Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Thyroid Hormone Indices and Histopathological Severity of Diabetic Nephropathy in Euthyroid Patients with Type 2 Diabetes: A Biopsy-Based Cross-Sectional Study

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Purpose: Thyroid hormones (THs) influence glucose homeostasis, vascular tone, and renal hemodynamics. Whether subtle variations in TH indices within the euthyroid range are associated with histopathological severity of diabetic nephropathy (DN) is unclear. We examined the association between TH indices and renal pathological severity in euthyroid patients with type 2 diabetes mellitus (T_2DM) and biopsy-proven DN.

Methods: In this single-center cross-sectional study, 362 euthyroid adults with T_2DM and biopsy-confirmed DN were included. DN lesions were classified according to the Renal Pathology Society classification as early (class I–II) or advanced (class III–IV). Serum free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and the FT3/FT4 ratio were measured. Multivariable logistic regression and restricted cubic splines (RCS) were used to evaluate associations with advanced DN.

Results: Of 362 patients, 143 had early DN and 219 had advanced DN. Compared with the early DN group, patients with advanced DN had lower FT3 levels (4.46 ± 0.66 vs 4.82 ± 0.73 pmol/L, $P < 0.001$) and a lower FT3/FT4 ratio (median 0.31 vs 0.33, $P = 0.013$). In fully adjusted models, lower FT3 levels were independently associated with higher odds of advanced DN (OR = 0.442, 95% CI 0.293–0.666, $P < 0.001$). In sensitivity analyses with further adjustment for estimated glomerular filtration rate (eGFR) and diabetic retinopathy, the inverse association between the FT3/FT4 ratio and advanced DN was attenuated and became borderline significant, whereas the association for FT3 remained robust. Moreover, higher FT3 quartiles were associated with progressively lower odds of advanced DN (Q4 vs Q1: OR = 0.160, 95% CI 0.070–0.365; P for trend < 0.001). RCS and quartile analyses suggested a predominantly linear inverse association between FT3 and the probability of advanced DN, with a similar but weaker pattern observed for the FT3/FT4 ratio.

Conclusion: Our findings extend prior studies based on eGFR or albuminuria by providing biopsy-confirmed histopathological evidence linking low-normal THs to the structural severity of DN. These results suggest that subtle reductions in peripheral T3 activity may be associated with underlying renal injury and could have potential value in identifying patients at higher risk.

Plain Language Summary: Diabetic nephropathy is a common kidney complication of type 2 diabetes and a major cause of kidney failure. Thyroid hormones, especially triiodothyronine (T3), not only regulate metabolism but also affect blood vessels and kidney cells. Even when routine thyroid tests are "normal", small differences in thyroid hormone levels may still be related to kidney damage.

In this study, we included 362 patients with type 2 diabetes whose kidney biopsies confirmed diabetic nephropathy. All participants had normal thyroid function tests. Based on their kidney biopsy results, we divided patients into early-stage and advanced-stage disease. We measured levels of free T3 (FT3), free T4 (FT4), and thyroid-stimulating hormone (TSH) in the blood. We also calculated the FT3/FT4 ratio, which reflects how efficiently the body converts FT4 into the active hormone FT3. We found that patients with more advanced kidney damage tended to have lower FT3 levels and a lower FT3/FT4 ratio. After we accounted for other risk factors such as age, blood pressure, blood sugar control, kidney function, and the amount of protein in urine, higher FT3 levels and a higher FT3/FT4 ratio were still linked to a lower likelihood of advanced kidney damage.

https://doi.org/10.2147/DMSO.S589576
Received: 12 January 2026
Accepted: 13 March 2026
Published: 23 March 2026

These results suggest that small differences in thyroid hormone levels, even within the normal range, may provide additional information about kidney disease severity in people with type 2 diabetes. Because these tests are already routinely available, they may help doctors better assess kidney health and potentially support decisions about further evaluation, including the need for kidney biopsy. More research is needed to determine whether tracking these hormone levels over time could improve patient care.

Keywords: diabetic kidney disease, free triiodothyronine, FT3/FT4 ratio, renal histopathology, euthyroid status

Introduction

Diabetes mellitus represents a major global health challenge, and type 2 diabetes mellitus (T_2DM) accounts for the majority of cases.[1,2] According to the International Diabetes Federation, the global number of individuals living with diabetes reached approximately 564 million in 2021 and is projected to increase to 783 million by 2045.[3] Diabetic nephropathy (DN), a principal microvascular complication of T2DM, affects an estimated 20–40% of patients and remains one of the leading causes of end-stage renal disease (ESRD), thereby imposing substantial clinical, societal, and economic burdens.[4] Moreover, recent global burden analyses have confirmed that DN continues to be a major and expanding contributor to chronic kidney disease (CKD) and ESRD worldwide, underscoring its persistent and increasing impact on public health.[5]

Thyroid hormones (THs) are central regulators of energy metabolism and glucose homeostasis and play an important role in renal physiology.[6–8] Experimental and clinical studies have shown that THs influence renal hemodynamics by regulating renal blood flow, intrarenal vascular resistance, and glomerular filtration rate, largely through effects on systemic hemodynamics and vascular tone.[9,10] In addition, THs modulate tubular function by affecting sodium handling, Na^+/K^+-ATPase activity, and renal oxygen consumption, thereby influencing tubular energy metabolism and susceptibility to hypoxic injury.[11] Experimental evidence suggests that, under diabetic stress, podocytes exhibit adaptive upregulation of the T3-inactivating enzyme deiodinase 3 (DIO3), resulting in locally decreased T3 signaling and reactivation of fetal-like thyroid hormone pathways.[9] Importantly, TH alterations may occur even without overt thyroid disease.[12] Previous studies in euthyroid T_2DM populations have reported associations between lower free triiodothyronine (FT3) and worse renal function or higher albuminuria.[13–16] However, most of the aforementioned studies have relied on functional renal markers, such as estimated glomerular filtration rate (eGFR) or albuminuria, and direct evidence linking thyroid hormone indices to biopsy-confirmed histopathological severity of DN remains limited.

