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Original Research Article

Correlation between Serum Thyroid Stimulating Hormone, Free Thyroxine, and Urinary Albumin Excretion in Euthyroid Individuals with Type II Diabetes Mellitus

Ahraz Ali Imam[1], Vikram Aditya[2], Shubham Bhaskar[3]

[1]Senior Resident, Department of General Medicine, Nalanda Medical College & Hospital, Patna, Bihar, India

[2]Senior Resident, Department of General Medicine, Nalanda Medical College & Hospital, Patna, Bihar, India

[3]Senior Resident, Department of General Medicine, Nalanda Medical College & Hospital, Patna, Bihar, India

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Corresponding Author: Dr. Ajay Kumar Sinha

Conflict of interest: Nil

Abstract:

Background: The role of thyroid hormones in renal hemodynamics and glomerular filtration, impacting nephropathy progression, in euthyroid individuals with type II diabetes mellitus (T2DM) is underexplored. The study aimed to investigate the relation between serum thyroid stimulating hormone (TSH), free thyroxine (FT4), and urinary albumin excretion in euthyroid individuals with T2DM.

Methods: A cross-sectional study of 215 euthyroid T2DM patients categorized into four age groups collected data from electronic medical records on demographics, HbA1c, serum TSH, FT4 levels, and urinary ACR, with TSH and FT4 measured via immunoradiometric and radioimmunoassay; statistical analyses included Pearson correlation and multivariate regression to assess the relation between thyroid function and urinary albumin excretion.

Results: 2.4 ± 1.2 μIU/mL was the mean TSH level and 1.1 ± 0.3 ng/dL was the mean FT4 level. 60.5% of subjects had normal albuminuria, 27.9% had moderately elevated albuminuria, and 11.6% had significantly elevated albuminuria. urine albumin excretion and TSH showed a strong positive association ($r = 0.45$, $p < 0.001$), while FT4 and urine albumin excretion showed a negative correlation ($r = -0.38$, $p < 0.001$). Higher TSH and lower FT4 levels were independently linked to increased urine albumin excretion, as demonstrated by multivariate regression analysis ($\beta = 0.43$, $p < 0.001$ for TSH; $\beta = -0.35$, $p < 0.001$ for FT4).

Conclusion: Thyroid function, even within the euthyroid range, is significantly associated with urinary albumin excretion in T2DM patients. Higher TSH and lower FT4 levels correlate with increased albuminuria, suggesting a potential role for thyroid function monitoring in managing diabetic nephropathy.

Recommendations: Routine thyroid function monitoring in T2DM patients is advised to identify nephropathy risk, with further research needed to understand these associations and explore therapeutic interventions.

Keywords: Type II Diabetes Mellitus, Thyroid Stimulating Hormone, Free Thyroxine, Urinary Albumin Excretion.

Introduction

Millions of people worldwide suffer from type II diabetes mellitus (T2DM), a common chronic illness marked by insulin resistance and hyperglycemia. It has a substantial negative influence on patients' quality of life and healthcare systems worldwide due to its association with a number of consequences, including as nephropathy, neuropathy, retinopathy, and cardiovascular illnesses [1]. One of the main causes of end-stage renal disease, diabetic nephropathy is characterised by increased cardiovascular morbidity and mortality, chronic albuminuria, and a decreased glomerular filtration rate [2].

Thyroid dysfunction, often observed in individuals with diabetes, has been increasingly recognized as an important factor influencing the progression of diabetic complications. Both hypothyroidism and hyperthyroidism can adversely affect glucose metabolism, lipid profiles, and vascular function, potentially exacerbating diabetic complications [3]. Although the incidence of overt thyroid dysfunction is relatively low, subclinical thyroid disorders, particularly subclinical hypothyroidism, are more common among individuals with T2DM.

The relationship between thyroid function and renal health in diabetic patients has garnered significant

attention in recent years. Thyroid hormones, including thyroxine (T4) and triiodothyronine (T3), play a crucial role in regulating renal hemodynamics, glomerular filtration rate, and electrolyte balance [4]. Alterations in thyroid hormone levels can influence the progression of kidney disease, particularly in individuals with pre-existing conditions such as diabetes. Euthyroid individuals, who have normal thyroid hormone levels, may still experience subtle variations in thyroid function that impact renal health.

