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Correlation of serum thyrotropin and thyroid hormone levels with diabetic kidney disease: a cross-sectional study

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Abstract

Objective The relationship between thyrotropin (TSH), free triiodothyronine (FT3), free thyroxine (FT4) and diabetic kidney disease (DKD) is still controversial, and this study analyzed the correlation between TSH, FT3, FT4 and DKD in patients with type 2 diabetes mellitus (T2DM).

Methods T2DM patients (1216) were divided into five groups based on serum TSH, FT3, and FT4 levels, differences in urinary albumin excretion rate (UACR), estimated glomerular filtration rate (eGFR) were compared. Binary logistic regression verified independent correlations among TSH, FT3, FT4 and UACR, eGFR. TSH and FT3 predictive values for DKD were analyzed using receiver operating characteristic (ROC) curves.

Results The prevalence of albuminuria with decreased eGFR was higher in T2DM patients with subclinical hypothyroidism and overt hypothyroidism than that in patients with normal thyroid function. TSH positively correlated with UACR ($r = 0.133$, $p < 0.001$) and positively correlated with eGFR ($r = -0.218$, $p < 0.001$), FT3 negatively correlated with UACR ($r = -0.260$, $p < 0.001$) and positively correlated with eGFR ($r = 0.324$, $p < 0.001$). With the change from the lower normal level to the increased level of TSH and the change from the higher normal level to the reduced level of FT3, the prevalence of albuminuria gradually increased, the prevalence of decreased eGFR gradually increased in TSH groups and FT3 groups. After adjusting for age, BMI, duration of diabetes, TPOAb, TGAb, smoking, drinking, hypertension, the use of anti-diabetic medications (metformin, sodium–glucose cotransporter 2 inhibitors), HbA1c, CRP, TC, TG, LDL-C, and HDL-C, both TSH and FT3 correlated with increased UACR (TSH: OR 1.253, $p = 0.001$; FT3: OR 0.166, $p < 0.001$) and decreased eGFR (TSH: OR 1.245, $p < 0.001$, FT3: OR 0.579, $p < 0.001$), but this correlation of TSH with eGFR < 60 mL/min/1.73 m^2 was not found in male. The area under the ROC curve (AUC) for FT3 was greater than that for TSH (FT3: 0.64; TSH: 0.61).

Conclusions Increased TSH and reduced FT3 levels were associated with DKD in T2DM patients, but in a sex-dependent manner. FT3 had a higher predictive value for DKD.

Keywords Thyrotropin, Thyroid hormone, Diabetic kidney disease, Hypothyroidism

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disease affecting human health. The prevalence of DM in adults has reached 10.5% with 780 million people currently living with diabetes and is expected to increase to 46% by 2045 [1]. DM increases the risk of chronic complications. Diabetic kidney disease (DKD), one of the most common microvascular complications, has a prevalence rate of up to 25% in DM patients and is the main cause of chronic kidney disease and end-stage kidney disease [2], often imposing a large economic burden on patients and causing high morbidity and mortality.

Thyroid-related hormones are closely related to glucose metabolism, and both overt and subclinical thyroid dysfunction have adverse effects on disease control in DM patients, especially those with T2DM. The prevalence of diabetes in patients with thyroid dysfunction is higher than that in the normal population [3], and the prevalence of hyperthyroidism and hypothyroidism in T2DM patients is higher than that in the normal population [4, 5].

As a chronic complication of DM, the clinical diagnosis of DKD is mainly based on an increase in urinary albumin-to-creatinine ratio (UACR) and a decrease in estimated glomerular filtration rate (eGFR). Studies have found an independent correlation between subclinical hypothyroidism and the incidence of DKD in DM patients, and the serum thyrotropin (TSH) level is an independent risk factor for proteinuria [6, 7]. Serum FT3 levels in DKD patients with normal thyroid function were also significantly lower than those in non-nephrotic patients [6, 8]. However, relatively few studies have addressed the relationship between overall thyroid-related hormones and DKD; several studies found no correlation between the two [9, 10]. Therefore, we conducted a cross-sectional study to explore the correlation between DKD and thyroid-related hormones (TSH, FT3, and FT4) in T2DM patients to provide references for the monitoring and treatment of thyroid dysfunction in diabetes patients.

