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ORIGINAL RESEARCH

The Correlation Between Impaired Thyroid Hormone Sensitivity and Diabetic Nephropathy in Euthyroid Patients with Type 2 Diabetes Mellitus

Dengrong Ma[1], Pingping Zhao[1], Jie Gao[1], Xinyuan Guo[1], Mei Han[1], Xiaohui Zan[1], Chongyang Chen[1], Xiaoyu Lv[1], Jingfang Liu[1,2]

[1]The First Clinical Medical College, Lanzhou University, Lanzhou, Gansu Province, People's Republic of China; [2]Department of Endocrinology, the First Hospital of Lanzhou University, Lanzhou, Gansu Province, People's Republic of China

Correspondence: Jingfang Liu, Department of Endocrinology, The First Hospital of Lanzhou University, No. 11 Donggang West Road, Chengguan District, Lanzhou City, Gansu Province, People's Republic of China, Tel +86-931-8356242, Email ljf824168@126.com

Purpose: To investigate the association between impaired thyroid hormone sensitivity and diabetic nephropathy (DN) in euthyroid patients with type 2 diabetes mellitus (T2DM).

Methods: 1305 euthyroid patients with T2DM who were hospitalized in the Endocrinology Department of the First Hospital of Lanzhou University between July 2021 and August 2023 were selected. Several indices, such as the parameters thyroid feedback quantile index (PTFQI), thyroid feedback quantile index (TFQI), thyroid stimulating hormone index (TSHI), serum-free triiodothyronine to free thyroxine (FT3/FT4) ratio, and thyrotropin thyroxine resistance index (TT4RI) to evaluate thyroid hormone sensitivity were used. The patients were subdivided into four groups (Q_1 to Q_4) based on the quartile levels of the five indices. The correlation between thyroid hormone sensitivity and DN was analyzed by binary logistic regression and restricted cubic spline (RCS) analysis.

Results: The levels of PTFQI, TFQI, and TSHI in the DN group were higher than those in the Non-DN group [0.04(−0.21, 0.31) vs −0.003(−0.27, 0.25), 0.05(−0.20, 0.30) vs 0.006(−0.26, 0.25), 2.54±0.52 vs 2.47±0.51, all $P<0.05$], while the FT3/FT4 levels were decreased in the DN group (0.40±0.07 vs 0.42±0.07, $P<0.05$). Multivariate logistic regression analysis showed that the increase in PTFQI and TFQI levels was positively correlated with DN [OR=1.518, 95% CI(1.074, 2.145) and OR=1.546, 95% CI(1.084, 2.204)]. RCS showed a linear dose-response relationship between PTFQI, TFQI, TSHI, FT3/FT4, TT4RI, and the tendency of DN (all $P_{non\text{-}linear}>0.05$). As the levels of PTFQI, TFQI, and TSHI increased, and the FT3/FT4 levels decreased, the prevalence of DN and the urinary albumin-to-creatinine (UACR) level showed an upward trend (all $P_{trend\ test}<0.05$), while the estimated glomerular filtration rate (eGFR) level showed a downward trend (all $P_{trend\ test}<0.05$).

Conclusion: Among euthyroid patients with T2DM, impaired thyroid hormone sensitivity is associated with DN, as well as elevated UACR levels and decreased eGFR levels.

Keywords: type 2 diabetes mellitus, thyroid hormone sensitivity, diabetic nephropathy

Introduction

Diabetes Mellitus (DM) is a chronic and multi-factorial disease characterised by impaired glucose homeostasis due to abnormal insulin action.[1,2] According to data from the International Diabetes Federation (IDF), by 2021, approximately 536 million people have been diagnosed with diabetes, and it is expected to increase to 783 million by 2045,[3] with type 2 diabetes mellitus (T2DM) accounting for more than 90%.[4] Diabetic nephropathy (DN), is one of the most common and severe chronic complications of DM, 30% to 40% of DM patients may develop DN.[5,6] DN is a major cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD), with approximately 30% to 50% of global ESRD cases attributed to DN.[7] Even with good control of risk factors such as plasma glucose and blood pressure, the prevalence of DN remains high, and it frequently progresses to ESRD, contributing to mortality associated with DN.[8] Furthermore, the clinical symptoms of early DN are not obvious and may only manifest as microalbuminuria, which can lead to delayed

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diagnosis and treatment. Therefore, further exploration of potential risk factors and effective biomarkers for DN is crucial for early screening, diagnosis, and treatment of DN.

Clinically, thyroid function is typically assessed based on serum levels of free triiodothyronine (FT3), free thyroxine (FT4), and thyroid-stimulating hormone (TSH), with TSH being the most sensitive. Studies have reported that in euthyroid patients with T2DM, TSH levels positively correlate with the diabetic nephropathy (DN).[9] However, some studies have suggested no statistical correlation between TSH and DN, only finding a negative correlation between FT3 and DN,[10] while other studies suggest that there is no correlation between thyroid dysfunction and DN in T2DM patients.[11] Considering that the secretion of thyroid hormones (THs) is regulated by the negative feedback loop of the hypothalamic-pituitary-thyroid (HPT) axis, and the metabolic status of THs in the periphery, a single serological indicator may not systematically reflect thyroid function. Composite indices of THs sensitivity may provide a new perspective for explaining the correlation between thyroid function and renal function.

THs sensitivity encompasses central sensitivity, which reflects the negative feedback regulation of THs by the HPT axis, and peripheral sensitivity, which reflects the metabolic effects of THs. Laclaustra et al proposed the parameters of the thyroid feedback quantile index (PTFQI) and thyroid feedback quantile index (TFQI) for accurately assessing central sensitivity to THs.[12] Similarly, the thyrotropin thyroxine resistance index (TT4RI) and the thyroid stimulating hormone index (TSHI) indicate central THs sensitivity, the FT3/FT4 ratio can estimate the conversion efficiency from FT4 to FT3, representing the peripheral sensitivity of THs.[13] Recent studies have shown that elevated TFQI levels and a low FT3/FT4 ratio are risk factors for the appearance of albuminuria in elderly healthy populations.[14] In euthyroid patients with T1DM, impaired thyroid hormone sensitivity is associated with DN. They believe that impaired thyroid hormone sensitivity leads to relative thyroid hormone deficiency, which in turn affects renal function through the RAAS system, vascular function, and blood volume.[13] However, the relationship between thyroid hormone sensitivity and the DN in T2DM patients remains unclear. Therefore, the purpose of this study is to explore the correlation between thyroid hormone sensitivity and the DN, as well as the urinary albumin-to-creatinine ratio (UACR), in euthyroid patients with T2DM, and to provide new scientific insights for the prevention and treatment of DN.

Subjects and Methods

Study Subjects

According to the inclusion and exclusion criteria, 1305 patients with T2DM hospitalized in the Endocrinology Department of the First Hospital of Lanzhou University in China from July 2021 to August 2023 were selected. According to the ethical standards of the Helsinki Declaration, this cross-sectional study was approved by the Ethics Committee of the First Hospital of Lanzhou University. Given the retrospective nature of this study, the Ethics Committee of the First Hospital of Lanzhou University waived the requirement for written informed consent (LDYYLL-2024-685). To preserve the patient's privacy, we de-identified and anonymized the patient's information before analysis.

Inclusion criteria: 1. age $\geq$ 18 years; 2. patients with complete clinical data.