Renal biopsy remains the gold standard for diagnosing DN and grading its structural severity. Therefore, we conducted a biopsy-based study focusing on euthyroid patients with T_2DM to evaluate whether TH indices, particularly FT3 and the FT3/FT4 ratio (a proxy of peripheral conversion and T3 bioactivity), are associated with the pathological severity of DN. We hypothesized that lower FT3 levels and a lower FT3/FT4 ratio would correlate with more severe histopathological findings on renal biopsy.

Methods

Study Design and Participants

This single-center retrospective cross-sectional study was conducted at the Second Hospital of Hebei Medical University. We retrospectively identified 803 adult patients with diabetes who had undergone native kidney biopsy between January 2015 and August 2025, with August 2025 serving as the cutoff date for retrospective data extraction. All kidney biopsies were performed according to institutional protocols and established clinical indications in routine clinical practice.[17] Indications for biopsy included, but were not limited to, a rapid decline in eGFR, a sudden increase in proteinuria, significant proteinuria in the absence of diabetic retinopathy (DR), and the presence of glomerular hematuria.

The following subjects were excluded from the study: (1) subjects with type 1 diabetes mellitus or other types of diabetes; (2) subjects with a transplanted kidney, insufficient glomeruli for pathological evaluation, or coexistence of nondiabetic nephropathy; (3) subjects with abnormal thyroid function, use of medications known to affect thyroid function (eg., amiodarone, glucocorticoids, antithyroid drugs, or levothyroxine), or other conditions potentially associated with unstable thyroid hormone status (eg., pregnancy or severe comorbidities such as malignant tumors and sepsis); and (4) subjects without available thyroid function measurements. Exposure to iodinated contrast media was not

routinely recorded in the database. However, thyroid function tests were performed as part of routine clinical evaluation at the time of renal biopsy, and all included participants fulfilled the predefined euthyroid criteria. After applying inclusion and exclusion criteria, 362 euthyroid patients with T_2DM and biopsy-confirmed DN were included in the final analysis. The flow of patient selection is shown in Figure 1.

Euthyroidism was defined as FT3, FT4, and TSH all within the laboratory reference ranges (FT3: 2.76–6.50 pmol/L; FT4: 11.50–22.70 pmol/L; TSH: 0.35–4.78 mIU/L). Serum FT3, FT4, and TSH levels were measured in the hospital's central laboratory using a chemiluminescence immunoassay analyzer (Atellica IM 1600; Siemens Healthineers, Erlangen, Germany). According to laboratory validation and manufacturer specifications, the inter-assay coefficients of variation for FT3, FT4, and TSH were all <3%.

The study protocol was approved by the Ethics Committee of the Second Hospital of Hebei Medical University (Approval No. 2025-R642) and conducted in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived by the ethics committee due to the retrospective design and use of anonymized data. Patient data were accessed and analyzed after ethics approval was granted.

Clinical and Laboratory Data

At biopsy admission, we collected sex, age, height, weight, smoking status, systolic blood pressure (SBP), diabetes duration, cardiovascular disease (CVD) history, diabetic retinopathy (DR), and medication use (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) and sodium–glucose cotransporter 2 inhibitors (SGLT2i). Fasting venous blood samples were used to measure FT3, FT4, TSH, albumin (ALB), HbA1c, serum creatinine (Scr), uric acid (UA), lipid profile (TC, TG, LDL-C, HDL-C), and blood counts. The neutrophil-to-lymphocyte ratio (NLR) was calculated.

A 24-hour urine collection was performed to quantify urinary protein excretion (g/24h). Proteinuria was assessed using 24-hour urine collections performed as part of routine clinical evaluation. When multiple measurements were available, the value closest to the time of biopsy was used for analysis. eGFR was calculated using the 2009 CKD-EPI creatinine equation.[18] However, we acknowledge that creatinine-based equations may be influenced by reduced muscle mass or malnutrition, particularly in patients with advanced DN. BMI was calculated as weight (kg) divided by height squared (m^2).

Renal Pathology Assessment

All biopsy specimens were independently evaluated by two experienced renal pathologists who were blinded to clinical data. Discrepancies were resolved through joint review and consensus discussion. Each specimen contained at least 10 glomeruli. All renal biopsy specimens were routinely examined by light microscopy (LM) and immunofluorescence (IF). Electron microscopy (EM) was performed when early DN was suspected based on LM findings or when the pathological features were inconclusive.

Importantly, all cases suspected of class I DN underwent EM examination to ensure accurate pathological classification. DN classes (I–IV) were determined according to the Renal Pathology Society classification.[19] For primary analyses, DN was dichotomized as early (class I–II) and advanced (class III–IV). This categorization was based on clinically meaningful differences in structural glomerular damage and prognostic implications reported in prior literature.[20] Moreover, dichotomization improved statistical interpretability and ensured adequate sample size within each group for multivariable modeling.