Subjects, materials, and methods

Subjects

T2DM patients hospitalized in the Department of Endocrinology of the First Hospital of Lanzhou University between 2022 and February 2023 were recruited for this study. This study was approved by the Ethics Committee of First Hospital of Lanzhou University, China.

The inclusion criteria were: (1) age > 18 years and (2) presence of T2DM. The exclusion criteria were: (1) patients with a history of thyroid diseases, such as Hashimoto's thyroid disease or thyroid surgery; (2) patients currently treated with thyroxine, amiodarone, glucocorticoids, or other drugs that affect thyroid function; and (3) patients with acute severe infections or serious cardiac or pulmonary vascular diseases, or other possible complications that can cause low T3 syndrome.

Clinical characteristics

The participants' general characteristics were collected, including sex, age, BMI, duration of diabetes, history of smoking or alcohol consumption, history of hypertension, the use of anti-diabetic medications (insulin, metformin (MET), sodium–glucose cotransporter 2 inhibitors (SGLT2i)), HbA1c, c-reactive protein (CRP), triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), UACR, eGFR, TSH, FT3, FT4, TT3, TT4, TPOAb, TGAb.

Laboratory measurements

The venous blood of each subject was collected after overnight fasting for 10 h to measure triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and serum creatinine (CR) via a BS-220 automatic biochemical analyzer (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., China). The serum CRP levels were measured using immunoturbidimetric assay, HbA1c was measured by High Performance Liquid Chromatography (Bio-RAD-10 glycated hemoglobin analyzer).

Serum FT3, FT4, TSH, antithyroid peroxidase antibody (TPOAb), and antithyroid globulin antibody (TGAb) levels were measured using chemiluminescence (Roche, Cobas e801, Germany). The within-batch variation was 1.60% for TSH, 1.90% for FT4, and 1.40% for FT3, and the between-batch variation was 1.20% for TSH, 1.40% for FT4, and 1.10% for FT3.

Morning fasting spot urine samples were collected, and the concentration of urinary albumin was measured using a rate-scatter turbidimetry with the creatinine oxidase method. The UACR (mg/g) was calculated, and the eGFR (mL/min/1.73 m^2) was calculated using the Chronic Kidney Disease Epidemiology Collaborative (CKD-EPI) formula [11].

Definition of variables

The normal reference range of thyroid-related hormones were: FT3, 2.3–4.8 pg/mL; FT4, 0.62–1.24 ng/dL; TSH 0.56–5.91 mIU/L; TPOAb 0–9 IU/L; and TGAb 0–4 IU/L. FT4 > 1.24 ng/dL with TSH < 0.56 mIU/L was defined as overt hyperthyroidism; FT4 > 1.24 ng/dL with TSH in the normal range was defined as subclinical hyperthyroidism. FT4 < 0.62 ng/dL with TSH > 5.91 mIU/L was defined as overt hypothyroidism; FT4 < 0.62 ng/dL with TSH in the normal range was defined as subclinical hypothyroidism. eGFR ≥ 90 mL/min/1.73 m^2 was defined as normal, whereas < 90 mL/min/1.73 m^2 was

defined as decreased [12, 13]. UACR < 30 mg/g was considered as normal albuminuria, whereas while ≥ 30 mg/g was considered albuminuria [14]. DKD following multiple laboratory measurements performed at intervals of < 6 months that showed a UACR ≥ 30 mg/g, and/or an eGFR < 90 mL/min/1.73 m^2.