Exclusion criteria: 1. type 1 diabetes and other special types of diabetes, like monogenic diabetes, diabetes due to pancreatic diseases, diabetes associated with endocrine disorders, drug-induced or chemical-induced diabetes, infections linked to diabetes, rare immune-mediated diabetes, genetic syndromes with diabetes, and diabetes caused by other specific mechanisms;[15] 2. complications of acute diabetes; 3. history of thyroid disease, history of taking thyroid medications, history of thyroid surgery, or history of radioactive iodine treatment; 4. patients with hypothalamic or pituitary diseases; 5. kidney damage not caused by diabetes; 6. severe liver dysfunction; 7. patients with severe infectious diseases, malignant tumors, or severe consumption status; 8. patients with missing data on the included indicators.

Methods

Collection of General Information

All clinical and demographic data were retrospectively collected from the medical records of patients attending the Endocrinology Department of the First Hospital of Lanzhou University in China between July 2021 and August 2023.

The general information of each patients such as gender, age, duration of diabetes, medical history, history of surgery or trauma, and history of thyroid treatment was collected.

Standard methods were used to measure the subjects' height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP). Body mass index (BMI) was calculated as follows: BMI = weight(kg)/(height*height) (m^2);

After fasting for 10~12 h, 5 mL of venous blood was extracted from each subject in the morning and serum was separated. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total serum protein (TP), serum albumin (ALB), serum creatinine (Scr), uric acid (UA), potassium (K), calcium (Ca), homocysteine (Hcy), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and fasting plasma glucose (FPG) were measured using a fully automated biochemical analyzer (AU5831, Shanghai Beckman Coulter Trading Co., Ltd., Shanghai, China). Glycosylated hemoglobin (HbA1c) levels were determined using high-performance liquid chromatography (Bio-Rad-D10, Shanghai Bio-Rad Life Science Products Co., Ltd., Shanghai, China). 25-hydroxyvitamin D3 [25(OH)$VitD_3$] levels were measured using a chemiluminescent enzyme-linked immunosorbent assay and analyzer (RT-6000, Shenzhen Leadman Biotech Co., Ltd., Shenzhen, China). Fasting insulin (FINS) and C-peptide (FCP) levels were measured using an automated chemiluminescence immunoassay (Siemens Centaur-XP, Shanghai Siemens Medical Equipment Co., Ltd., Shanghai, China).

Homeostatic model of assessment of insulin resistance index (HOMA-IR) was calculated as FPG (mmol/L) × FINS (mIU/L)/22.5.[16]

The estimated glomerular filtration rate (eGFR) was calculated using the Modified Diet in Renal Disease: eGFR (mL/min/1.73 m^2) = 186 * Scr (mg/dl) $^{-1.154}$ * Age (years) $^{-0.203}$ * 0.742 (if female) * 1.233 (if Chinese).[17]

UACR was calculated using urine albumin and urine creatinine levels: UACR (mg/g)= urine albumin (mg/L) / urine creatinine (g/L).

Serum FT3, FT4, TSH, antithyroid globulin antibody (TGAb), and antithyroid peroxidase antibody (TPOAb) levels were measured using a chemiluminescence (Roche, Cobas E801, Germany). The normal reference range of thyroid-related hormones were: FT4 (8.06~16.12 pmol/L), FT3 (3.54 ~ 7.39 pmol/L), TSH (0.56~5.91 mIU/L), TGAb (0~4 IU/mL) and TPOAb (0~9 IU/mL). The within-batch variation was 1.60% for TSH, 1.40% for FT3, and 1.90% for FT4. The between-batch variation was 1.20% for TSH, 1.10% for FT3 and 1.40% for FT4.

Calculation of Thyroid Hormone Sensitivity Index

Firstly, the FT4 and TSH of patients in this clinical retrospective study were ranked from minimum to maximum. Then, according to the principle of the empirical cumulative distribution function (CDF), the probability distribution of FT4 and TSH in the population is transformed into the probability quantile between 0 (The percentage of people lower than this value in the total population is 0) and 1. The specific formulas are as follows.[18]

(1) TFQI = CDF_FT4 - (1 - CDF_TSH);
(2) The PTFQI is an approximation of the TFQI and is suitable for different study populations. PTFQI = NORM.DIST (FT4_cell, μ_FT4, σ_FT4, TRUE) + NORM.DIST[ln(TSH_cell), μ_lnTSH, σ_lnTSH, TRUE)] - 1;
(3) TSHI = ln(TSH) + 0.1345 * FT4;
(4) TT4RI = FT4 * TSH;
(5) FT3/FT4 ratio = FT3/FT4.

The PTFQI and PTFQI range from −1 to 1, with negative values indicating higher pituitary sensitivity to thyroid hormones and positive values indicating lower central sensitivity. Higher values of TSHI and TT4RI indicate lower central thyroid hormone sensitivity. A higher FT3/FT4 ratio suggests higher peripheral thyroid hormone sensitivity.

Diagnostic Criteria

(1) T2DM was diagnosed according to the 1999 WHO criteria for diabetes mellitus symptoms, with typical symptoms including polydipsia, polyuria, and unexplained weight loss, plus one of the following 3 items: (1) random blood

glucose (refers to blood glucose at any time of the day) ≥11.1 mmol/L; (2) FPG ≥7.0 mmol/L; and (3) 2hPG ≥11.1 mmol/L.

(2) UACR≥30 mg/g for at least 3 months, and/or an eGFR<60 mL/min/1.73 m^2, excluding other causes of nephropathy, regarded as DN.[19]

(3) Euthyroid was defined as FT4, FT3, and TSH in the normal range, without a known history of thyroid disease.

Statistical Analysis

All data were analyzed using the IBM SPSS 26.0 software and R Studio (version 4.4.1). Normally distributed continuous variables were expressed as means±standard deviations ($\bar{x} \pm s$), and group differences were compared using samples *t*-test or one-way analysis of variance (ANOVA). Non-normally distributed continuous variables were expressed as medians (P_{25}, P_{75}), and group comparisons were conducted using the Mann–Whitney *U*-test or the Kruskal–Wallis *H*-test. The enumeration data were expressed as frequencies and percentages (n [%]), and group comparisons were compared using the Chi-square test. Bonferroni correction was applied to adjust *P* values for multiple comparisons. Mantel-Haenszel chi-square test and univariate linear regression were employed for trend tests between groups. Pearson correlation coefficient was utilized to analyze whether multicollinearity existed between the included independent variables, with a correlation coefficient > 0.7 suggesting potential multicollinearity. Binary logistic regression was performed to assess the correlation between thyroid hormone sensitivity indices and the DN in T2DM patients. Restricted cubic spline (RCS) models were utilized to investigate the dose-response relationship between thyroid hormone sensitivity indices and the tendency of DN in T2DM patients, and the appropriate number of nodes was selected to fit the RCS model based on the akaike information criterion (AIC). The significance level α was set at 0.05.

Results

Clinical Characteristics of the Study Population

A total of 1305 patients with T2DM were divided into the Non-DN and the DN groups, the prevalence of DN is 36.2%, including 339 males (71.7%) and 134 females (28.3%).

Compared with the Non-DN group, the levels of Age, SBP, DBP, Duration, HbA1c, FPG, FINS, HOMA-IR, Scr, UA, K, LDL-C, Hcy, FT4, PTFQI, TFQI, and TSHI were higher, while ALB, eGFR, FT3, FT3/FT4 levels and Thyroid Ab positive rate were lower than those in the Non-DN group (all *P*<0.05) (Table 1).