The percentage of global glomerulosclerosis was calculated. We also recorded semi-quantitative scores of tubulointerstitial and vascular lesions, including interstitial fibrosis and tubular atrophy (IFTA, 0–3), interstitial inflammation (0–2), and vascular lesions. These were assessed according to the Renal Pathology Society (RPS) classification criteria.[19] The basic pathological criteria are shown in Supplementary Table S1.

Outcomes and Exposures

The primary outcome was advanced DN (class III–IV). Primary exposures were serum FT3, FT4, TSH, and the FT3/FT4 ratio.

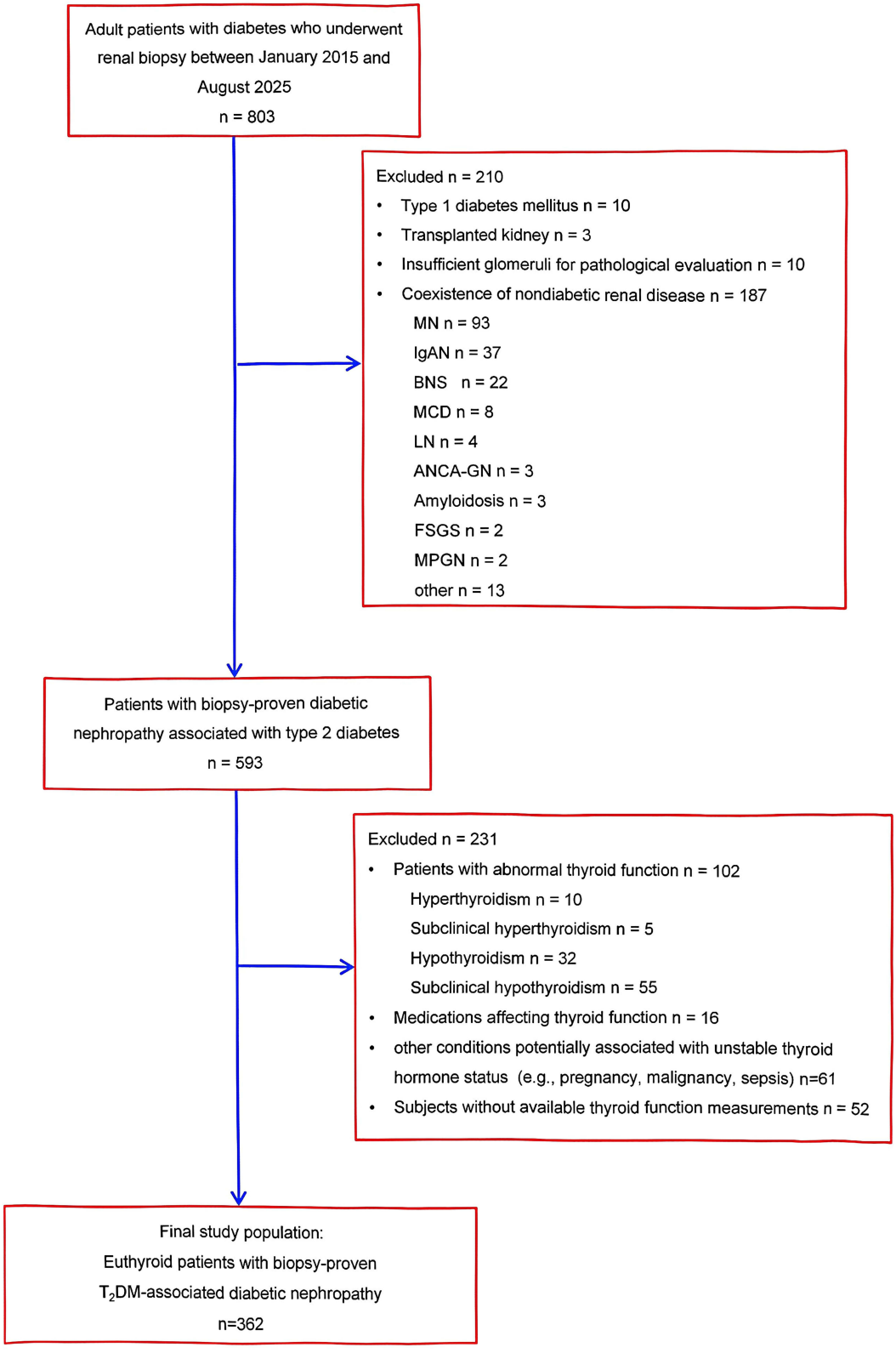

Figure 1 Flowchart of the study participants.
Abbreviations: MN, membranous nephropathy; IgAN, IgA nephropathy; BNS, benign nephrosclerosis; MCD, minimal change disease; LN, lupus nephritis; ANCA-GN, antineutrophil cytoplasmic antibody–associated glomerulonephritis; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis; T_2DM, type 2 diabetes mellitus.

Statistical Analysis

Continuous variables were assessed for distributional characteristics and summarized as mean ± standard deviation (SD) when normally distributed or as median (interquartile range, IQR) otherwise. Categorical variables are presented as counts and percentages. Between-group comparisons were performed using Student's *t*-test for normally distributed continuous variables and the Mann–Whitney *U*-test for non-normally distributed variables.