Grouping of subjects

First, all T2DM patients were divided into normal, increased, and decreased groups according to the respective TSH, FT3, and FT4 levels. Second, the normal level group was divided into a lower-, medium-, and higher-level normal groups according to the respective tertiles of TSH, FT3, and FT4.

For TSH levels, T2DM patients were grouped as follows: reduced level group (TSH < 0.56 mIU/L, group 1), lower normal levels group (TSH = 0.57–1.97 mIU/L, group 2), medium normal levels group (TSH = 1.98–3.23 mIU/L, group 3), higher normal level group (TSH = 3.24–5.91 mIU/L, group 4), and increased level group (TSH > 5.91 mIU/L, group 5).

For FT3 levels, T2DM patients were grouped as follows: reduced level group (FT3 < 2.30 ng/dL, group 1), lower normal levels group (FT3 = 2.30–3.03 ng/dL, group 2), medium levels group (FT3 = 3.04–3.46 ng/dL, group), higher normal levels group (FT3 = 3.47–4.80 ng/dL, group 4), and increased level group (FT3 > 4.80 ng/dL, group 5).

For FT4 levels, T2DM patients were grouped as follows: reduced level group (FT4 < 0.62 ng/dL, group 1), lower normal levels group (FT4 = 0.62–0.87 ng/dL, group 2), medium normal levels group (FT4 = 0.88–0.99 ng/dL, group 3), higher normal levels group (FT4 = 1.00–1.24 ng/dL, group 4), and increased level group (FT4 > 1.24 ng/dL, group 5).

Statistical analysis

All data were analyzed by SPSS (24.0 version) statistical software (IBM Corp., Armonk, NY, USA). The chi-square test was used to compare ratios, the correlation between two continuous variables (non-normally distributed) was analyzed using the Spearman test, the correlation between binary variables and continuous variables (non-normally distributed) was analyzed using the Mann–Whitney test, and the differences in levels of TSH, FT3, and FT4 between the different groups were analyzed using the Kruskal–Wallis test. The Bonferroni correction was used again if the above tests were significant. Binary logistic regression was used to analyze the independent correlations of eGFR and UACR with TSH, FT3, and FT4 levels. Considering the physiological differences in the thyroid gland in different sexes, the relationships between eGFR, UACR, TSH, FT3, and FT4 in the different sexes were analyzed separately. Finally, the diagnostic values of TSH and FT3 for DKD were analyzed using the receiver operating characteristic (ROC) curve and the area under the curve (AUC). All reported p-values were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Characteristics and comparison of prevalence of the different renal damage in T2DM patients with different thyroid function status groups

After screening, a total of 1216 patients were included in this study, including 780 males and 436 females, and the specific patient information are shown in Table 1.

Among them, T2DM patients were divided into normal thyroid function, subclinical hyperthyroidism, subclinical hypothyroidism, overt hyperthyroidism, and overt hypothyroidism groups, and differences in the prevalence of different degrees of kidney damage were compared. As shown in Table 2, compared with the normal thyroid function group, the prevalence of albuminuria with decreased eGFR was higher in the subclinical hypothyroidism group and overt hypothyroidism group ($p < 0.05$), whereas no significant difference was found among the subclinical hyperthyroidism and overt hyperthyroidism groups. No significant difference was found in the prevalence of albuminuria with normal eGFR among the normal thyroid function, subclinical hyperthyroidism, subclinical hypothyroidism, overt hyperthyroidism, and overt hypothyroidism groups (all $p > 0.05$).