Table 1 Clinical Characteristics of the Study Population

Variables	Overall (n=1305)	Non-DN (n=832)	DN (n=473)	*P*
Sex, [n(%)]				0.077
Male	896 (68.7%)	557 (66.9%)	339 (71.7%)	
Female	409 (31.3%)	275 (33.1%)	134 (28.3%)	
Age (Years)	59.50±10.67	58.93±10.45	60.51±10.98	0.010
BMI (kg/m^2)	24.15±3.02	24.13±2.98	24.18±3.09	0.755
SBP (mmHg)	144.88±23.51	141.47±22.12	150.88±24.67	<0.001
DBP (mmHg)	86.08±14.48	84.96±13.94	88.05±15.21	<0.001
Duration (Years)	10.00 (4.00, 15.00)	8.00 (3.00, 14.00)	11.00 (6.00, 18.50)	<0.001
HbA1c (%)	8.75±2.12	8.41±2.01	9.34±2.19	<0.001
FPG (mmol/L)	9.16±3.32	8.69±3.11	9.97±3.51	<0.001
FINS (mIU/L)	6.31 (4.16, 9.73)	6.10 (4.03, 9.34)	7.11 (4.53, 10.09)	0.002
FCP (ng/mL)	1.24 (0.90, 1.68)	1.30 (0.94, 1.68)	1.24 (0.88, 1.64)	0.133
HOMA-IR	2.32 (1.40, 3.90)	2.27 (1.37, 3.53)	3.11 (1.74, 4.72)	<0.001
25(OH)VitD_3 (ng/mL)	13.60±5.90	13.76±5.93	13.33±5.85	0.216

(*Continued*)

Table 1 (Continued).

Variables	Overall (n=1305)	Non-DN (n=832)	DN (n=473)	*P*
AST (U/L)	21.08±9.62	21.13±9.67	20.99±9.53	0.807
ALT (U/L)	19.00 (14.00, 28.00)	19.00 (14.00, 28.50)	18.00 (14.00, 27.00)	0.062
TP (g/L)	69.86±6.31	69.91±5.79	69.77±7.14	0.717
ALB (g/L)	42.93±3.81	43.44±3.33	42.03±4.40	<0.001
Scr (μmol/L)	71.08±30.73	65.50 (57.53, 75.30)	68.10 (56.95, 84.05)	<0.001
eGFR (mL/min/1.73 m^2)	95.70 (79.34, 116.60)	98.40 (81.40, 118.91)	94.56 (74.50, 111.90)	<0.001
UA (μmol/L)	335.12±87.15	327.71±87.05	340.60±96.29	0.016
K (mmol/L)	3.83±0.36	3.84±0.36	3.90±0.43	0.003
Ca (mmol/L)	2.19±0.10	2.19±0.12	2.18±0.12	0.624
TC (mmol/L)	4.24±1.05	4.22±1.00	4.33±1.17	0.097
TG (mmol/L)	1.52 (1.09, 2.25)	1.51 (1.09, 2.16)	1.56 (1.09, 2.36)	0.228
HDL-C (mmol/L)	1.04±0.24	1.04±0.24	1.06±0.24	0.159
LDL-C (mmol/L)	2.75±0.79	2.70±0.75	2.88±0.99	0.001
Hcy (mmol/L)	15.54±8.11	14.72±5.65	16.50±9.14	<0.001
FT3 (pmol/L)	4.87±0.67	4.91±0.66	4.80±0.69	0.003
FT4 (pmol/L)	11.92±1.65	11.82±1.67	12.10±1.61	0.003
TSH (mIU/L)	2.53 (1.75, 3.61)	2.50 (1.73, 3.60)	2.58 (1.81, 3.64)	0.211
Thyroid Ab positive, [n(%)]	138 (10.6%)	101 (12.1%)	37 (7.8%)	0.015
PTFQI	0.01 (−0.25, 0.26)	−0.003 (−0.27, 0.25)	0.04 (−0.21, 0.31)	0.004
TFQI	0.02 (−0.24, 0.27)	0.006 (−0.26, 0.25)	0.05 (−0.20, 0.30)	0.003
TSHI	2.50±0.51	2.47±0.51	2.54±0.52	0.024
FT3/FT4	0.42±0.07	0.42±0.07	0.40±0.07	<0.001
TT4RI	30.38 (21.02, 42.47)	29.56 (20.61, 41.97)	31.55 (21.42, 43.31)	0.053

Notes: Data are expressed as the mean±standard deviations or medians (P_{25}, P_{75}) or numbers (%).

Abbreviations: T2DM, type 2 diabetes mellitus; DN, nephropathy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; FPG, fasting blood glucose; FINS, fasting insulin; FCP, fasting C peptide; HOMA-IR, homeostasis model assessment of insulin resistance; 25(OH)VitD_3, 25-Hydroxyvitamin D_3; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TP, total protein; ALB, serum albumin; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; UA, uric acid; K, kalium; Ca, calcium; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Hcy, homocysteine; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroidstimulating hormone; PTFQI, parameter thyroid feedback quantile index; TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; FT3/FT4, free triiodothyronine/free thyroxine; TT4RI, thyrotropin thyroxine resistance index.

Collinearity Diagnosis

Variables that demonstrated statistical significance in the univariate linear regression analysis were evaluated for collinearity before being incorporated into the binary logistic regression model. After the collinearity diagnosis, we included Age, SBP, DBP, Duration, HbA1c, HOMA-IR, ALB, Scr, UA, K, LDL-C, and Hcy in the binary logistic regression analysis (Figure 1).

Association Between the Thyroid Hormone Sensitivity Index and the DN in Patients with T2DM

In Model 1, before adjusting for variables, compared to the Q_1 group, the Q_4 groups of PTFQI [OR=1.602, 95% CI (1.161, 2.209)], TFQI [OR=1.587, 95% CI (1.151, 2.190)] and TSHI [OR=1.472, 95% CI (1.070, 2.025)] showed a positive association with the DN in euthyroid patients with T2DM, while the Q_3 [OR=0.718, 95% CI (0.524, 0.985)] and Q_4 [OR=0.525, 95% CI (0.379, 0.727)] groups of FT3/FT4 exhibited a negative association with the DN. PTFQI [OR=1.663, 95% CI (1.220, 2.267)], TFQI [OR=1.703, 95% CI (1.240, 2.339)], TSHI [OR=1.292, 95% CI (1.035, 1.614)], and TT4RI [OR=1.008, 95% CI (1.001, 1.016)] were all associated positively with the DN; FT3/FT4 [OR=0.026, 95% CI (0.005, 0.126)] was associated with the DN negatively (Table 2).