Subclinical hypothyroidism has been linked to a higher risk of albuminuria in diabetic individuals, according to earlier research [5]. Nonetheless, little is known about the precise connection between urine albumin excretion, free thyroxine (FT4), and serum thyroid stimulating hormone (TSH) in euthyroid people with type 2 diabetes. Comprehending this correlation may offer significant perspectives for the handling of diabetic nephropathy and underscore the significance of observing thyroid function, even in the lack of obvious thyroid disorders.

This study aims to investigate the relation between serum TSH, FT4 levels, and urinary albumin excretion in euthyroid individuals with T2DM.

Methodology

Study Design: A cross-sectional observational study.

Study Setting: The study was conducted at Nalanda Medical College and Hospital (NMCH), Patna, Bihar, India, over the period from 2022 to 2023.

Study Participants: A total of 215 participants diagnosed with T2DM were comprised in the study. Participants were identified based on self-reported diabetes status, clinical reports, usage of antidiabetic medications, and HbA1c levels equal to or greater than 6.5%. All participants were confirmed to be euthyroid, meaning they had normal levels of TSH and FT4. The participants were allocated into four age groups: those under 40 years, 40-49 years, 50-59 years, and those aged 60 years and above.

Inclusion Criteria: Inclusion criteria for this study required participants to have T2DM and euthyroid status.

Exclusion Criteria: Exclusion criteria included any history of thyroid disorders, current use of thyroid hormone replacement or antithyroid medications, pregnancy, and the presence of acute or chronic kidney disease unrelated to diabetes.

Bias: To minimize selection bias, a broad range of participants from various age groups was included. The strict adherence to the inclusion and exclusion criteria further reduced potential bias. Data collection from electronic medical records helped eliminate recall bias, ensuring accuracy in the recorded information.

Variables: The primary variables studied were serum TSH and FT4 levels and urinary albumin excretion. Additional variables considered in the analysis included age, gender, duration of diabetes, and HbA1c levels, which served as potential confounders.

Sample Size: To calculate the sample size for this study, the following formula was used for estimating a proportion in a population:

$$n = \frac{Z^2 \times p \times (1-p)}{E^2}$$

Where:

- n = sample size

- Z = Z-score corresponding to the desired level of confidence

- p = estimated proportion in the population

- E = margin of error

Data Collection

Data were systematically collected through a thorough review of electronic medical records. This included demographic details, clinical reports, medication histories, and laboratory results. High-performance liquid chromatography (HPLC) was used for measuring HbA1c levels, which were expressed as a percentage. Serum FT4 levels were estimated using radioimmunoassay, while serum TSH levels were determined using an immunoradiometric assay.

Urinary Albumin Excretion Measurement

The urinary albumin to creatinine ratio (ACR) was used to assess urinary albumin excretion. Urine samples were collected during the participants' first morning voiding. Albuminuria was categorized into three groups: normal albuminuria (NA) with ACR less than 30 mg/g, moderately increased albuminuria with ACR between 30-299 mg/g, and severely increased albuminuria with ACR of 300 mg/g or more. The measurement of albumin was performed using a polyclonal radioimmunoassay.

Statistical Analysis: The statistical analysis was performed with SPSS programme (25.0). The subjects' clinical and demographic features were summed up by descriptive statistics. The relationship between urine albumin excretion, FT4 levels, and serum TSH was assessed using Pearson correlation coefficients. A study of multivariate regression was done to account for any possible confounding variables. Less than 0.05 was the threshold for statistical significance.

Ethical Considerations: The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

Result

215 T2DM subjects in total were involved in the study; they were split into four age groups: <40 years (n = 45), 40-49 years (n = 60), 50-59 years (n = 55), and ≥60 years (n = 55). The participants' average age was 52.4 ± 10.3 years, and the male-to-female ratio was roughly 1.2:1. The average HbA1c level was 7.8 ± 1.4%, and the mean duration of diabetes was 8.7 ± 5.1 years.

