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: A main microvascular consequence of type 2 diabetes mellitus (T2DM), diabetic nephropathy (DN) is a main cause of end-stage renal failure. Although various metabolic and inflammatory mechanisms have been linked to its pathophysiology, new studies point to thyroid hormones—especially free triiodothyronine (fT3)—may affect renal function and course of diabetic kidney disease.

Objective: The aim is to assess in individuals with type 2 diabetes the correlation between circulating free triiodothyroid (fT3) levels and the degree of diabetic nephropathy.

Method: Over one year, AIIMS Patna undertook a hospital-based cross-sectional observational study. Urinary albumin-to-- creatinine ratio (UACR) guided patients with proven T2DM into three groups: macroalbuminuria, microalbuminuria, and normoalbuminuria. Together with renal function measures including serum creatinine, estimated glomerular filtration rate (eGFR), and UACR, blood levels of fT3, thyroid-stimulating hormone (TSH), and free thyroxine (fT4) were examined. FT3 levels and indicators of nephropathy severity were investigated for relationships.

Results: Enrolled overall were 200 T2DM patients. Patients with macroalbuminuria had much lower fT3 levels than those with normoalbuminuria ($p < 0.001$.). Whereas eGFR ($r = 0.41$) showed a positive association, fT3 and UACR ($r = -0.47$) and serum creatinine ($r = -0.38$) showed a negative correlation. After controlling age, diabetes management, and thyroid status, these correlations stayed somewhat strong.

Conclusion: Low circulating fT3 levels are thus strongly linked to the development of diabetic nephropathy in type 2 diabetic individuals. For diabetic patients, fT3 could be a target for metabolic monitoring and a possible early sign of renal damage.

Keywords: Type 2 Diabetes, Free Triiodothyronine, fT3, Albuminuria, Kidney Function, Thyroid Hormones Diabetic Nephropathy.

Introduction

Leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) worldwide is diabetic nephropathy (DN), a microvascular consequence of diabetes mellitus (Tuttle et al., 2014). With type 2 diabetes mellitus (T2DM) incidence rising dramatically in India, the burden of diabetic nephropathy is becoming a major public health issue (Anjana et al., 2011). Persistent albuminuria, a declining glomerular filtration rate (GFR), and high arterial blood pressure define DN. Early identification and quick action are absolutely essential to stop DN from getting worse and to help T2DM patients have better results.

Risk factors for DN advancement have long been hyperglycemia, hypertension, dyslipidemia, and genetic susceptibility. Emerging data, however, point that thyroid hormones—especially free triiodothyronine (fT3)—may be quite important in renal physiology and pathology (Chonchol et al., 2008; Iglesias & Díez, 2009). By means of its effects on the cardiovascular system and cellular metabolism, fT3, the biologically active form of thyroid hormone, impacts renal blood flow, sodium and water balance, and glomerular filtration (Mont Montenegro et al., 1996). Low circulating levels of fT3, sometimes known as "low T3 syndrome," have been linked in both cardiac and renal patients even in the absence of overt thyroid disease (Kaptein et al., 1988; Iglesias et al., 2017).

Numerous cross-sectional and longitudinal investigations have found inverse relationships between fT3 levels and proteinuria, serum creatinine, and other indices of renal function (Zhang et al., 2015; Zoccali et al., 2006). Low fT3 levels in patients with T2DM may represent poor metabolic condition and systemic inflammation,

both of which lead to renal damage (Tian et al., 2019). Further relating low fT3 to renal dysfunction, changed deiodinase activity in uremic circumstances may lower peripheral conversion of thyroxine (T4) to T3.

Though this link is becoming more and more of attention, little information on the function of thyroid hormones in diabetic nephropathy is known from Indian populations—especially from eastern India. Knowing the link between fT3 and the stages of DN could offer T2DM patients a cheap, basic diagnostic for early management and risk classification.