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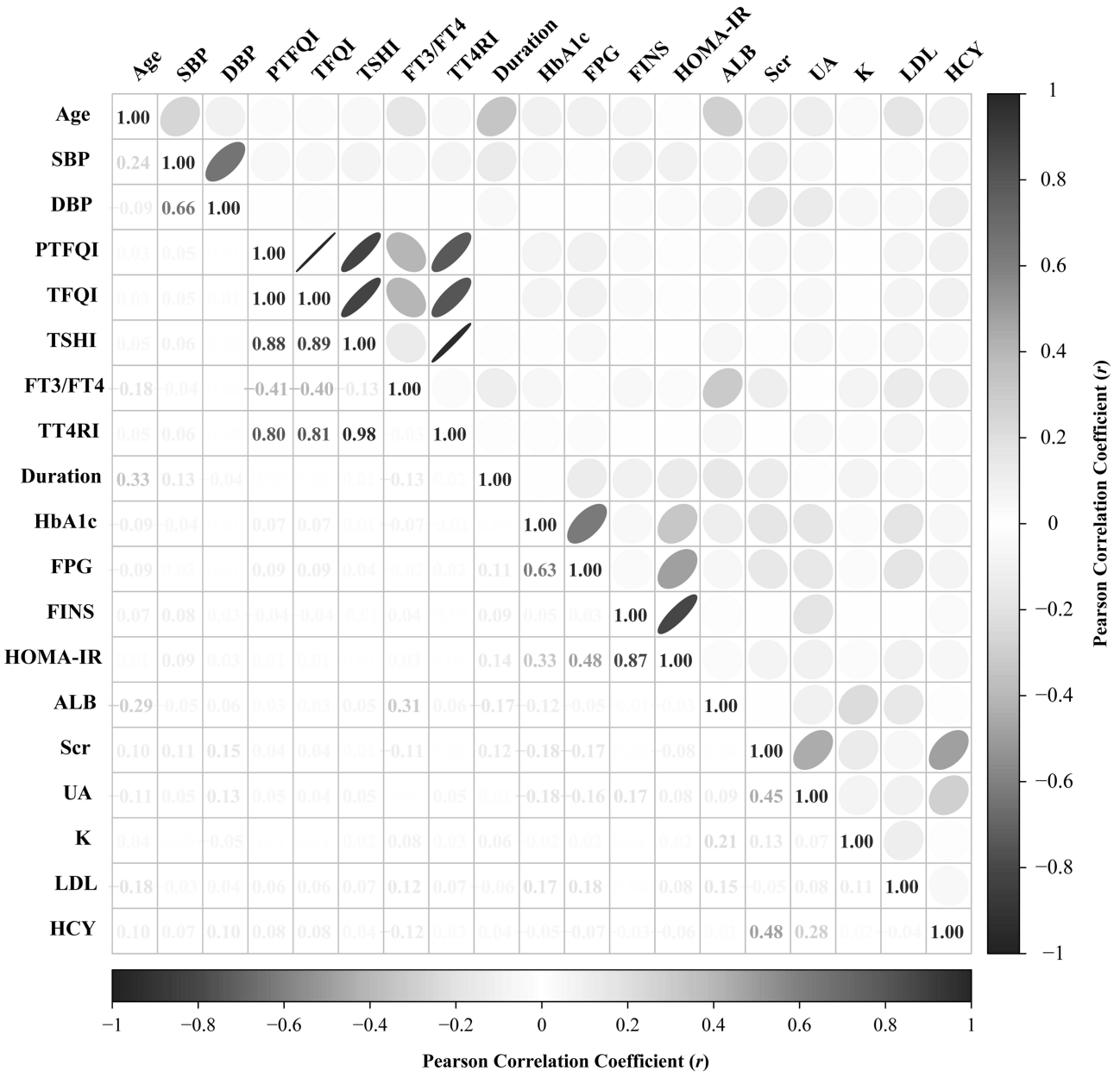

Figure 1 Heat map of correlation between independent variables.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model of assessment of insulin resistance; ALB, serum albumin; Scr, serum creatinine; UA, uric acid; K, kalium; LDL-C, low-density lipoprotein cholesterol; Hcy, homocysteine; PTFQI, parameter thyroid feedback quantile index; TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; FT3/FT4, free triiodothyronine/free thyroxine; TT4RI, thyrotropin thyroxine resistance index.

In Model 2, after adjusting for Age, SBP, DBP, Duration, HbA1c, HOMA-IR, ALB, Scr, UA, K, LDL-C, and Hcy, PTFQI, and TFQI still showed a positive association with the DN (all $P<0.05$). For every one-unit increase in PTFQI and TFQI, the tendency of DN increased to 1.518 times (95% CI[1.074, 2.145]) and 1.546 times (95% CI [1.084, 2.204]), respectively. However, TSHI, FT3/FT4, and TT4RI were not associated with the DN ($P>0.05$). Compared to the Q_1 group, the Q_4 groups of PTFQI (OR=1.501, 95% CI [1.048, 2.150]) and TFQI (OR=1.464, 95% CI [1.021, 2.100]) were associated with the DN positively (Table 2).

Table 2 Binary Logistic Regression Analysis of DN and Thyroid Sensitivity Index in Patients with T2DM

Variables	Case	Model 1	*P*	Model 2	*P*
PTFQI		1.663 (1.220, 2.267)	0.001	1.518 (1.074, 2.145)	0.018
Q_1 (≤ −0.25)	101/473	Reference		Reference	
Q_2 (−0.25~0.01)	122/473	1.332 (0.963, 1.842)	0.084	1.421 (0.992, 2.036)	0.055
Q_3 (0.01~0.26)	114/473	1.209 (0.872, 1.677)	0.255	1.222 (0.849, 1.759)	0.280
Q_4 (≥ 0.26)	136/473	1.602 (1.161, 2.209)	0.004	1.501 (1.048, 2.150)	0.027
TFQI		1.703 (1.240, 2.339)	0.001	1.546 (1.084, 2.204)	0.016
Q_1 (≤ −0.24)	107/473	Reference		Reference	
Q_2 (−0.24~0.02)	121/473	1.296 (0.937, 1.794)	0.117	1.337 (0.933, 1.915)	0.114
Q_3 (0.02~0.27)	115/473	1.209 (0.872, 1.676)	0.255	1.234 (0.858, 1.776)	0.257
Q_4 (≥ 0.27)	136/473	1.587 (1.151, 2.190)	0.005	1.464 (1.021, 2.100)	0.038
TSHI		1.292 (1.035, 1.614)	0.024	1.252 (0.975, 1.606)	0.078
Q_1 (≤ 2.18)	107/473	Reference		Reference	
Q_2 (2.18~2.55)	111/473	1.062 (0.767, 1.470)	0.719	0.979 (0.683, 1.403)	0.906
Q_3 (2.55~2.89)	119/473	1.182 (0.856, 1.632)	0.310	1.194 (0.834, 1.710)	0.332
Q_4 (≥ 2.89)	136/473	1.472 (1.070, 2.025)	0.018	1.370 (0.955, 1.966)	0.087
FT3/FT4		0.026 (0.005, 0.126)	<0.001	0.181 (0.029, 1.132)	0.181
Q_1 (≤ 0.36)	140/473	Reference		Reference	
Q_2 (0.36~0.41)	127/473	0.852 (0.624, 1.165)	0.316	1.089 (0.768, 1.545)	0.631
Q_3 (0.41~0.46)	114/473	0.718 (0.524, 0.985)	0.040	0.955 (0.666, 1.371)	0.804
Q_4 (≥ 0.46)	92/473	0.525 (0.379, 0.727)	<0.001	0.753 (0.518, 1.096)	0.139
TT4RI		1.008 (1.001, 1.016)	0.030	1.007 (0.999, 1.016)	0.097
Q_1 (≤ 21.03)	114/473	Reference		Reference	
Q_2 (21.03~30.38)	107/473	0.913 (0.660, 1.263)	0.582	0.849 (0.593, 1.215)	0.370
Q_3 (30.38~42.47)	127/473	1.192 (0.867, 1.639)	0.278	1.171 (0.822, 1.669)	0.382
Q_4 (≥ 42.47)	125/473	1.162 (0.845, 1.598)	0.356	1.117 (0.778, 1.604)	0.548

Notes: Model 1: Unadjusted; Model 2: Adjusted for Age, SBP, DBP, Duration, HbA1c, HOMA-IR, ALB, Scr, UA, K, LDL-C, Hcy and Thyroid Ab positive.

Abbreviations: T2DM, type 2 diabetes mellitus; DN, diabetic nephropathy; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model of assessment of insulin resistance; ALB, serum albumin; Scr, serum creatinine; UA, uric acid; K, kalium; Ca, calcium; LDL-C, low-density lipoprotein cholesterol; Hcy, homocysteine; PTFQI, parameter thyroid feedback quantile index; TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; FT3/FT4, free triiodothyronine/free thyroxine; TT4RI, thyrotropin thyroxine resistance index.