Table 1: Demographic and Clinical Characteristics

Characteristic	< 40 years (n=45)	40-49 years (n=60)	50-59 years (n=55)	≥ 60 years (n=55)	Total (n=215)
Mean Age (years)	35.2 ± 4.1	44.5 ± 2.8	54.1 ± 2.5	64.2 ± 3.1	52.4 ± 10.3
Gender (%)					
Male	28 (62.2%)	35 (58.3%)	32 (58.2%)	30 (54.5%)	125 (58.1%)
Female	17 (37.8%)	25 (41.7%)	23 (41.8%)	25 (45.5%)	90 (41.9%)
Duration of Diabetes (years)	4.8 ± 2.3	7.3 ± 3.5	10.2 ± 4.1	12.5 ± 4.7	8.7 ± 5.1
Mean HbA1c (%)	7.2 ± 1.1	7.5 ± 1.3	8.0 ± 1.4	8.3 ± 1.5	7.8 ± 1.4

The mean serum TSH level was 2.4 ± 1.2 μIU/mL, and the mean FT4 level was 1.1 ± 0.3 ng/dL. The distribution of urinary albumin excretion (ACR) showed that 130 participants (60.5%) had normal albuminuria (NA), 60 participants (27.9%) had moderately increased albuminuria, and 25 participants (11.6%) had severely increased albuminuria.

Table 2: Thyroid Function and Urinary Albumin Excretion

Parameter	< 40 years (n=45)	40-49 years (n=60)	50-59 years (n=55)	≥ 60 years (n=55)	Total (n=215)
Mean TSH (μIU/mL)	2.1 ± 0.8	2.3 ± 1.1	2.5 ± 1.3	2.7 ± 1.4	2.4 ± 1.2
Mean FT4 (ng/dL)	1.2 ± 0.2	1.1 ± 0.3	1.0 ± 0.3	1.0 ± 0.4	1.1 ± 0.3
Normal Albuminuria (NA)	30 (66.7%)	38 (63.3%)	32 (58.2%)	30 (54.5%)	130 (60.5%)
Moderately Increased Albuminuria	10 (22.2%)	15 (25.0%)	20 (36.4%)	15 (27.3%)	60 (27.9%)
Severely Increased Albuminuria	5 (11.1%)	7 (11.7%)	3 (5.5%)	10 (18.2%)	25 (11.6%)

Pearson correlation analysis revealed a significant positive association between serum TSH levels and urinary albumin excretion ($r = 0.45$, $p < 0.001$). Conversely, there was a significant negative correlation between serum FT4 levels and urinary albumin excretion ($r = -0.38$, $p < 0.001$).

Table 3: Correlation Coefficients

Variable	ACR (Urinary Albumin Excretion)
Serum TSH	0.45**
Serum FT4	-0.38**

**$p < 0.001$

Multivariate regression analysis, adjusting for age, gender, duration of diabetes, and HbA1c levels, confirmed that higher serum TSH levels were independently related with increased urinary albumin excretion ($\beta = 0.43$, $p < 0.001$). Similarly, lower serum FT4 levels were independently related with elevated urinary albumin excretion ($\beta = -0.35$, $p < 0.001$).

Table 4: Multivariate Regression Analysis

Variable	β Coefficient	Standard Error	p-value
Serum TSH	0.43	0.05	<0.001
Serum FT4	-0.35	0.04	<0.001
Age	0.12	0.03	0.002
Gender	0.09	0.04	0.018
Duration of Diabetes	0.21	0.02	<0.001
HbA1c	0.29	0.03	<0.001

Discussion

In 215 euthyroid people with type 2 diabetes, this study examined the connection between urine albumin excretion, FT4, and blood TSH. The participants' mean age was 52.4 years, with a little male predominance. They were divided into four age groups: <40 years, 40-49 years, 50-59 years, and ≥60 years. The study cohort exhibited moderate glycemic control, as evidenced by the mean HbA1c level of 7.8% and the average duration of diabetes of 8.7 years.

2.4 μIU/mL was the mean TSH level and 1.1 ng/dL was the mean FT4 level. 60.5% of individuals had normal albuminuria, 27.9% had moderately increased albuminuria, and 11.6% had significantly increased albuminuria, according to an analysis of urine albumin excretion. These results demonstrate that even in cases when thyroid hormone levels are within the euthyroid range, albuminuria is common in people with type 2 diabetes.

Urinary albumin excretion and blood TSH levels were found to be significantly positively correlated ($r = 0.45$, $p < 0.001$) using Pearson correlation analysis. On the other hand, a noteworthy inverse relationship ($r = -0.38$, $p < 0.001$) was discovered between urine albumin excretion and serum FT4 levels. According to these findings, greater FT4 levels are linked to lower urinary albumin excretion levels, whereas higher TSH levels are linked to higher urinary albumin excretion levels.