The primary outcome, advanced DN, was defined as a binary variable; therefore, logistic regression models were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). To evaluate the robustness of associations and account for potential confounding, a series of hierarchical multivariable models were constructed. Model 1 was adjusted for basic demographic and clinical confounders. Model 2 was constructed as an extended model with additional adjustment. Specifically:

- Model 1: age, sex, BMI, smoking status, diabetes duration, ACEI/ARB use, and SGLT2i use.
- Model 2: Model 1 plus SBP, HbA1c, UA, NLR, ALB, TC, TG, HDL-C, LDL-C, and log-transformed 24-hour urinary protein (ln-UP).

To address the potential impact of reduced kidney function and microvascular disease burden on the observed associations, additional sensitivity analyses were performed.

- Model 3: Model 2 plus eGFR
- Model 4: Model 3 plus DR

Linearity between continuous covariates and logit(p) was assessed using the Box–Tidwell procedure; 24-hour urinary protein was log-transformed to meet modeling assumptions. Multicollinearity was evaluated using variance inflation factors (VIFs), with all VIFs below 5, indicating no substantial collinearity. Serum albumin and urinary protein were both retained in the models as they reflect complementary aspects of disease severity. Missing data were minimal and were handled using complete-case analysis in all multivariable models.

Dose–response relationships were examined using quartiles of FT3 and the FT3/FT4 ratio, with *p* for trend derived from quartile medians treated as continuous variables. Restricted cubic splines (RCS) were applied to explore potential non-linear associations between FT3 and the FT3/FT4 ratio and advanced DN. The number of knots was set to four, placed at the 25th, 50th, 75th, and 90th percentiles of the distribution of each continuous variable. We further explored effect modification by baseline proteinuria level (<3.5 vs ≥3.5 g/24h) using interaction terms. In addition, an ordinal logistic regression model using the original Renal Pathology Society classes (I–IV) was performed as a sensitivity analysis, which allowed us to fully utilize the ordered nature of histopathological severity and further supported the robustness of our findings.

All statistical analyses were performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and R software, version 4.5.1. Two-sided $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

The cohort included 362 euthyroid patients with T_2DM and biopsy-confirmed DN: 143 with early DN (class I–II) and 219 with advanced DN (class III–IV). The baseline characteristics are summarized in Table 1. The median age was 54 years, and 70.2% were male. Compared with the early group, patients with advanced DN had a longer diabetes duration [10.0 (4.8–15.0) vs. 6.0 (1.1–10.0) years, $P = 0.002$] and a markedly higher prevalence of DR (80.4% vs. 42.3%, $P < 0.001$). They also had lower eGFR and serum ALB and higher UA and 24-hour urinary protein.

Regarding thyroid indices, advanced DN was characterized by lower FT3 and a lower FT3/FT4 ratio. TSH was modestly higher in the advanced group, while FT4 did not differ significantly, which may reflect subclinical stress of the hypothalamic-pituitary-thyroid axis in more advanced disease states.

Table 1 Baseline Characteristics of Participants

Characteristic	All (n = 362)	Early DN (Grade I–II, n = 143)	Advanced DN (Grade III–IV, n = 219)	SMD	*P*
Age (years)	54 (45, 60)	56 (44, 61)	54 (46, 60)	0.026	0.732
Male, n (%)	254 (70.2)	106 (74.1)	148 (67.6)	0.144	0.183
BMI (kg/m^2)	26.0 (24.3, 28.9)	26.2 (23.9, 28.9)	26.0 (24.4, 28.5)	0.082	0.500
Duration of diabetes (years)	8.0 (2.0, 13.0)	6.0 (1.1, 10.0)	10.0 (4.8, 15.0)	0.342	0.002*
SBP (mmHg)	150 ± 24	146 ± 23	153 ± 25	0.327	0.003**
Cigarette smoking, n (%)	137 (37.8)	48 (33.6)	89 (40.6)	0.147	0.175
HbA1c (%)	7.2 (6.4, 8.7)	7.1 (6.4, 8.8)	7.40 (6.3, 8.7)	0.091	0.697
DR, n (%)	229 (63.3)	61 (42.3)	168 (80.4)	0.841	< 0.001**
CVD, n (%)	141 (39.0)	42 (29.4)	99 (45.2)	0.332	0.003**
ACEI/ARB, n (%)	175 (48.3)	65 (45.4)	110 (50.2)	0.096	0.374
SGLT2i, n (%)	63 (17.4)	24 (16.8)	39 (17.8)	0.027	0.801
eGFR (mL/min/1.73 m^2)	61.4 ± 30.5	72.2 ± 31.7	54.4 ± 27.5	0.599	< 0.001**
UA (μmol/L)	351.5 (308.5, 417.0)	346.0 (280.0, 408.5)	355.5 (317.5, 427.5)	0.317	0.019*
ALB (g/L)	33.1 (27.2, 38.0)	37.3 (33.0, 40.7)	30.0 (26.0, 34.8)	0.961	< 0.001**
TC (mmol/L)	4.40 (3.75, 5.31)	4.20 (3.59, 5.00)	4.61 (3.78, 5.50)	0.325	0.005**
TG (mmol/L)	1.62 (1.23, 2.28)	1.54 (1.22, 2.19)	1.92 (1.27, 2.65)	0.336	0.006**
LDL-C (mmol/L)	2.96 (2.25, 3.75)	2.77 (2.21, 3.41)	3.04 (2.38, 3.93)	0.299	0.012*
HDL-C (mmol/L)	0.99 (0.85, 1.26)	0.98 (0.82, 1.20)	1.00 (0.85, 1.30)	0.172	0.254
NLR	2.30 (1.74, 3.09)	2.26 (1.68, 2.94)	2.34 (1.86, 3.43)	0.005	0.163
24-h UP (g/24 h)	3.01 (0.95, 5.96)	0.96 (0.42, 2.67)	4.39 (2.40, 8.07)	0.766	< 0.001**
FT3 (pmol/L)	4.58 ± 0.73	4.82 ± 0.73	4.46 ± 0.66	0.547	< 0.001**
FT4 (pmol/L)	14.85 ± 2.43	14.83 ± 2.54	14.31 ± 2.31	0.174	0.106
FT3/FT4	0.32 (0.27, 0.37)	0.33 (0.28, 0.40)	0.31 (0.26, 0.36)	0.238	0.013*
TSH (mIU/L)	2.43 (1.56, 3.82)	2.32 (1.50, 3.50)	2.52 (1.60, 4.01)	0.235	0.032*