Dose-Response Relationship Between Thyroid Hormone Sensitivity Indicators and the Risk of DN

After adjusting for Age, SBP, DBP, Duration, HbA1c, HOMA-IR, ALB, Scr, UA, K, LDL-C and Hcy, a linear dose-response relationship was performed between PTFQI, TFQI, TSHI, FT3/FT4, TT4RI, and the tendency of DN by restricted cubic spline analysis (all $P_{overall}$<0.001, $P_{non\text{-}linear}$>0.05). With the PTFQI, TFQI, TSHI, and TT4RI increased, the FT3/FT4 level decreased, while the tendency of DN increased (Figure 2).

Analysis of Prevalence of DN, UACR, and eGFR Levels Among Different Thyroid Hormone Sensitivity Index Level Groups

With the increase of PTFQI, TFQI, and TSHI levels, and the decrease of FT3/FT4 levels, the prevalence rate of DN showed an upward trend. Among them, the prevalence of DN in the Q_4 groups of PTFQI and TFQI (41.7% and 41.7%) was higher than that in the Q_1 groups (30.9% and 31.1%), and the prevalence of DN in the Q_1 and Q_2 groups of FT3/FT4 (42.8% and 39.0%) was higher than that in the Q_4 group (28.2%) (all P<0.05) (Figure 3).

With the increase of PTFQI, TFQI, and TSHI levels, and the decrease of FT3/FT4 levels, UACR levels showed an upward trend. Specifically, the UACR levels of PTFQI, TFQI, and TSHI in the Q_4 groups were higher than those in the

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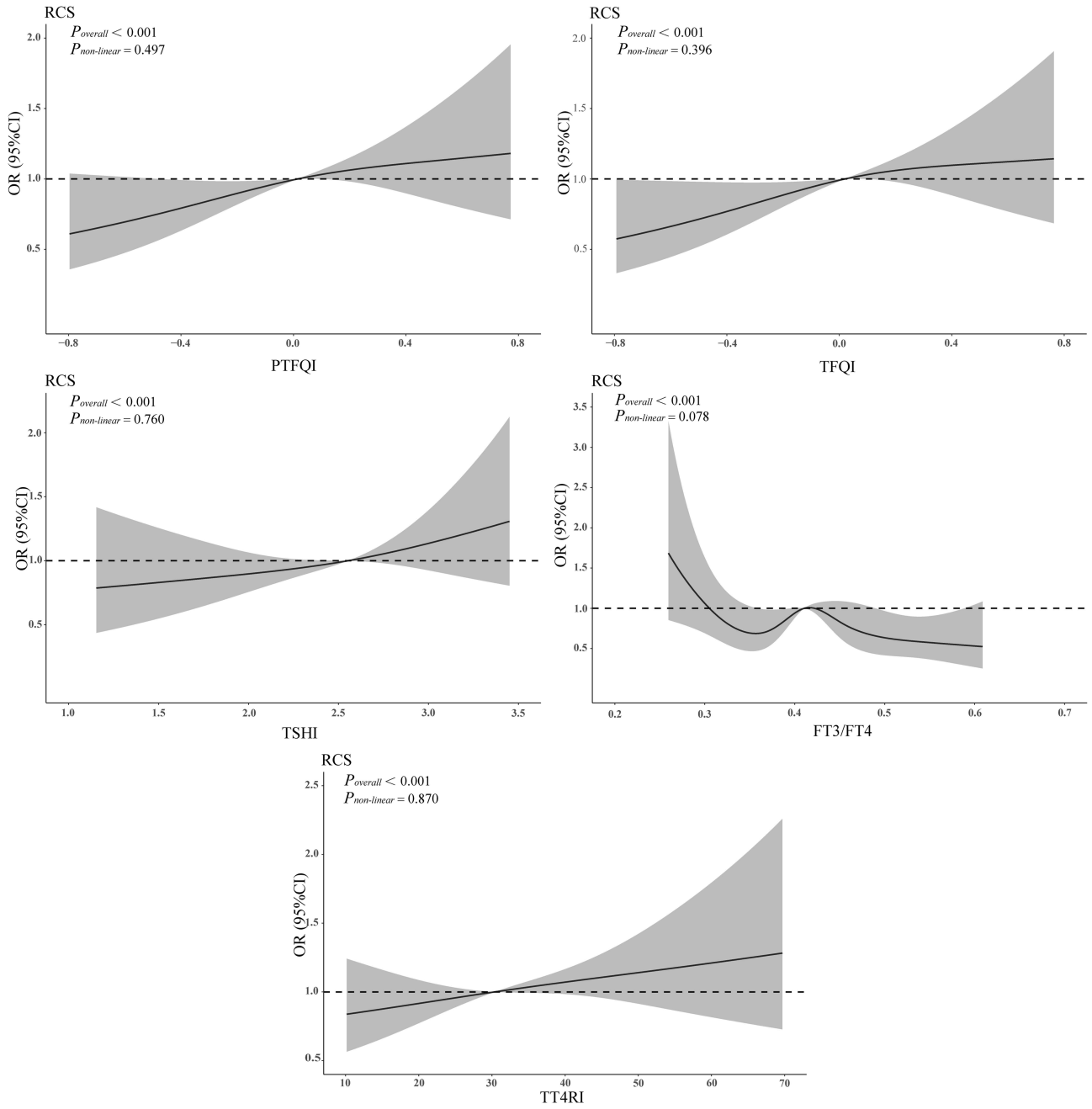

Figure 2 Dose-response relationship between thyroid hormone sensitivity index and the risk of DN in patients with T2DM.
Abbreviations: DN, diabetic nephropathy; T2DM, type 2 Diabetes Mellitus; PTFQI, parameter thyroid feedback quantile index; TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; FT3/FT4, free triiodothyronine/free thyroxine; TT4RI, thyrotropin thyroxine resistance index.

Q_1 group [22.69 (10.37, 65.43) vs 15.60 (8.05, 45.42), 22.39(9.92, 64.40) vs 15.60 (7.97, 45.54), 23.42(10.70, 57.49) vs 16.04 (8.65, 45.92), all P<0.05]. The Q_1 and Q_2 groups of FT3/FT4 showed elevated UACR levels[23.89(9.70, 92.34), 20.69(10.35, 49.94)] compared to those in group Q_4 [15.85(8.20, 35.42), both P<0.05] (Figure 4).

With the increase of PTFQI, TFQI, TSHI, and TT4RI levels, and the decrease of FT3/FT4 levels, eGFR levels showed a downward trend. To be specific, the eGFR levels of PTFQI, TFQI in the Q_1 group were higher than those in the Q_4 group [97.80(82.50, 116.30) vs 92.28(73.74, 113.36), 97.80(82.35, 115.95) vs 92.23(73.74, 112.40), both P<0.05]. Similarly, the eGFR levels of TSHI in the Q_1 and Q_3 groups [99.10(82.86, 119.50) and 96.20(81.03, 118.13)] were higher than those in the Q_4 group [91.20(73.30, 109.15), both P<0.05]. The Q_4 group of FT3/FT4 showed elevated eGFR levels[101.60(87.30,