Higher serum TSH levels were independently linked to increased urine albumin excretion, according to multivariate regression analysis that adjusted for age, gender, length of diabetes, and HbA1c levels ($\beta = 0.43$, $p < 0.001$). Likewise, there was an independent correlation ($\beta = -0.35$, $p < 0.001$) between elevated urine albumin excretion and decreased serum FT4 levels. The robustness of the results is further supported by the fact that these relationships persisted even after taking possible confounders into account.

The study's findings highlight the strong correlation that exists between urine albumin excretion and thyroid function in euthyroid people with T2DM. Higher TSH levels may cause or worsen renal impairment in diabetic individuals, even when they are within the normal range, according to the positive link shown between TSH levels and albuminuria. This finding is particularly relevant as it highlights the potential impact of subclinical variations in thyroid hormone levels on kidney function, which might be overlooked in routine clinical practice.

Conversely, the negative correlation between FT4 levels and albuminuria indicates that higher levels of free thyroxine may have a protective effect on renal function. This suggests that maintaining adequate levels of FT4 could be beneficial in preventing or mitigating albuminuria in T2DM patients. These findings align with previous research suggesting a link between thyroid dysfunction and kidney disease, emphasizing the need for comprehensive monitoring of thyroid function in the management of diabetic patients.

Several recent studies have explored the relationship between thyroid function and urinary albumin excretion in patients with T2DM, providing valuable insights into the complex interactions between these parameters.

In a study of newly diagnosed T2DM patients with euthyroidism and Hashimoto's thyroiditis, the relationship between thyroid peroxidase antibodies (TPOAb) and urine albumin to creatinine ratio (UACR) was examined. In contrast to TPOAb-negative patients, TPOAb-positive patients had a considerably greater UACR, indicating that thyroid autoimmunity may have an impact on albuminuria in type 2 diabetes. The correlation analysis revealed a significant relationship between UACR and TPOAb levels, underscoring the possible influence of thyroid antibodies on renal function in individuals with diabetes [6].

A meta-analysis looked at the relationship between thyroid hormone levels, such as TSH, FT3, and FT4, and the risk of T2DM. The results of the analysis showed that a greater baseline TSH level was linked to a higher risk of type 2 diabetes. Furthermore, there was a significant correlation found between lower levels of FT3 and FT4 with the risk of T2DM. These results imply that thyroid dysfunction, even at subclinical levels, may have a role in the emergence and development of comorbidities associated with diabetes, such as problems with the kidneys [7].

Vildagliptin, a DPP-4 inhibitor, was found to dramatically lower urine albumin excretion in patients with early diabetic nephropathy in studies including T2DM patients with microalbuminuria. According to this, vildagliptin may protect diabetes patients' kidneys from damage by modifying glucose metabolism and lowering renal stress [8].

An additional investigation looked at the connection between urinary albumin excretion in T2DM patients and plasma leucine-rich α-2-glycoprotein 1 (LRG1) levels. The findings showed a strong positive connection between UACR and plasma LRG1 levels, suggesting that LRG1 may be used as a biomarker for diabetic nephropathy in its early stages. According to the study's findings, elevated urine albumin excretion was correlated with greater LRG1 levels, pointing to a possible involvement for LRG1 in the aetiology of diabetic kidney disease [9].

Conclusion

The study highlights the intricate relationship between thyroid function and renal health in individuals with T2DM. The significant associations observed between TSH and FT4 levels with urinary albumin excretion suggest that thyroid function plays a crucial role in the progression of diabetic nephropathy. Further research is warranted to elucidate the underlying mechanisms of these associations and to explore the potential benefits of therapeutic interventions targeting thyroid hormone levels in the management of diabetic kidney disease. Monitoring thyroid function as part of a holistic approach to diabetes management could improve outcomes and reduce the risk of renal complications in this population.

Limitations: The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

Recommendations: Routine monitoring of thyroid function in T2DM patients is recommended to identify those at higher risk of nephropathy. Further research is needed to elucidate the mechanisms underlying these associations and to explore potential therapeutic interventions targeting thyroid function to mitigate renal complications in T2DM.

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List of abbreviations:

T2DM - Type II Diabetes Mellitus

TSH - Thyroid Stimulating Hormone

FT4 - Free Thyroxine

ACR - Albumin to Creatinine Ratio

HbA1c - Glycated Hemoglobin

NA - Normal Albuminuria

TPOAb - Thyroid Peroxidase Antibodies

UACR - Urine Albumin to Creatinine Ratio

DPP-4 - Dipeptidyl Peptidase-4

LRG1 - Leucine-rich α-2-Glycoprotein 1

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