Notes: Data are presented as n (%), median (interquartile range), or mean ± standard deviation. Standardized mean differences (SMDs) were calculated to assess baseline imbalance between groups, with values <0.10 indicating negligible imbalance. *P < 0.05, **P < 0.01.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DR, diabetic retinopathy; CVD, cardiovascular disease; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; SGLT2i, sodium-glucose cotransporter-2 inhibitor; eGFR, estimated glomerular filtration rate; UA, uric acid; ALB, albumin; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; NLR, neutrophil-to-lymphocyte ratio; 24-h UP, 24-hour urinary protein; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone.

Association of Thyroid Indices with Advanced DN

In multivariable logistic regression, FT3 was consistently inversely associated with advanced DN. As shown in Table 2, after full adjustment (Model 2), each 1 pmol/L increase in FT3 was associated with lower odds of advanced DN (OR=0.442, 95% CI 0.293–0.666, P < 0.001), and the FT3-inclusive fully adjusted model demonstrated good discrimination for advanced DN (C-statistic = 0.84, 95% CI 0.79–0.88). The association of TSH with advanced DN became non-significant after full adjustment. FT4 was not associated with pathological severity in any model, which may underscore the biological relevance of peripheral T4-to-T3 conversion rather than circulating FT4 levels in advanced DN.

Table 2 Multivariable Logistic Regression Analysis of THs and Advanced DN

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)
FT3 (pmol/L)	0.465 (0.335–0.646)**	0.442 (0.293–0.666)**
FT4 (pmol/L)	0.947 (0.864–1.038)	0.981 (0.874–1.104)
FT3/FT4 (per 0.1-unit increase)	0.700 (0.519–0.944)*	0.607 (0.416–0.886)*
TSH (mIU/L)	1.198 (1.005–1.429)*	0.919 (0.736–1.147)

Notes: Model 1 and Model 2 were adjusted for covariates as described in Methods. FT3/FT4 ratio was scaled per 0.1-unit increase in regression models. *P < 0.05, **P < 0.01.

Abbreviations: OR, odds ratio; CI, confidence interval.

For the FT3/FT4 ratio, an inverse association was observed in both models. When scaled per 0.1-unit increase, the ratio was significantly associated with lower odds of advanced DN in the fully adjusted model (Model 2: OR = 0.607, 95% CI: 0.416–0.886, P = 0.010). This association was also significant in Model 1, albeit at a lower threshold (OR = 0.700, 95%, CI: 0.519–0.944, P = 0.019).

Dose–Response Relationships (Quartiles and RCS)

Quartile analyses further supported a graded association between FT3 and advanced DN, with FT3 quartiles defined based on the distribution of the overall study population. In fully adjusted analyses, patients in the highest FT3 quartile (Q4) had a substantially lower likelihood of advanced DN compared with the lowest quartile (Q1) (OR=0.160, 95% CI 0.070–0.365, $P < 0.001$), with a significant linear trend across quartiles (P for trend < 0.001). For the FT3/FT4 ratio, higher quartiles were also associated with lower odds of advanced DN (Q4 vs. Q1: OR = 0.299, 95% CI 0.136–0.660, P = 0.006), and a modest but statistically significant linear trend was observed (P for trend = 0.023). The results are presented in Table 3 and Supplementary Figure S1 respectively. RCS analyses suggested predominantly linear inverse relationships between FT3 and the risk of advanced pathology (P overall < 0.001, P for nonlinearity = 0.364), whereas the spline-based association for the FT3/FT4 ratio was comparatively weaker and of only borderline statistical strength (P overall = 0.047, P for nonlinearity = 0.497), as shown in Supplementary Figure S2.

Pathological Features Across FT3 and the FT3/FT4 Ratio Quartiles

Lower FT3 quartiles were associated with advanced glomerular lesions (Class III/IV, $P < 0.001$), higher global glomerulosclerosis (P = 0.012), and more severe vascular lesions ($P < 0.001$). Lower FT3/FT4 ratio quartiles were associated with more pronounced interstitial inflammation (p = 0.028) and vascular lesions (P = 0.032). These vascular associations may reflect systemic endothelial involvement in the context of impaired TH signaling, consistent with the known role of T3 in maintaining microvascular integrity. Associations with IFTA were modest (P = 0.047), and interstitial inflammation did not differ significantly across FT3 quartiles (P = 0.499), as shown in Supplementary Tables S2 and S3. Given the multiple comparisons performed in these quartile-based analyses, the results should be interpreted as exploratory and hypothesis-generating rather than confirmatory.