Correlations between thyroid-related hormones and UACR and eGFR

UACR correlated positively with TSH ($r = 0.133$, $p < 0.001$) and negatively with FT3 ($r = -0.260$, $p < 0.001$). eGFR correlated negatively with TSH ($r = -0.218$, $p < 0.001$) and positively with FT3 ($r = 0.324$, $p < 0.001$); however, neither UACR nor eGFR correlated with FT4 (all $p > 0.05$). In addition, eGFR correlated negatively with positive TGAb ($Z = -0.105$, $p = 0.001$), and did not correlate with TPOAb. Age, sex, BMI, duration of diabetes, drinking, smoking, hypertension, MET, SGLT2i, HbA1c, CRP, HDL-C levels were correlated with eGFR (all $p < 0.05$). Age, diabetes duration, hypertension, MET, SGLT2i, HbA1c, CRP and TG levels were correlated with UACR (all $p < 0.05$) (Table 3).

Comparison of the levels of UACR and eGFR among the different thyroid-related hormone level groups

According to the TSH, FT3 and FT4 levels, T2DM patients were divided into five groups: reduced, lower normal, medium normal, higher normal, and increased level groups (groups 1–5, respectively). Differences were then compared between the levels of UACR and eGFR among the five groups, respectively. As shown in Fig. 1, with the change from the lower normal level to

Table 1 Clinical characteristics of all participants

Variables	All	Male	Female
N	1216	780	436
Age (y)	59.75 ± 10.86	58.51 ± 10.81	62.02 ± 10.63
BMI (kg/m2)	24.19 ± 3.28	24.46 ± 3.18	23.72 ± 3.41
Duration of diabetes (y)	9.71 ± 7.54	9.48 ± 7.35	10.13 ± 7.85
Smoking (Yes/No)	364/852	361/419	3/433
Drinking (Yes/No)	243/973	235/545	8/428
Hypertension (Yes/No)	606/610	369/411	236/200
Anti-diabetic medications (%)			
Insulin	54.93	56.67	52.06
MET	78.21	81.79	71.79
SGLT2i	22.70	24.23	19.95
HbA1c (%)	8.68 ± 2.31	8.79 ± 2.35	8.48 ± 2.23
CRP (mg/L)	1.21 (1.44)	1.05 (1.36)	1.30 (1.72)
TC (mmol/L)	4.18 ± 1.06	4.02 ± 1.02	4.47 ± 1.09
TG (mmol/L)	1.93 ± 1.74	1.93 ± 1.90	1.93 ± 1.38
LDL-C (mmol/L)	2.74 ± 0.81	2.64 ± 0.77	2.92 ± 0.85
HDL-C (mmol/L)	1.06 ± 0.28	1.00 ± 0.25	1.16 ± 0.30
UACR (mg/g)	12.55 (28.99)	12.58 (27.01)	12.48 (31.47)
eGFR (ml/min/1.73m2)	96.40 (21.53)	98.30 (21.27)	93.30 (25.53)
Stage of eGFR (%)			
≧90	71.05	76.41	61.70
60–89	21.63	18.46	27.06
< 60	7.32	5.13	11.24
Stage of UACR (%)			
< 30	62.09	61.03	63.99
≥ 30	28.54	38.97	36.01
Thyroid parameters			
TSH (mIU/L)	2.76 (2.65)	2.48 (2.29)	3.32 (3.16)
FT3 (pg/mL)	3.28 ± 0.53	3.31 ± 0.52	3.22 ± 0.52
FT4 (ng/dL)	0.98 ± 0.54	0.99 ± 0.56	0.98 ± 0.50
TT3 (ng/mL)	0.98 ± 0.28	0.99 ± 0.29	0.97 ± 0.26
TT4 (ug/dL)	8.82 ± 1.98	8.72 ± 1.91	9.00 ± 2.08
TPOAb positive (%)	9.95	7.18	14.91
TgAb positive (%)	11.68	8.46	17.43