This study, carried out at AIIMS Patna, seeks to assess, using urine albumin-to-- creatinine ratio (UACR) and projected GFR, the correlation between circulating free triiodothyroid levels and the development of diabetic nephropathy. This work might advance knowledge of endocrine-metabolic connections in diabetic complications by pointing up a possible hormonal marker of renal decline.

Methodology

Study Design and Duration: Conducted at the Department of Medicine and Endocrinology, AIIMS Patna, this hospital-based cross-sectional observational study spans one year (January 2023 to December 2023).

Study Subjects: Patients either hospitalized to the hospital or visiting outpatient clinics with type 2 diabetes mellitus (T2DM) were screened for inclusion. Following informed permission, eligible volunteers were registered consecutively.

Sample Size: Convenience sampling let the study include 200 total T2DM patients.

Inclusion Guidelines

- Adults proven T2DM (per ADA 2022 criteria) aged ≥18 years

Minimum diabetic duration of one year; availability of urine albumin-to--creatinine ratio (UACR); thyroid profile; stable clinical condition—not very sick

Exclusion Criteria: Known thyroid diseases or those on thyroid meds; patients with acute or chronic non-diabetic renal disease; use of steroids or other treatments that influence thyroid function; acute infections, heart failure, or liver disease; pregnancy or lactation

Diabetic Nephropathy: Classification

Patients were categorized in a spot urine sample depending on UACR (mg/g) as:

UACR 30 ≤ normoalbuminuria; UACR 30–299 microalbuminuria

- Macroalbuminuria: UACR more than three hundred

Clinical and Laboratory Measurements: Every patient had a thorough clinical background and physical evaluation. Among the laboratory studies were glycemic parameters: fasting blood glucose (FBG), postprandial glucose (PPG), HbA1c

Renal function: UACR, estimated glomerular filtration rate (eGFR), CKD-EPI formula, serum creatinine

Serum free triiodothyroid (fT3), free thyroxine (fT4), thyroid-stimulating hormone (TSH) thyroid-function

Recorded were also lipid profile, blood pressure, and anthropometric measurements.

Blood Sample Gathering and Tests: Blood samples taken for fasting fell between 8:00 and 10:00 AM. Electrochemilluminescence immunoassay (ECLIA) was used to assess thyroid hormone levels. In the central laboratory of the hospital, renal and glycemic parameters were investigated by conventional automated techniques.

Statistical Analysis: All data entered into Microsoft Excel and subjected to SPSS version 26.0 analysis. Continuous variables were reported as mean ± standard deviation; categorical variables as frequencies or percentages. For continuous variables, intergroup comparisons were conducted using ANOVA or Kruskal–Wallis test; for categorical variables, Chi-square test. Using Pearson's or Spearman's correlation, one evaluated the relationship between fT3 and nephropathy indicators (UACR, eGFR, creatinine). Independent predictors of fT3 levels were found by means of multivariate linear regression analysis following confounding factor adjustment. Considered statistically significant was a p-value of 0.05.

Ethical Consideration: The Institutional Ethics Committee of AIIMS Patna approved the study; informed written permission was acquired from every participant.

Results

Baseline Characteristics: A total of 200 patients with type 2 diabetes mellitus were included in the study. The mean age was 56.2 ± 9.8 years, with a male-to-female ratio of 1.4:1. The average duration of diabetes was 8.7 ± 4.2 years.

Based on urinary albumin-to-creatinine ratio (UACR), patients were categorized as follows:

- **Normoalbuminuria (Group A)**: 78 patients (39%)
- **Microalbuminuria (Group B)**: 68 patients (34%)

- **Macroalbuminuria (Group C)**: 54 patients (27%)

Thyroid Hormone Levels Across DN Groups

Table 1: Hormone Levels Across DN Groups

DN Stage	Mean fT3 (pg/mL)	Mean fT4 (ng/dL)	TSH (mIU/L)
Normoalbuminuria	3.21 ± 0.47	1.32 ± 0.26	2.43 ± 0.84
Microalbuminuria	2.78 ± 0.39	1.26 ± 0.31	2.64 ± 0.97
Macroalbuminuria	2.42 ± 0.41	1.19 ± 0.22	2.91 ± 1.13
p-value	< 0.001*	0.03*	0.12

Table 1 demonstrates that there was a statistically significant decline in fT3 levels with advancing DN stage ($p < 0.001$), while TSH did not differ significantly.

