemic control, as assessed by HbA1c, was significantly poorer in Group I (8.12 ± 0.74%) compared to controls (5.58 ± 0.24%) (p<0.001)

Table -1: Demographic Characteristics and Glycaemic Status of Study Participants

Parameter	Group I: T2DM with Hypothyroidism (n=76)	Group II: Controls (n=76)	p-value
Age (years)	52.62 ± 9.90	50.54 ± 13.28	0.27
Female, n (%)	46 (60.5%)	43 (56.6%)	0.62
Male, n (%)	30 (39.5%)	33 (43.4%)	
HbA1c (%)	8.12 ± 0.74	5.58 ± 0.24	<0.001

Comparison of Thyroid Profile and Glycaemic Status

Mean serum fT3 levels were comparable between Group I and Group II (4.33 ± 0.48 vs 4.46 ± 0.99 pmol/L; p=0.29). However, mean fT4 levels were significantly lower in the T2DM with hypothyroidism

group compared to controls (11.89 ± 0.46 vs 16.46 ± 0.57 pmol/L; p<0.001). Mean TSH levels were significantly higher in Group I than Group II (5.15 ± 0.52 vs 2.35 ± 0.19 mIU/L; p<0.001). (Table2).

Table 2: Comparison of Thyroid Hormone Profile Between Study Groups

Parameter	Group I (n=76) Mean ± SD	Group II (n=76) Mean ± SD	p-value
fT3 (pmol/L)	4.33 ± 0.48	4.46 ± 0.99	0.29
fT4 (pmol/L)	11.89 ± 0.46	16.46 ± 0.57	<0.001
TSH (mIU/L)	5.15 ± 0.52	2.35 ± 0.19	<0.001

Renal Function Parameters

Mean serum creatinine levels were significantly higher in the T2DM with hypothyroidism group compared to controls (1.21 ± 0.08 vs 0.81 ± 0.07 mg/dL; p<0.001). Mean urine albumin-to-creatinine ratio (uACR) was markedly elevated in Group I (196.70 ± 82.35 mg/g) compared to Group II (18.08 ± 16.20 mg/g), and this difference was statistically significant (p<0.001). Spot

urine creatinine levels were comparable between the two groups (p=0.46) (Table 3).

In the T2DM with hypothyroidism group, 80.3% of participants had microalbuminuria (uACR 30–300 mg/g), while 10.5% had macroalbuminuria (>300 mg/g). In contrast, 89.5% of control subjects had normal uACR values, and none had macroalbuminuria. The distribution of albuminuria differed significantly between the two groups (p<0.001) (Table 3).

Table 3: Renal Function Parameters and Albuminuria Status

Parameter	Group I (n=76) Mean ± SD	Group II (n=76) Mean ± SD	p-value
Serum creatinine (mg/dL)	1.21 ± 0.08	0.81 ± 0.07	<0.001
Spot urine creatinine (mg/dL)	49.35 ± 5.81	50.05 ± 5.99	0.46
Urine ACR (mg/g)	196.70 ± 82.35	18.08 ± 16.20	<0.001
Urine ACR (mg/g)			
<30 mg/g (Normal)	7 (9.2%)	68 (89.5%)	<0.001
30–300 mg/g (Microalbuminuria)	61 (80.3%)	8 (10.5%)	
>300 mg/g (Macroalbuminuria)	8 (10.5%)	0 (0%)	

Correlation Analysis

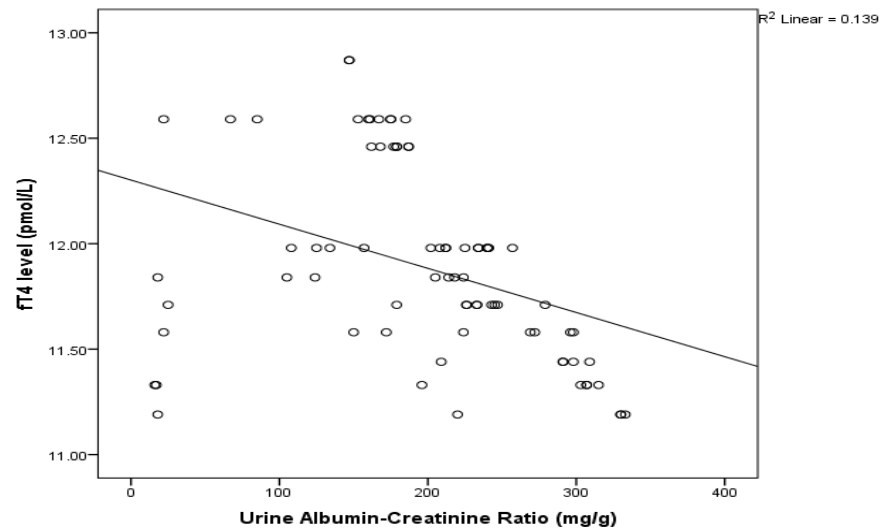
Correlation analysis among T2DM patients demonstrated a significant negative correlation between urine ACR and fT3 ($r=-0.422$, $p<0.001$) and fT4 ($r=-0.487$, $p<0.001$), while a significant positive correlation was observed between urine ACR and TSH ($r=0.395$, $p<0.001$). Urine ACR also showed a positive correlation with serum creatinine ($r=0.445$, $p<0.001$).

HbA1c demonstrated a significant negative correlation with fT3 ($r=-0.276$, $p=0.016$) and fT4 ($r=-0.395$, $p<0.001$), and a positive correlation with TSH ($r=0.276$, $p=0.016$). The correlation between HbA1c and urine ACR was positive but not statistically significant ($r=0.186$, $p=0.107$) (Table 4).