MET, the use of metformin; SGLT2i, the use of sodium–glucose cotransporter 2 inhibitors; CRP, c-reactive protein; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. UACR, urinary albumin-to-creatinine ratio; eGFR, glomerular filtration rate. The normal lab-values of Variables: HbA1c (%): 4–6, CRP (mg/L): 0–4, TC (mmol/L): 3.6–5.7, TG (mmol/L): 1.0-2.2, LDL-C (mmol/L): 1.6–3.7, HDL-C (mmol/L): 0.8–1.8, TSH (mIU/L): 0.56–5.91, FT3 (pg/mL): 2.3–4.8, FT4 (ng/dL): 0.62–1.24, TT3 (ng/mL): 0.6–1.55, TT4 (ug/dL): 5.42–12.74, TPOAb positive (IU/mL): 0–9, TgAb positive (IU/mL): 0–4

Table 3 Correlation between TSH, FT3, FT4 and potentially related variables and UACR, eGFR

Variables	UACR		eGFR	
	r	*p*	*r*	*p*
TSH	0.133	< 0.001	-0.218	< 0.001
FT3	-0.260	< 0.001	0.324	< 0.001
FT4	-0.035	0.219	0.040	0.161
TPOAb	0.032	0.265	-0.045	0.057
TGAb	0.049	0.085	-0.105	0.001
Age	0.115	< 0.001	-0.488	< 0.001
Sex	0.015	0.602	-0.205	< 0.001
BMI	0.005	0.874	0.263	< 0.001
Duration of diabetes	0.205	< 0.001	-0.289	< 0.001
Drinking	0.007	0.813	-0.117	< 0.001
Smoking	0.041	0.151	-0.157	< 0.001
Hypertension	0.255	< 0.001	-0.159	< 0.001
MET	-0.158	< 0.001	0.240	< 0.001
SGLT2i	0.099	0.001	0.079	0.006
HbA1c	0.060	0.038	0.102	< 0.001
CRP	0.246	< 0.001	-0.452	< 0.001
TC	-0.025	0.388	-0.038	0.189
TG	0.059	0.039	0.049	0.086
LDL-C	-0.032	0.272	-0.027	0.346
HDL-C	-0.021	0.471	-0.148	< 0.001

UACR, urinary albumin-to-creatinine ratio; eGFR, glomerular filtration rate. MET, the use of metformin; SGLT2i, the use of sodium–glucose cotransporter 2 inhibitors; CRP, c-reactive protein; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol. * $p < 0.05$

the increased level of TSH (group 2–5), UACR gradually increased (all $p < 0.05$) and eGFR gradually decreased (all $p < 0.05$). With the change from the higher normal level to the reduced level of FT3 (group 4–1), UACR gradually increased (all $p < 0.05$) and eGFR gradually decreased (all $p < 0.05$). No significant differences were present in UACR and eGFR among the different FT4 levels (all $p > 0.05$).

Comparison of the prevalence of different degrees of kidney damage in T2DM patients among the different thyroid-related hormones level groups

Similarly, T2DM patients were again divided into five groups (groups 1–5) based on TSH, FT3 and FT4 levels, and the differences compared among these of

Table 2 Comparison of prevalence of the different renal damage in T2DM patients with different thyroid function groups

	Subclinical hyperthyroidism	Overt hyperthyroidism	Normal thyroid function	Subclinical hypothyroidism	Overt hypothyroidism
Normal albuminuria [n (%)]	24 (80.00)	9 (75.00)	805 (79.86)	87 (54.38) *	5 (45.45) *
Albuminuria with normal eGFR [n (%)]	1 (3.33)	1 (8.33)	56 (5.56)	9 (5.63)	0 (0.00)
Albuminuria with decreased eGFR [n (%)]	5 (16.67)	2 (16.67)	147 (14.58)	64 (40.00) *	6 (54.55) *

Normal albuminuria: UACR < 30 mg/g; Albuminuria with normal eGFR: UACR ≧ 30 mg/g and eGFR ≧ 90 mL/min/1.73m^2; Albuminuria with decreased eGFR: UACR ≧ 30 mg/g and eGFR < 90 mL/min/1.73m^2. UACR, urinary albumin-to-creatinine ratio; eGFR, glomerular filtration rate. Compared with the normal thyroid function group, * $p < 0.05$