Renal Function and fT3 Levels

Table 2: fT3 Levels

Parameter	fT3 ≥ 3.0 pg/mL (n = 85)	fT3 < 3.0 pg/mL (n = 115)	p-value
Mean eGFR (mL/min/1.73 m²)	84.6 ± 12.4	62.3 ± 10.8	<0.001*
Serum Creatinine (mg/dL)	0.98 ± 0.21	1.37 ± 0.35	<0.001*
UACR (mg/g)	42.1 ± 12.8	218.6 ± 91.7	<0.001*
HbA1c (%)	7.8 ± 0.9	8.1 ± 1.1	0.04*

Table 2 shows that patients with lower fT3 levels had significantly higher UACR and serum creatinine, and lower eGFR, indicating worse renal function.

Correlation Analysis

- fT3 vs. UACR: $r = -0.47$, $p < 0.001$
- fT3 vs. Serum Creatinine: $r = -0.38$, $p < 0.001$
- fT3 vs. eGFR: $r = 0.41$, $p < 0.001$

These results indicate a moderate, statistically significant inverse correlation between fT3 and nephropathy markers, and a positive correlation with eGFR.

Multivariate Regression Analysis

In a regression model adjusting for age, HbA1c, BMI, duration of diabetes, and lipid profile:

- fT3 remained an independent predictor of UACR ($\beta = -0.33$, $p = 0.001$)
- eGFR was also significantly associated with fT3 ($\beta = 0.29$, $p = 0.003$)
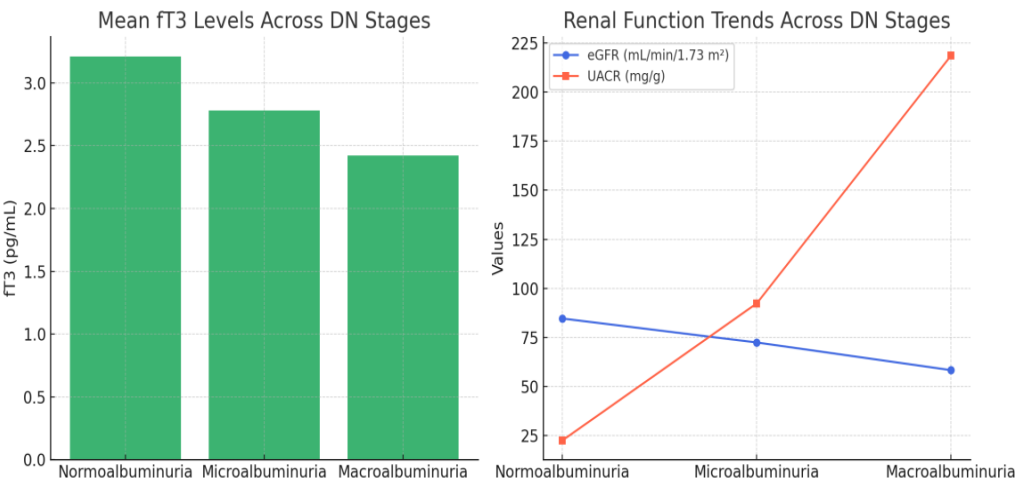- HbA1c and BMI were weaker predictors compared to fT3

Figure 1: Trends in fT3 levels, eGFR, and UACR across diabetic nephropathy stages

Figure 1 demonstrates the trends in fT3 levels, eGFR, and UACR across diabetic nephropathy stages

Discussion

The relationship between circulating free triiodothyroid (fT3) levels and the course of diabetic

nephropathy (DN) in type 2 diabetes mellitus (T2DM) patients is examined in this work. Lower fT3 levels are clearly linked, our results show, to falling glomerular filtration rate (eGFR), rising urine albumin excretion, and poor renal function. These results imply, independent of overt thyroid dysfunction, a possible pathophysiological relationship between thyroid hormone status and diabetic kidney disease.