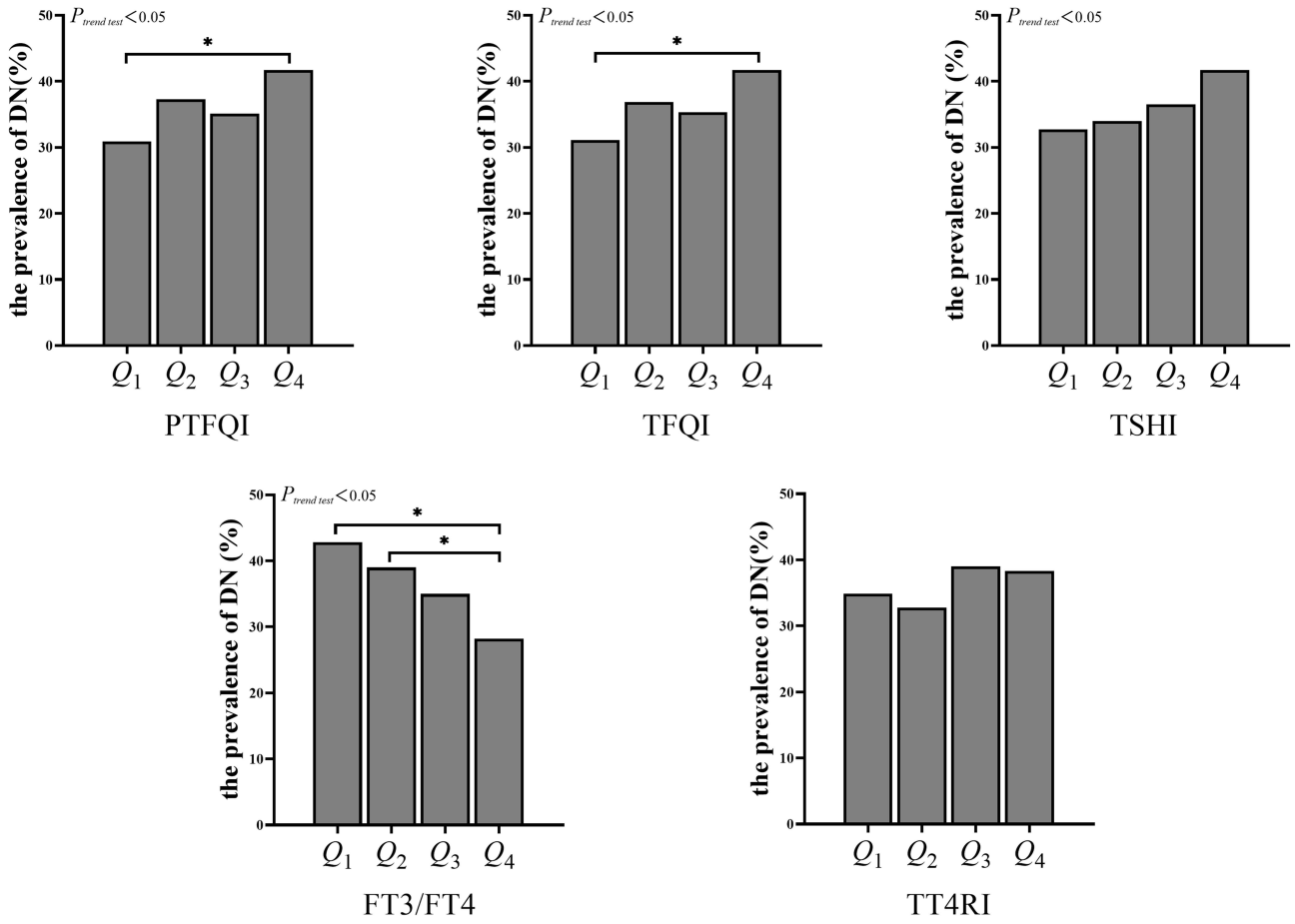

Figure 3 Changes in the prevalence of DN at the quartile levels of thyroid hormone sensitivity index.
Note: *P<0.05.
Abbreviations: DN, diabetic nephropathy; PTFQI, parameter thyroid feedback quantile index; TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; FT3/FT4, free triiodothyronine/free thyroxine; TT4RI, thyrotropin thyroxine resistance index.

124.63)] compared to those in the Q_1 and Q_2 groups [90.70(67.60, 108.70) and 94.56(78.31, 112.5), both P<0.05], and similarly the Q_3 group of FT3/FT4 showed elevated eGFR levels compared to those in the Q_1 group [97.05(80.55, 118.93) vs 90.70(67.60, 108.70), P<0.05]. The eGFR levels of TT4RI in the Q_1 and Q_3 groups[99.20(81.80, 119.65) and 97.15(81.58, 117.78)] were higher than those in the Q_4 group [91.21(73.68, 109.15), both P<0.05] (Figure 5).

Discussion

Diabetic nephropathy (DN) is one of the main causes of death in T2DM patients, and its pathogenesis is very complex, which may be related to hemodynamic abnormalities, oxidative stress and RASS system activation caused by hyperglycemia.[20,21] Hyperglycemia dilates into the arterioles by increasing the release of vasoactive substances such as insulin-like growth factor-1, and the increased levels of angiotensin II and endothelin-1 cause constriction of the arterioles, resulting in glomerular hypertension, which leads to glomerular sclerosis and hypertrophy.[22] In addition, the activation of protein kinase C pathway and polyol pathway, as well as the decrease of antioxidant capacity in the state of high glucose, lead to the production of a large number of glycoylation end products and reactive oxygen species, destroy endothelial nitric oxide synthase, reduce nitric oxide production, while high blood glucose stimulates the RAS system to produce a large number of angiotensin II, damage glomerular endothelial cells, promote renal fibrosis.[23,24]

As a key hormone regulating body growth and development and energy homeostasis, THs is dynamically regulated through the classical negative feedback loop mechanism -HPT axis. Studies have found that thyroid dysfunction is a risk factor for metabolic diseases such as T2DM, hyperhomocysteinemia, and metabolic syndrome.[25–27] As previously