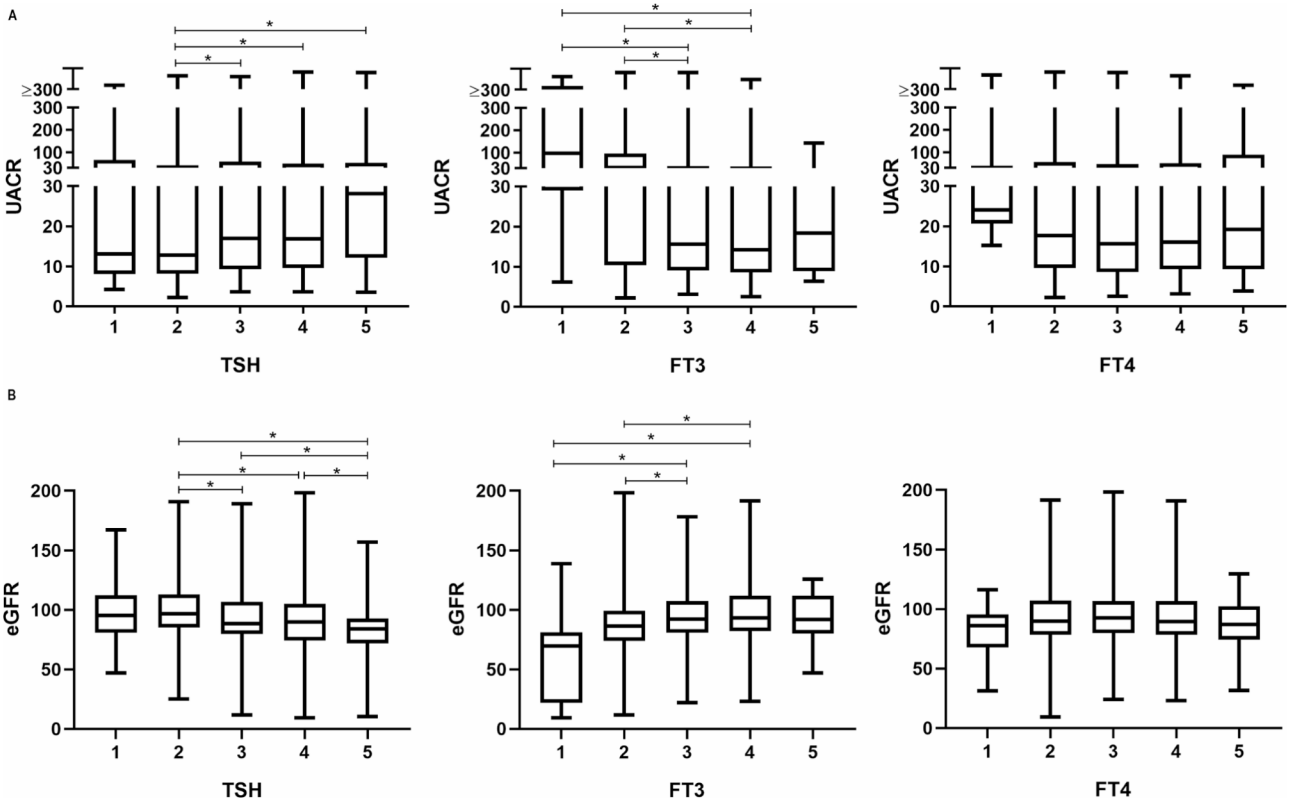

Fig. 1 Comparison of the differences in UACR, eGFR levels among the different TSH, FT3, FT4 levels groups. **A**. Comparison of UACR levels. **B**. Comparison of eGFR levels. The groups of TSH, FT3, and FT4 in A and B were as described above, with reduced levels group (group 1), lower normal levels group (group 2), medium normal levels group (group 3), higher normal levels group (group 4), and increased levels group (group 5). *: $p < 0.05$

the prevalence of albuminuria and the prevalence of decreased eGFR.

