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Original Research Article

Low Circulating Free Triiodothyronine Levels Are Associated with the Progression of Diabetic Nephropathy in Patients with Type 2 Diabetes

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Abstract:

Background: Diabetic nephropathy is a leading cause of end-stage renal disease (ESRD) worldwide, particularly among patients with Type 2 diabetes mellitus. Thyroid hormones, particularly free triiodothyronine (FT3), have been implicated in the progression of chronic kidney disease (CKD), but their role in diabetic nephropathy remains underexplored.

Aim: This study aims to investigate the association between circulating FT3 levels and the progression of diabetic nephropathy in patients with Type 2 diabetes.

Methods: Based on their serum FT3 levels, participants were divided into three groups: low, normal, and high. Urine albumin-to-creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) were used to evaluate kidney function. After controlling for confounders, statistical analysis was done using multivariate analysis, linear regression, and Pearson's correlation to determine whether FT3 levels and kidney function are related.

Results: Individuals with eGFR (59.8 ± 16.5 mL/min/1.73 m²) and urine ACR (236.7 ± 154.8 mg/g) that were significantly lower and higher, respectively, than those with normal or high FT3 levels ($p < 0.001$) were those with low FT3 levels. According to Pearson's correlation analysis, there was a substantial negative connection ($r = -0.32$, $p < 0.001$) between FT3 levels and urine ACR and a significant positive correlation ($r = 0.35$, $p < 0.001$) between FT3 levels and eGFR. Once age, gender, length of diabetes, HbA1c, BMI, and blood pressure were taken into account, multivariate regression analysis demonstrated that low FT3 levels were significantly linked to impaired kidney function.

Conclusion: Lower circulating FT3 levels are significantly associated with the progression of diabetic nephropathy in patients with Type 2 diabetes. Monitoring FT3 levels may serve as a valuable tool in predicting and managing diabetic kidney disease.

Recommendations: Further longitudinal studies are recommended to establish the causal relationship between FT3 levels and diabetic nephropathy and to explore the potential benefits of thyroid hormone supplementation in managing diabetic kidney disease.

Keywords: Diabetic nephropathy, Type 2 diabetes, Free triiodothyronine (FT3), Kidney function, Chronic kidney disease.

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Introduction

One of the most prevalent and dangerous side effects of Type 2 diabetes mellitus is diabetic nephropathy, which greatly increases the worldwide burden of ESRD. It is distinguished by a steady decrease in GFR, ongoing albuminuria, and a higher risk of cardiovascular morbidity and death. Diabetic nephropathy has a complicated and multifaceted pathophysiology that includes haemodynamic alterations, chronic inflammation, and metabolic perturbations brought on by hyperglycemia, all of which lead to damage to the tubules and glomeruli [1].

Thyroid hormones, including T4 and T3, are essential for controlling growth, differentiation, and metabolism in a variety of tissues, including the kidneys. Thyroid dysfunction, especially in its subclinical manifestations, may have an impact on the development of diabetic nephropathy and CKD, according to recent research. In patients with CKD, low levels of FT3, the active form of thyroid hormone, have been linked to worse renal outcomes and an increased risk of cardiovascular events. As a result, there is increasing curiosity about the possible involvement of thyroid

hormones, specifically FT3, in the development and course of diabetic nephropathy [2].

Kidney disease and thyroid function are correlated in both directions. Thyroid hormones are metabolised and cleared by the kidneys; however, abnormalities in kidney function can affect thyroid hormone levels, including FT3. Nevertheless, there are few research examining this connection, and it is still unknown exactly what part FT3 plays in the development of diabetic nephropathy [3].

Finding innovative biomarkers that can help with the early diagnosis and treatment of diabetic nephropathy is vital given the rising incidence of Type 2 diabetes and its related consequences. Tracking FT3 levels could be a useful tool for directing treatment actions and forecasting how diabetic nephropathy will develop.

This study aims to investigate the association between circulating FT3 levels and the progression of diabetic nephropathy in patients with Type 2 diabetes.

Methodology

Study Design: This study is a cross-sectional observational study.

Study Setting: The study was conducted at PMCH General Medicine and Nephrology outpatient departments over a period of 12 months, from July 2022 to June 2023.

Participants: A total of 300 patients with Type 2 diabetes, aged 30-70 years, who visited the outpatient departments during the study period, were enrolled in the study.

Inclusion Criteria

- Adults aged 30-70 years.
- Had Type 2 diabetes for at least five years.
- Diabetic nephropathy is indicated by higher ACR or decreased estimated eGFR.
- Willingness to give written informed consent.