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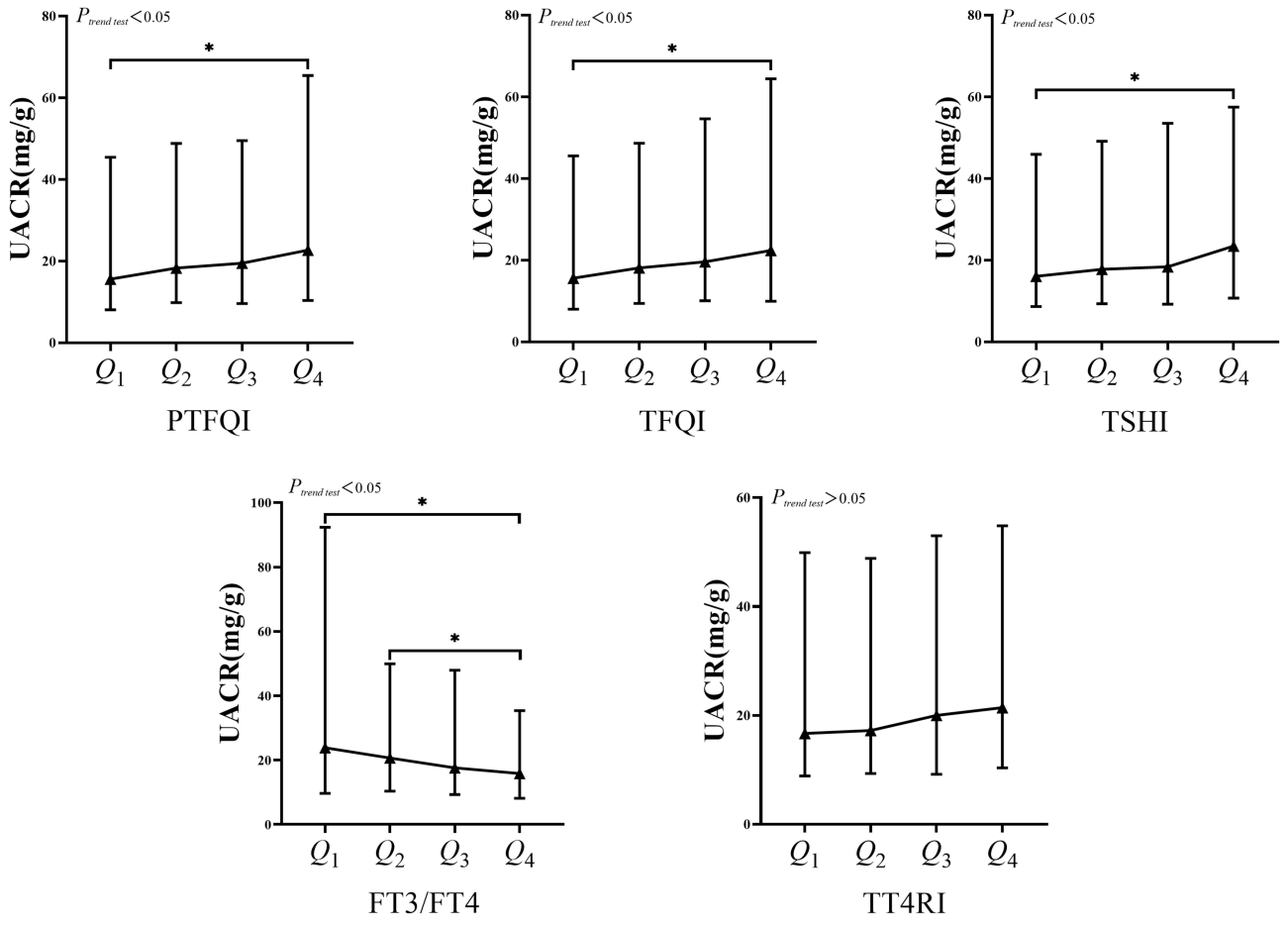

Figure 4 Changes in UACR levels at the quartile levels of thyroid hormone sensitivity index.
Note: *P<0.05.
Abbreviations: UACR, urinary albumin-to-creatinine ratio; PTFQI, parameter thyroid feedback quantile index; TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; FT3/FT4, free triiodothyronine/free thyroxine; TT4RI, thyrotropin thyroxine resistance index.

mentioned, most of the current research conclusions tend to be closely related to hypothyroidism and the occurrence of DN, but there are also studies that suggest that there is no correlation between thyroid dysfunction and DN in T2DM patients. Part of the reason for the inconsistent conclusions may be attributed to differences in the characteristics of the subjects, including race, age, iodine intake, and sex hormone differences.[11] More importantly, it also further indicates that relying solely on single indicators of TSH, FT3, and FT4 may not adequately reflect the relationship between thyroid functional status and DN.Interestingly, it was found in this study that compared with the non-DN group, FT3 level was decreased and FT4 level was increased in the DN group, but the most sensitive index TSH was not significantly different between the two groups, which further validates this point.

Laclaustra et al believe that acquired thyroid hormone resistance is not only a rare genetic syndrome but may also be relatively common in the general population. It is characterized by high TT4 and TSH in patients at the same time, which may provide a reasonable explanation for the above contradictory results. They first proposed the TFQI index. TSHI, TT4RI, and FT3/FT4 indices were used to explore the relationship between impaired thyroid hormone sensitivity and metabolic diseases, and it was found that impaired thyroid hormone sensitivity was associated with obesity, metabolic syndrome, DM, and DM-related mortality.[12] In euthyroid patients with T2DM, recent studies have shown that impaired thyroid hormone sensitivity is associated with a higher risk of osteoporosis, diabetic retinopathy, elevated homocysteine, metabolic dysfunction-related fatty liver disease, atherosclerosis, and other diseases.[28–32]

This study found that increased levels of PTFQI and TFQI were associated with the DN, and RCS analysis suggested that there was a linear dose-response relationship between PTFQI, TFQI, TSHI, FT3/FT4 and TT4RI and the tendency of

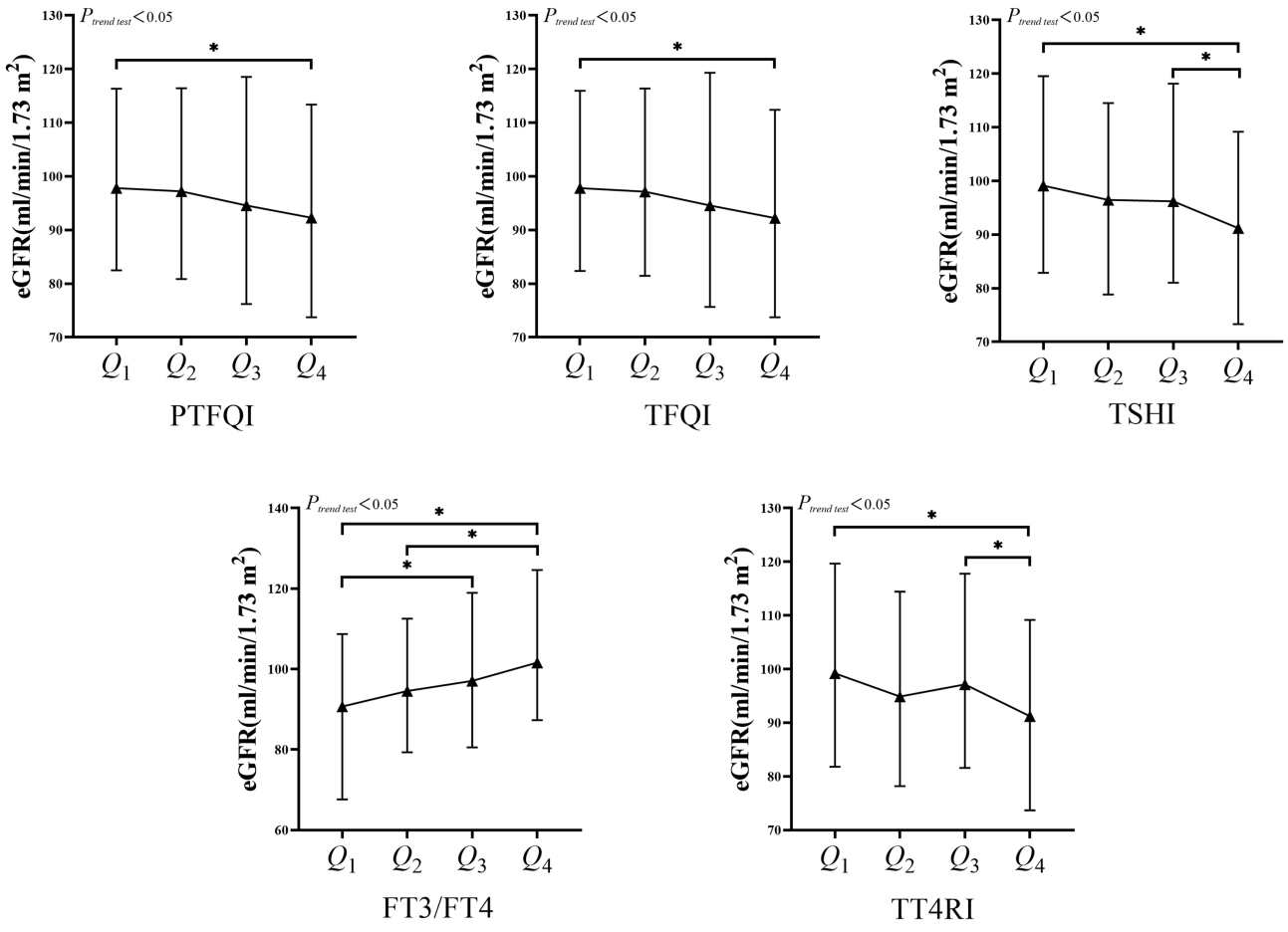

Figure 5 Changes in eGFR levels at the quartile levels of thyroid hormone sensitivity index.
Note: *P<0.05.
Abbreviations: eGFR, estimated glomerular filtration rate; PTFQI, parameter thyroid feedback quantile index; TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; FT3/FT4, free triiodothyronine/free thyroxine; TT4RI, thyrotropin thyroxine resistance index.