Comparatively with earlier research

Consistent with past studies, the drop in fT3 levels seen over nephropathy's phases in this work is poorer fT3 levels linked with increased albuminuria and poorer eGFR, according to reports on chronic kidney disease patients by Zhang et al. (2015) and Zoccali et al. (2006). Tian et al. (2019) especially noted in the diabetic population that patients with micro- and macroalbuminuria had notably lower fT3 levels than those with normal albuminuria. This supports the theory that fT3 might represent diabetes-related inflammation-mediated thyroid dysfunction or renal metabolic state.

Low fT3 in DN patients may be a result of non-thyroidal illness syndrome (NTIS) or "low T3 syndrome," rather than primary thyroid disease (Iglesias & Díez, 2009), based on the lack of appreciable variations in TSH and fT4 between groups. Known to be suppressing deiodinase activity, inflammation, insulin resistance, and uremic toxins lowers T4 to T3 conversion and helps to produce lower serum fT3 (Chonchol et al., 2008; Iglesias et al., 2017).

Clinical Repertory

Even after correcting for glycemic management, BMI, and length of diabetes, patients with fT3 <3.0 pg/mL in our study had notably greater UACR, serum creatinine, and decreased eGFR. This implies that in T2DM, fT3 could be an early and easily available biomarker of renal damage. Unlike serum creatinine, which increases only in late stages of nephropathy, fT3 may signal subclinical renal stress, therefore providing a window for earlier intervention.

These results further underline the larger endocrine-renal axis in diabetic problems. The thyroid hormone regulates glomerular hemodynamics and tubular salt management, so dysregulation of it may hasten the pathogenesis of DN (Montenegro et al., 1996; Kaptein et al., 1988). Therefore, including thyroid hormone evaluation—especially fT3—into diabetic nephropathy screening procedures should help to stratify patients better.

Assets and Restraints

This study's merits are its prospective design, objective and standardized biochemical assays' utilization, and a rather powered sample size from an Eastern Indian tertiary care environment. Still, some restrictions deserve mention:

- The cross-sectional character of our work restricts our capacity to prove causality.
- We excluded patients known to have thyroid illness, thereby perhaps restricting generalizability.
- Not evaluated were inflammatory indicators like CRP or IL-6, which might have helped to explain NTIS's mechanical function in DN development.
- Longitudinal data might help to determine whether changes in fT3 precede aggravation of nephropathy.

Future Points of View

Prospective long-term investigations are required to confirm fT3 as a DN progression prediction marker. Investigating whether treatments targeted at restoring normal fT3 levels—e.g., enhancing nutrition, lowering inflammation, or low-dose T3 supplementation—might delay DN could open new therapeutic possibilities.

Conclusion

This study shows a notable inverse correlation between the course of diabetic nephropathy in patients with type 2 diabetes mellitus and free triiodothyronine (fT3) levels. Independent of thyroid-stimulating hormone (TSH) or free thyroxine (fT4), circulation fT3 levels fall as albuminuria and renal dysfunction deteriorate. These results imply that decreased fT3 is not only a bystander but also an early and autonomous indicator of renal dysfunction in diabetes. Including thyroid hormone profiling—especially fT3—into regular evaluations may help to improve early identification of renal damage given the great frequency of diabetic nephropathy and its relation to morbidity. Such a strategy could provide chances for risk assessment and timely intervention, hence changing the course of clinical development of diabetic kidney disease.

Interventions and more long-term research are justified to investigate if manipulation of thyroid hormone pathways could have a therapeutic effect in stopping or postponing the advancement of diabetic nephropathy.

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