Exclusion Criteria

- It includes a history of thyroid illness or current usage of thyroid hormone replacement therapy.
- Pregnant or breastfeeding ladies. Patients with serious chronic illnesses, such as liver disease, cancer, or severe cardiovascular issues. Used thyroid-related drugs (e.g., amiodarone or glucocorticoids) during the past 6 months
- Participants with incomplete medical records or unwilling to comply with study procedures.

Bias: Potential sources of bias were addressed by standardizing the data collection process, using predefined inclusion and exclusion criteria, and controlling for confounding factors such as age, gender, duration of diabetes, and medication use through statistical adjustments.

Data Collection

Data were gathered through patient interviews, medical record reviews, and laboratory tests. The following variables were recorded:

- Demographic information (age, gender, BMI).
- Diabetes duration and treatment regimen.
- Monitor blood pressure, fasting glucose, and HbA1c levels.
- Assess renal function using serum creatinine, eGFR, and urine ACR levels.
- Measure serum FT3, FT4, and TSH levels.

Procedure: All participants underwent a comprehensive medical examination, and fasting blood samples were drawn for biochemical analysis. Serum FT3, FT4, and TSH levels were measured using chemiluminescent immunoassays. Kidney function was evaluated based on serum creatinine, eGFR, and urine ACR. Data collection was performed by trained healthcare professionals to ensure consistency and accuracy.

Statistical Analysis: SPSS version 23.0 was used to analyse the data. For continuous variables, the standard deviation (SD) was represented as mean ±, while frequencies and percentages were used for categorical variables. The Pearson's correlation coefficient and linear regression analysis were used to evaluate the relationship between FT3 levels and the development of diabetic nephropathy. Confounding variables were taken into account when building multivariate regression models. Statistical significance was attained when the p-value was less than 0.05.

Results

The mean age of the participants was 56.2 ± 8.3 years, with 164 (54.7%) males and 136 (45.3%) females. The mean duration of diabetes was 10.5 ± 4.2 years. The baseline characteristics of the participants are summarized in Table 1.

Table 1: Baseline Characteristics of the Study Population (N = 300)

Characteristic	Total Population (N=300)	Males (N=164)	Females (N=136)
Age (years)	56.2 ± 8.3	57.1 ± 7.9	55.1 ± 8.7
Duration of Diabetes (years)	10.5 ± 4.2	10.7 ± 4.3	10.2 ± 4.1
Body Mass Index (BMI, kg/m²)	27.8 ± 4.1	28.2 ± 4.3	27.3 ± 3.9
HbA1c (%)	7.8 ± 1.2	7.9 ± 1.1	7.7 ± 1.3
Systolic BP (mmHg)	136.4 ± 12.5	138.1 ± 13.2	134.3 ± 11.6

Diastolic BP (mmHg)	82.7 ± 8.1	83.9 ± 7.9	81.2 ± 8.3
eGFR (mL/min/1.73 m²)	68.2 ± 18.7	67.5 ± 19.1	69.1 ± 18.3
Urine ACR (mg/g)	188.5 ± 142.3	194.6 ± 145.7	180.2 ± 137.4
FT3 (pmol/L)	4.2 ± 0.8	4.1 ± 0.7	4.3 ± 0.9
FT4 (pmol/L)	15.3 ± 2.4	15.1 ± 2.3	15.6 ± 2.5
TSH (mIU/L)	2.1 ± 1.0	2.0 ± 1.1	2.2 ± 0.9

Association Between FT3 Levels and Diabetic Nephropathy: Participants were categorized into three groups based on their serum FT3 levels: Low FT3 (<3.5 pmol/L), Normal FT3 (3.5-4.9 pmol/L), and High FT3 (>4.9 pmol/L). The distribution of kidney function parameters across these groups is shown in Table 2.

Table 2: Kidney Function Parameters Across FT3 Groups

Parameter	Low FT3 (N=82)	Normal FT3 (N=174)	High FT3 (N=44)	p-value
eGFR (mL/min/1.73 m²)	59.8 ± 16.5	70.2 ± 18.0	75.4 ± 19.2	<0.001
Urine ACR (mg/g)	236.7 ± 154.8	172.3 ± 137.6	145.1 ± 126.4	<0.001

As shown in Table 2, participants with low FT3 levels had significantly lower eGFR and higher urine ACR compared to those with normal or high FT3 levels, indicating more advanced diabetic nephropathy ($p < 0.001$ for both parameters).