DN. Similar to our results, previous studies also showed that the reduction of FT3/FT4 levels in T1DM patients with normal thyroid function was associated with a high risk of developing DN. However, RCS analysis found that PTFQI, TSHI, TT4RI, and the risk of developing DN showed an M-shaped nonlinear dose-response relationship,[13] the reasons leading to the difference in conclusions may be related to the different study population and sample size. In addition, albuminuria is the most significant feature of DN. In this study, with the increase of PTFQI, TFQI, and TSHI levels and the decrease of FT3/FT4 levels, the level of UACR in T2DM patients showed an upward trend, while the eGFR level showed a downward trend. Similarly, a cross-sectional study of 1729 euthyroid patients with T2DM showed that decreased FT3/FT4 ratio was significantly correlated with increased UACR (r=−0.13, P<0.01) and elevated FT3/FT4 ratio was positively correlated with eGFR (r=0.19, P<0.01),which showed that low FT3/FT4 were independent risk factors for DKD [OR = 2.36, 95 CI% (1.63, 3.43), P<0.05].[33] A retrospective study of 2831 euthyroid patients of chronic kidney disease showed that the increase of TFQI is independently correlated with the decrease of eGFR.[18] Moreover, other studies have also shown that an increase in TFQI levels and a decrease in FT3/FT4 in healthy populations are positively correlated with UACR levels,[14] and PTFQI, TSHI, TT4RI are negatively correlated with eGFR,[18] suggesting that thyroid hormone sensitivity was correlated with the severity of DN patients.

The mechanism by which the THs and sensitivity of THs affects DN is not very clear at present and may be related to the following potential mechanisms: (1) Influence on the RAAS system. In Calu-6 cells, THs can stimulate the promoter activity of the renin gene, affect the RAAS system and hemodynamics, and thus affect the size, weight, and structure of the kidney;[34] (2) THs also directly affects the expression or activity of some ion channels and transporters, thereby affecting renal tubule function,

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renal blood flow and urinary flow rate;[35] (3) Affect of systemic hemodynamics. In hypothyroidism, cardiac output decreased, along with decreased expression of vascular endothelial growth factor and insulin-like growth factor-1, peripheral vascular resistance increased, renal vasoconstriction decreased, and renal blood flow decreased;[36] (4) Influence on the glomerular structure, renal vessels, and glomerular capillary permeability. In hypothyroidism, the glomerular basement membrane thickens and the mesangial matrix dilates, which may also lead to decreased renal blood flow.[36] Elevated TSH levels may lead to renal vascular endothelial dysfunction and promote urinary albumin excretion;[37] (5) Hyperglycemia is an independent risk factor for DN. THs are closely related to glucose metabolism, they can promote the phosphorylation of insulin receptor substrate tyrosine and the activation of phosphoinositol 3-kinase, which indirectly affects insulin signaling. Serum FT3 level is also related to insulin secretion.[38] (6) FT3 in THs is the main form that binds to thyroid hormone receptors. Type II deiodinase (DIO2) plays a key role in the transformation of peripheral FT4 deiodination into more active FT3. DIO2 activates THs in cells, which can reduce the cell's dependence on aerobic glycolysis, reduce mitochondrial respiration and ROS production, and thus minimize oxidative stress,[13,39] the decrease of FT3/FT4 ratio reflected the decrease of DIO2 activity,[40] which led to the increase of oxidative stress and inflammation, thus promoting the development of DN. In addition, a decrease in the FT3/FT4 ratio typically reflects a relative decline in FT3 levels or a relative increase in FT4 levels. When FT3 levels are reduced, it may not only affect the development of DN through the previously mentioned mechanisms but also lead to a decrease in the expression of silent information regulator 1 (SIRT1). The reduction in SIRT1 expression weakens the inhibitory effect on the NF-κB and JNK pathways, both of which play a key role in the progression of DN.[41] The mechanism of the association between thyroid hormone sensitivity and renal function remains to be further explored, but the relative deficiency of thyroid hormone caused by reduced thyroid hormone sensitivity may also affect renal function through the above mechanisms.

Conversely, renal insufficiency affects the peripheral metabolism of the HPT axis and THs. Previous studies have shown that CKD is a common cause of non-thyroid syndrome. When the expression of the TRH gene in the paraventricular nucleus of the hypothalamus is reduced and the stimulation of the hypothalamus is inhibited, the setting-point of the HPT axis may shift downward, resulting in the reduction of T3, normal or decreased T4, and decreased TSH level.[42] ESRD can inhibit the pituitary response to thyrotropin-releasing hormone (TRH), and interfere with TSH glycosylation and circadian rhythms, resulting in prolonged TSH half-life and decreased clearance.[43] In addition, various complications caused by ESRD, such as metabolic acidosis, micronutrient deficiency, and malnutrition, can also cause thyroid dysfunction.[44] The accumulation of iodine and toxins in uremia patients can inhibit the binding of THs and transporters, and reduce the conversion of peripheral T4 to T3, thus affecting the peripheral metabolism of THs.[45] It has been suggested that patients with severe proteinuria lose THs bound to the protein, resulting in a significantly increased risk of hypothyroidism.[46]

This study also has limitations: (1) As a cross-sectional study, it cannot determine the causal relationship between impaired thyroid hormone sensitivity and DN in euthyroid patients with T2DM; (2) This study is a single-center retrospective study, and the study subjects may have selection and admission rate biases. Further confirmation requires larger samples and multicenter prospective studies; (3) Although this study adjusted for multiple confounding factors, it did not consider the impact of diet, nutrition, and medication on DN, which may affect thyroid hormone sensitivity and DN; (4) Furthermore, we did not consider some environmental or genetic factors that may influence thyroid hormone sensitivity. Therefore, these potential residual confounding factors must be considered when interpreting the results of this study.

Conclusion

In summary, compared to TSH, FT3, or FT4, thyroid hormone sensitivity indices provide a more comprehensive and systematic method for evaluating thyroid function status. This study found that in euthyroid patients with T2DM, impaired thyroid hormone sensitivity is associated with DN, as well as elevated UACR levels and decreased eGFR levels. We recommend that T2DM patients with impaired thyroid hormone sensitivity should promptly assess for the presence of DN. For patients with DN, even if thyroid function is normal, we suggest monitoring changes in thyroid sensitivity indices and promptly implementing appropriate treatment measures to prevent further disease progression. However, the underlying mechanisms linking thyroid hormone sensitivity and DN remain to be further investigated.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

According to the ethical standards of the Helsinki Declaration, this cross-sectional study was approved by the Ethics Committee of the First Hospital of Lanzhou University. Given the retrospective nature of this study, the Ethics Committee of the First Hospital of Lanzhou University waived the requirement for written informed consent (LDYYLL-2024-685). To preserve the patient's privacy, we de-identified and anonymized the patient's information before analysis.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; 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.

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Disclosure

All authors declare that they have no competing interests in this work.

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