As shown in Fig. 2, the prevalence of albuminuria gradually increased as TSH levels changed from reduced to increased (groups 1–5, all $p<0.05$). The prevalence of decreased eGFR gradually increased with TSH levels changing from the lower normal level to the increased level (groups 2–5, all $p<0.05$). The prevalences of albuminuria and decreased eGFR gradually increased as FT3 levels changed from the higher normal level to the reduced level (groups 4–1, all $p<0.05$). Moreover, no significant difference was present in the prevalence of albuminuria and decreased eGFR among the groups with different levels of FT4 ($p>0.05$).

Independent correlation of UACR and eGFR with thyroid-related hormones

To investigate the independent relationship among UACR, eGFR and TSH, FT3, FT4, binary regression analyses were performed with albuminuria and decreased eGFR as dependent variables (normal albuminuria with normal eGFR as the control).

As shown in Table 4, After adjusting for the two thyroid antibodies in model 1, TSH positively correlated with albuminuria and decreased eGFR (UACR, 95% CI: 1.156–1.307, $p<0.001$; eGFR, 95% CI: 1.064–1.246, $p<0.001$), whereas FT3 negatively correlated with albuminuria and decreased eGFR (UACR, 95% CI: 0.089–0.182, $p<0.001$; eGFR, 95% CI: 0.154–0.412, $p<0.001$). After adjusting for sex, age, BMI, and duration of diabetes based on model 1, TSH remained positively correlated with albuminuria and decreased eGFR (UACR, 95% CI: 1.156–1.312, $p<0.001$; eGFR, 95% CI: 1.168–1.319, $p<0.001$) while FT3 remained negatively correlated with albuminuria and decreased eGFR (UACR, 95% CI: 0.109–0.228, $p<0.001$; eGFR, 95% CI: 0.411–0.742, $p<0.001$) in model 2. After adjusting for smoking, drinking, hypertension, MET, SGLT2i, HbA1c, CRP, TC, TG, LDL-C, and HDL-C in model 2, TSH independently and positively correlated with albuminuria and decreased eGFR (UACR, 95% CI: 1.171–1.341, $p<0.001$; eGFR, 95% CI: 1.168–1.328, $p<0.001$), and FT3 independently and negatively correlated with albuminuria and decreased eGFR in model 3 (UACR, 95% CI: 0.113–0.245, $p<0.001$; eGFR, 95% CI: 0.426–0.787, $p<0.001$).

Correlation of thyroid-related hormones with UACR and eGFR among different sexes

Considering the significantly sex differences in eGFR observed in the correlation analysis, and that sensitivity