Correlation Analysis: Pearson's correlation analysis revealed a significant positive correlation between FT3 levels and eGFR ($r = 0.35$, $p < 0.001$) and a significant negative correlation between FT3 levels and urine ACR ($r = -0.32$, $p < 0.001$). These findings suggest that lower FT3 levels are associated with worse kidney function in patients with Type 2 diabetes.

Multivariate Regression Analysis: To adjust for potential confounders, a multivariate regression analysis was performed with eGFR and urine ACR as dependent variables and FT3 levels as the primary independent variable. The models were adjusted for age, gender, duration of diabetes, HbA1c, BMI, and blood pressure.

Table 3: Multivariate Regression Analysis for eGFR and Urine ACR

Variable	eGFR (β, p-value)	Urine ACR (β, p-value)
FT3 (pmol/L)	5.21, <0.001	-28.3, <0.001
Age (years)	-0.41, 0.003	2.1, 0.015
Gender (Male)	0.12, 0.782	-6.5, 0.232
Duration of Diabetes (years)	-0.27, 0.045	1.8, 0.042
HbA1c (%)	-0.83, 0.002	5.4, 0.008
BMI (kg/m²)	-0.24, 0.051	1.3, 0.038
Systolic BP (mmHg)	-0.65, 0.009	3.9, 0.004

The multivariate analysis confirmed that lower FT3 levels were independently associated with reduced eGFR ($\beta = 5.21$, $p < 0.001$) and increased urine ACR ($\beta = -28.3$, $p < 0.001$), after adjusting for confounding factors. Other significant predictors of eGFR and urine ACR included age, duration of diabetes, HbA1c, and systolic blood pressure.

Discussion

The study looked into the link between circulating FT3 levels and the evolution of diabetic nephropathy in Type 2 diabetes patients. The study comprised 300 individuals with a mean age of 56.2 years, the majority of whom had been diagnosed with diabetes for an average of 10.5 years. The study discovered a link between reduced FT3 levels and poorer kidney function, as evidenced by a lower rate (eGFR) and a greater urine albumin-to-creatinine ratio (ACR), both of which are important indicators of diabetic nephropathy. Patients with low FT3 levels (<3.5 pmol/L) had significantly lower eGFR and greater urine ACR than those with normal or high FT3 levels. In particular, the low FT3 group's eGFR was significantly lower than that of the normal and high FT3 groups, at 59.8 mL/min/1.73 m². In the low FT3 group, the urine ACR was also much higher, suggesting more serious kidney injury. Pearson's correlation analysis, which revealed a negative association between FT3 levels and urine ACR and a positive correlation between FT3 levels and eGFR, corroborated these findings. These results were further supported by the multivariate regression analysis, which showed that low FT3 levels were independently linked to lower kidney function even after controlling for possible confounding variables such age, length of diabetes, HbA1c, and blood pressure. According to the findings, FT3 levels may be a useful biomarker for determining a patient's risk of developing diabetic nephropathy in the event that they have Type 2 diabetes.

Recent research has demonstrated an increasingly strong correlation between thyroid hormone

levels—specifically, free triiodothyronine, or FT3—and the development of DN in individuals with T2DM. In a cross-sectional investigation, it was found that patients with DN had considerably lower serum FT3 levels than those without the illness. Reduced FT3 levels may be a key component in the development of DN, as the study also showed a negative link between FT3 levels and the chance of having DN [4].

A cross-sectional investigation in euthyroid patients with T2DM provides more evidence for this association by showing that lower FT3 levels were inversely connected with the existence of DN even when the range was within normal limits. Wang demonstrate that thyroid function, even in patients without overt thyroid disease, can have a considerable impact on DN risk factors [5].

In a different investigation, Zhao looked at thyroid function in patients with T2DM and DN and discovered that these individuals had lower FT3 levels and greater thyroid-stimulating hormone (TSH) levels than those without DN. The study came to the conclusion that since thyroid dysfunction might make the illness worse, routine monitoring of thyroid function is crucial for controlling DN [6]. All of these results point to the critical role that thyroid hormones—especially FT3—play in the development of diabetic nephropathy. In patients with T2DM, lower FT3 levels are consistently linked to a higher risk of DN and DKD development, indicating that thyroid function monitoring may be an essential part of comprehensive diabetes therapy.

Conclusion

In conclusion, this study highlights the potential role of FT3 in the pathophysiology of diabetic nephropathy. The findings suggest that monitoring FT3 levels in patients with Type 2 diabetes could help identify those at higher risk for kidney complications, allowing for earlier intervention and potentially better clinical outcomes. These results underscore the importance of thyroid function in the management of diabetic nephropathy and suggest that FT3 could be considered in future risk assessment models for patients with Type 2 diabetes.

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