Secondary Analyses

As illustrated in Figure 2, higher FT3 quartiles were associated with lower 24-hour urinary protein (P = 0.020) and higher eGFR ($P < 0.001$). The FT3/FT4 ratio quartiles were positively associated with eGFR (P = 0.027), while its association with urinary protein was less evident (P = 0.501). No significant interaction between FT3 and proteinuria category was found (P = 0.660); the

Table 3 FT3 and FT3/FT4 Ratio Quartiles in Relation to Advanced DN

Variable	Model 1 OR (95% CI)	Model 2 OR (95% CI)
FT3 (pmol/L)		
Q1 (≤ 4.09)	Reference	Reference
Q2 (4.10–4.55)	0.799 (0.405–1.578)	0.825 (0.368–1.847)
Q3 (4.56–5.06)	0.530 (0.273–1.029)	0.611 (0.279–1.335)
Q4 (≥ 5.07)	0.212 (0.110–0.412)**	0.160 (0.070–0.365)**
FT3/FT4		
Q1 (≤ 0.27)	Reference	Reference
Q2 (0.28–0.32)	0.611 (0.311–1.126)	0.784 (0.375–1.641)
Q3 (0.33–0.37)	0.616 (0.326–1.163)	0.672 (0.311–1.451)
Q4 (≥ 0.38)	0.362 (0.193–0.682)**	0.299 (0.136–0.660)**

Notes: Results were adjusted according to Model 1 and Model 2, as described in the Methods. **$P < 0.01$.

https://doi.org/10.2147/DMSO.S589576

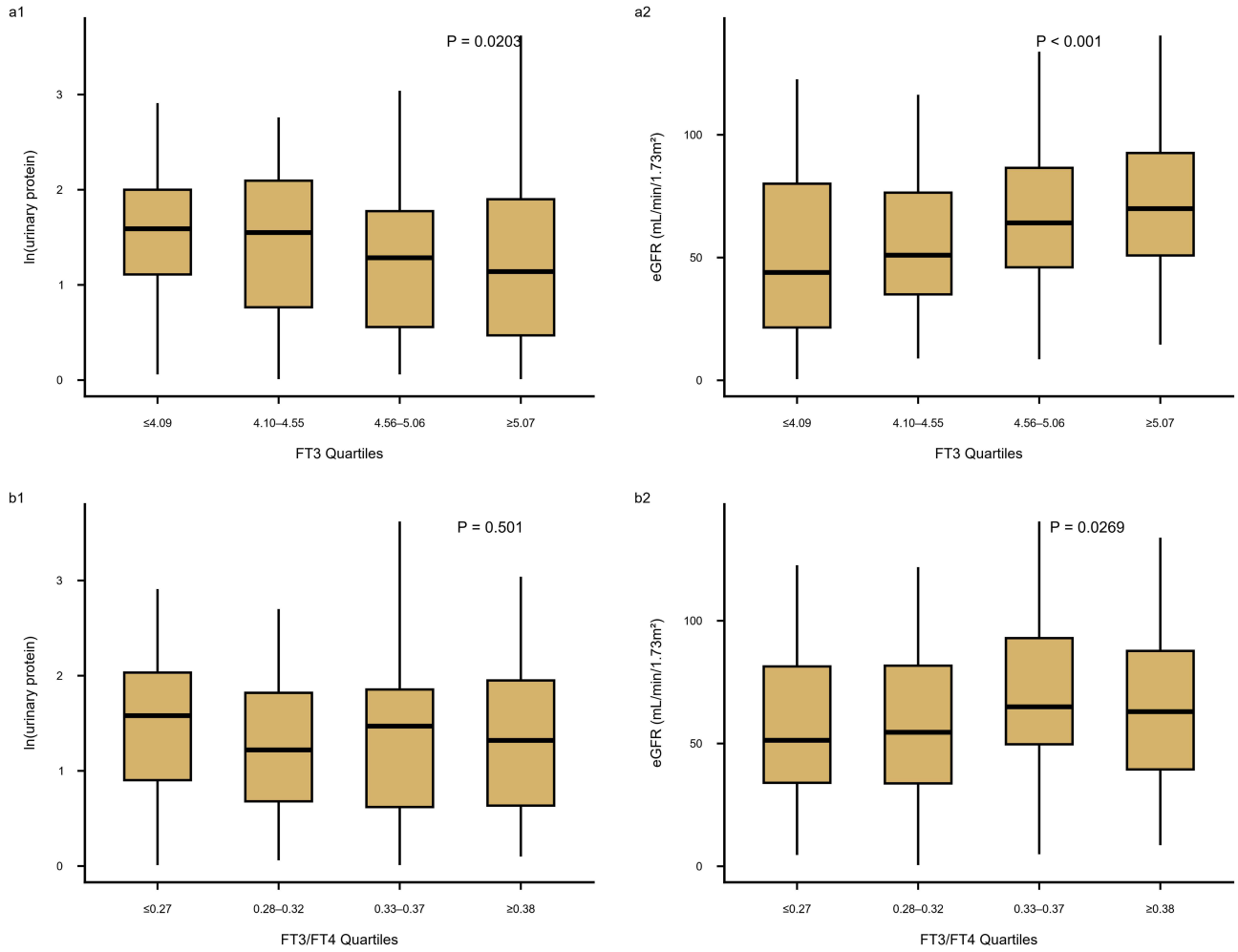

Figure 2 Association of FT3 and FT3/FT4 ratio quartiles with urinary protein excretion and eGFR. (**a** and **b**) Boxplots showing the distribution of 24-hour urinary protein excretion and eGFR across FT3 quartiles. (**c** and **d**) Boxplots showing the distribution of 24-hour urinary protein excretion and eGFR across FT3/FT4 ratio quartiles.

interaction for the FT3/FT4 ratio was of borderline statistical significance ($P = 0.054$), and should therefore be interpreted with caution, suggesting potential heterogeneity rather than a definitive effect (Supplementary Figure S3).