Table 4: Correlation Between Thyroid Profile, Glycaemic Status, and Urine ACR in T2DM Patients

Parameter	Urine ACR (r)	p-value
fT3	-0.422	<0.001
fT4	-0.487	<0.001
TSH	0.395	<0.001
HbA1c	0.186	0.107
Serum creatinine	0.445	<0.001

Figure 1: Graph showing correlation of Urine ACR level Ft4 level in T2DM patients



DISCUSSION

Diabetes mellitus (DM) is a multifactorial metabolic disorder frequently complicated by microvascular damage, among which diabetic nephropathy remains a major cause of chronic kidney disease. Microalbuminuria represents the earliest clinical marker of diabetic nephropathy and reflects generalized endothelial dysfunction. Thyroid hormones play a crucial role in metabolic regulation, vascular integrity, and renal hemodynamics. The present study evaluated the relationship between free thyroid hormone profile and microalbumin excretion in patients with type 2 diabetes mellitus (T2DM), highlighting the potential contribution of thyroid dysfunction to early renal involvement.

Demographic and Glycaemic Profile

In the present study, the mean age and gender distribution were comparable between the study and control groups, indicating appropriate matching and minimizing demographic confounding. The majority of participants were in the 46–60-year age group, which is consistent with the age distribution reported in previous studies on diabetic nephropathy and thyroid dysfunction [13,14]. A female predominance was observed in both groups, which may be attributed to the higher prevalence of thyroid disorders among females, as reported earlier [9].

Glycaemic control, assessed by HbA1c, was significantly poorer in T2DM patients with hypothyroidism compared to controls. This finding supports earlier observations that thyroid dysfunction adversely affects glucose metabolism and insulin sensitivity [7,16]. The significant negative correlation of HbA1c with fT3 and fT4 and its positive correlation with TSH observed in this study further emphasizes the interplay between thyroid status and glycaemic control,

consistent with findings reported by El-Eshrawy et al. and Yasuda et al. [16,17].

Thyroid Hormone Profile in T2DM

The present study demonstrated significantly lower fT4 levels and significantly higher TSH levels in T2DM patients compared to controls, while fT3 levels were comparable between groups. These findings are in agreement with studies by Rai et al. and Alijabri et al., who reported a higher prevalence of subclinical and overt hypothyroidism in patients with T2DM [9,13]. Even subtle alterations in thyroid hormones may influence metabolic homeostasis and endothelial function, thereby contributing to diabetic complications.

Renal Function and Albuminuria

Renal function parameters revealed significantly higher serum creatinine and markedly elevated urine albumin-to-creatinine ratio (uACR) in T2DM patients with hypothyroidism compared to controls. A high prevalence of microalbuminuria was observed among diabetic patients, reinforcing the association between thyroid dysfunction and early renal involvement. Similar findings have been reported by Bulum et al., who demonstrated impaired renal function in diabetic patients with altered thyroid hormone levels [12].

Thyroid hormones are known to influence renal plasma flow, glomerular filtration rate, and tubular function [10,11]. Hypothyroidism leads to reduced renal perfusion and increased systemic vascular resistance, which may exacerbate glomerular injury and promote albumin leakage, particularly in the presence of diabetic microangiopathy.

Association Between Thyroid Hormones and Microalbuminuria

A key finding of the present study was the significant negative correlation between urine ACR and both fT3

and fT4 levels, along with a significant positive correlation between urine ACR and TSH. These results suggest that declining free thyroid hormone levels and rising TSH are associated with worsening albuminuria in T2DM patients. Wang et al. reported similar inverse associations between fT4 levels and diabetic nephropathy, even in euthyroid individuals [14]. Zhao et al. also demonstrated that altered thyroid hormone metabolism, reflected by the FT4/FT3 ratio, was significantly associated with urinary albumin excretion [15].

When T2DM patients were stratified based on albuminuria status, those with albuminuria exhibited significantly higher TSH and altered fT4 levels compared to those with normal uACR, further supporting the role of thyroid dysfunction in renal endothelial damage. These findings align with reports by Najmaldin et al. and Shang et al., who observed a strong association between thyroid dysfunction and early kidney disease in diabetic patients [18,19].

The mechanisms linking thyroid dysfunction to microalbuminuria are likely multifactorial. Hypothyroidism is associated with endothelial dysfunction, increased oxidative stress, dyslipidemia, and altered nitric oxide production, all of which contribute to microvascular injury [6,10]. Additionally, reduced thyroid hormone levels may impair renal autoregulation and exacerbate diabetic glomerular damage, leading to increased urinary albumin excretion.

The findings of this study suggest that assessment of thyroid function, particularly free thyroid hormone levels and TSH, may provide additional insight into the risk of diabetic nephropathy. Identification of thyroid dysfunction in T2DM patients may help in early risk stratification and implementation of preventive strategies to slow renal disease progression.

CONCLUSION

The present study demonstrates a significant association between thyroid dysfunction and increased microalbumin excretion in patients with type 2 diabetes mellitus. Elevated TSH and altered free thyroid hormone levels were associated with higher urine albumin-to-creatinine ratio, indicating early renal involvement. These findings suggest that thyroid dysfunction may contribute to the development of diabetic nephropathy independent of glycaemic control. Routine assessment of thyroid function along with microalbuminuria screening in patients with T2DM may aid in early risk identification and timely intervention to prevent progression of renal complications.

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