Ordinal logistic regression analyses treating renal pathological class (grades I–IV) as an ordered outcome yielded consistent results. FT3 remained significantly associated with increasing pathological severity in both Model 1 and Model 2 (both $P < 0.001$). By contrast, the association for the FT3/FT4 ratio was weaker but remained statistically significant ($P = 0.006$ in Model 1 and $P = 0.005$ in Model 2; Supplementary Table S4).

In additional sensitivity analyses incorporating kidney function and microvascular disease burden, the inverse association between FT3 and advanced DN remained statistically significant after further adjustment for baseline eGFR (Model 3) ($P= 0.002$) and DR status (Model 4) ($P= 0.004$). Notably, these adjustments address two key markers of disease severity, underscoring the independence of the FT3–DN association from renal function decline and diabetic microvascular complications. By contrast, the association between the FT3/FT4 ratio and advanced DN was attenuated after adjustment for eGFR ($P = 0.028$) and became borderline significant after further adjustment for DR ($P = 0.056$), as shown in Supplementary Table S5.

Discussion

In this cohort of euthyroid T_2DM patients with biopsy-confirmed DN, lower FT3 and a reduced FT3/FT4 ratio were independently associated with more advanced renal pathological severity. Notably, the association for FT3 was robust

across multivariable models and supported by graded dose–response analyses, whereas the association for the FT3/FT4 ratio was comparatively weaker. By leveraging renal histopathology—the diagnostic gold standard for DN—our findings extend prior studies that linked euthyroid-range FT3 abnormalities to clinical DKD markers such as albuminuria and eGFR. Unlike studies including overt thyroid dysfunction,[21,22] our cohort was restricted to euthyroid individuals, highlighting that subtle reductions in peripheral T3 activity may accompany structural kidney injury even when conventional thyroid function tests remain within reference ranges.

Our findings are broadly consistent with previous clinical studies linking thyroid hormone alterations, particularly reduced FT3, to DN. For example, a prospective cohort study reported that lower FT3 levels independently predicted the risk of developing DN among patients with type 2 diabetes.[16] Cross-sectional analyses have also demonstrated significant associations between FT3 and the presence or severity of DN, primarily based on clinical indicators such as albuminuria or eGFR.[23–25]

Several mechanisms may plausibly explain these observations. FT3 is the principal biologically active form of TH and plays a central role in glucose and lipid metabolism, endothelial function, and vascular homeostasis.[26–29] Experimental and clinical studies indicate that a low-FT3 state is accompanied by insulin resistance, oxidative stress, and impaired nitric oxide-mediated vasodilation, all of which correspond to key pathways involved in DN progression.[30,31] Importantly, diabetic kidneys exhibit tissue-level alterations in TH metabolism characterized by reduced deiodinase type 2 (DIO2) activity and increased deiodinase type 3 (DIO3) expression, leading to diminished local FT3 availability.[9] This intrarenal "functional low-T3 state" has been associated with podocyte structural remodeling and early glomerular injury in experimental models.[31] The convergence of these pathways provides a biological rationale for why lower FT3 was more frequently observed in patients with advanced pathological lesions in our cohort. Importantly, given the cross-sectional design, reduced FT3 levels may function primarily as a marker of disease severity and altered TH metabolism in advanced DN. Meanwhile, FT3 may also be involved in pathways related to metabolic disturbance and inflammation that are relevant to renal structural injury, a relationship that has been observed even in euthyroid populations.[32,33] Further research is required to clarify its exact role.

Circulating FT3 is primarily derived from peripheral conversion of FT4 mainly via DIO2 activity in organs such as the liver and kidney. However, FT4 showed no significant association with renal pathological severity in our study, a finding consistent with several previous investigations,[25,34] indicating that FT4—being a relatively stable precursor—poorly reflects tissue-level TH activity in chronic metabolic conditions.

In contrast, the FT3/FT4 ratio reflects alterations in thyroid hormone homeostasis and has been increasingly applied as an index of thyroid hormone sensitivity in studies linking thyroid function to metabolic stress, vascular vulnerability, and organ-specific outcomes.[35–37] Previous studies have shown that the FT3/FT4 ratio is particularly informative under conditions of chronic illness, inflammation, and metabolic stress, in which deiodinase activity and tissue-level thyroid hormone regulation are frequently disrupted.[38,39] Notably, emerging evidence from euthyroid populations has also demonstrated the predictive value of the FT3/FT4 ratio for diabetic kidney disease, even in the absence of overt thyroid dysfunction.[40] In this context, the FT3/FT4 ratio may capture changes in bioactive T3 availability at the tissue level, which is especially relevant in DN.[24,41] Collectively, these observations support the FT3/FT4 ratio as a valuable integrated marker of thyroid hormone bioactivity and help explain its association with renal structural injury beyond traditional single-hormone measurements.

We observed that some studies have reported a correlation between TSH and DN,[24,25] whereas in the present study, no independent association was identified between TSH and renal pathological severity. This discrepancy may be explained by the fact that TSH primarily reflects the pituitary feedback response to circulating TH levels and is relatively insensitive to subtle alterations in peripheral TH activation during diabetic kidney injury.[42] In euthyroid individuals, TSH is tightly regulated within a narrow physiological range, making it difficult to detect early metabolic or structural changes in renal tissue. Furthermore, the diabetic kidney exhibits localized disruptions in TH signaling—such as altered intracellular T3 processing and receptor responsiveness. Such alterations may occur independently of serum TSH levels.[31] Therefore, minor fluctuations in TSH within the normal range are unlikely to adequately reflect pathological progression.

Some variables included in the fully adjusted model, particularly urinary protein excretion and serum ALB, are closely related to disease severity and may act as potential mediators rather than pure confounders. Accordingly, a hierarchical modeling strategy was adopted, with Model 1 adjusting for basic demographic and clinical confounders and Model 2 serving as an extended model incorporating metabolic, inflammatory, and disease severity–related indicators. To address concerns regarding reverse causality and microvascular disease burden, eGFR and DR were further included in sensitivity analyses. The

persistence of a significant FT3–pathology association across these models supports FT3 as a biomarker associated with advanced renal structural injury, rather than reflecting simple confounding by disease severity.

Clinically, these findings suggest that FT3-related indices could serve as adjunct biomarkers for identifying euthyroid T_2DM patients at higher risk of severe DN pathology. However, causality cannot be inferred from our cross-sectional design. Lower FT3 may be a marker of kidney disease severity (non-thyroidal illness) rather than a causal driver. Prospective studies with repeated TH measurements and mechanistic data (eg., intrarenal deiodinase activity or tissue TH signaling) are needed.

This study has several strengths, including a relatively large biopsy-confirmed cohort, standardized pathological assessment by blinded pathologists, and comprehensive multivariable adjustment. Several limitations should also be acknowledged. First, the cross-sectional design precludes causal inference and raises the possibility of reverse causality, whereby more advanced renal pathology or systemic illness severity may contribute to reduced FT3 levels rather than the reverse. Second, the single-center design and biopsy-based inclusion criteria may introduce selection bias, as patients undergoing kidney biopsy often represent a more selected subset with atypical or severe disease, potentially limiting generalizability. Third, although multiple clinical covariates were adjusted for, residual confounding cannot be fully excluded. In addition, the absence of circulating inflammatory cytokines, lack of longitudinal follow-up data, and the unavailability of intrarenal thyroid hormone signaling markers (eg., deiodinase activity or local TH receptor expression) limited our ability to further explore inflammatory pathways, temporal relationships, and tissue-level mechanisms.

Conclusion

Among euthyroid patients with T_2DM and biopsy-proven DN, lower FT3 levels and a reduced FT3/FT4 ratio are independently associated with more advanced renal pathological severity. These findings suggest that subtle reductions in peripheral T3 activity within the reference range may at least reflect underlying structural kidney injury and identify patients at higher risk, although causal relationships cannot be established from this cross-sectional study. Notably, such subtle alterations in thyroid hormone homeostasis are particularly relevant in euthyroid patients with T_2DM, as they may serve as easily overlooked but valuable markers of early renal structural damage that precedes or accompanies DN progression. From a clinical perspective, routine assessment of FT3-related indices may provide complementary information for risk stratification and monitoring of disease severity in patients with DN. Prospective studies are needed to clarify the temporal and causal relationships between TH indices and DN progression and to evaluate whether targeting TH pathways could improve renal outcomes.

Abbreviations

DN, diabetic nephropathy; T_2DM, type 2 diabetes mellitus; THs, thyroid hormones; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; ESRD, end-stage renal disease; SBP, systolic blood pressure; CVD, cardiovascular disease; ACEI/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; SGLT2i, sodium–glucose cotransporter 2 inhibitors.; Scr, serum creatinine; DR, diabetic retinopathy; eGFR, estimated glomerular filtration rate; UA, uric acid; ALB, albumin; NLR, neutrophil-to-lymphocyte ratio; LM, light microscopy; IF, immunofluorescence; EM, electron microscopy; IFTA, interstitial fibrosis and tubular atrophy; RCS, restricted cubic splines; OR, odds ratio; IQR, interquartile range; CI, confidence interval; SD, standard deviation; MN, membranous nephropathy; IgAN, IgA nephropathy; BNS, benign nephrosclerosis; MCD, minimal change disease; LN, lupus nephritis; ANCA-GN, antineutrophil cytoplasmic antibody–associated glomerulonephritis; FSGS, focal segmental glomerulosclerosis; MPGN, membranoproliferative glomerulonephritis.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Second Hospital of Hebei Medical University (Approval No. 2025-R642) and conducted in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived due to the retrospective design and use of anonymized clinical data.

Author Contributions

Xiaorong Wang: Conceptualization, Data curation, Investigation, Validation, Writing – original draft.
Congqin Zhang: Data curation, Investigation, Writing – review & editing.
Xue Zhao: Formal analysis, Methodology, Software, Writing – review & editing.
Sinan Zhao: Formal analysis, Methodology, Software, Writing – review & editing.
Fang Zhang: Conceptualization, Methodology, Supervision, Writing – review & editing.
Chunhui Li: Visualization, Writing – review & editing.
Yongmei Hao: Conceptualization, Methodology, Supervision, Project administration, Writing – review & editing.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by the Hebei Provincial Medical Science Research Project (No. 20220984).

Disclosure

The authors received grants from Hebei Provincial Medical Science Research Project. The authors report no other conflicts of interest.

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