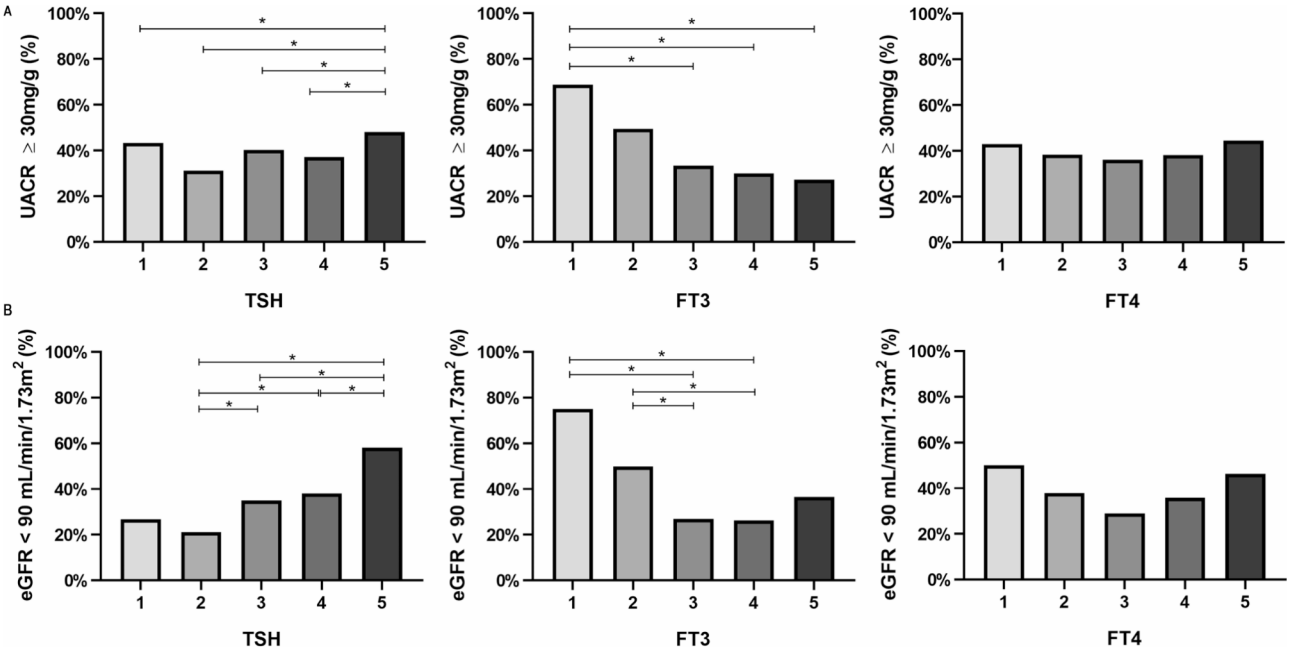

Fig. 2 The prevalence of albuminuria, decreased eGFR among the different TSH, FT3, FT4 levels groups. **A**. Comparison of the prevalence of albuminuria, **B**. Comparison of the prevalence of decreased eGFR. The groups of TSH, FT3, and FT4 in A and B were as described above, with reduced levels group (group 1), lower normal levels group (group 2), medium normal levels group (group 3), higher normal levels group (group 4), and increased levels group (group 5). *: $p < 0.05$

Table 4 Binary logistic regression reveals independent relationship between UACR, eGFR and thyroid-related hormones

		Model 1			Model 2			Model 3		
		OR	95%CI	*P* value	OR	95%CI	*P* value	OR	95%CI	*P* value
UACR	TSH	1.229	1.156–1.307	< 0.001	1.232	1.156–1.312	< 0.001	1.253	1.171–1.341	0.001
	FT3	0.127	0.089–0.182	< 0.001	0.157	0.109–0.228	< 0.001	0.166	0.113–0.245	< 0.001
	FT4	1.147	0.895–1.470	0.280	1.135	0.885–1.456	0.629	1.137	0.879–1.471	0.327
	TgAb	1.110	0.637–1.934	0.714	1.148	0.647–2.036	0.404	1.134	0.634–2.031	0671
	TPOAb	0.681	0.400-1.159	0.157	0.689	0.397–1.196	0.135	0.710	0.404–1.250	0.236
eGFR	TSH	1.151	1.064–1.246	< 0.001	1.168	1.168–1.319	< 0.001	1.245	1.168–1.328	< 0.001
	FT3	0.252	0.154–0.412	< 0.001	0.443	0.411–0.742	< 0.001	0.579	0.426–0.787	< 0.001
	FT4	1.135	0.814–1.583	0.454	1.214	0.768–1.307	0.990	1.009	0.765–1.330	0.951
	TgAb	0.816	0.333–1.997	0.656	0.899	0.613–1.788	0.865	1.010	0.584–1.747	0.973
	TPOAb	0.738	0.316–1.723	0.483	0.753	0.447–1.250	0.267	0.774	0.456–1.313	0.341

Model1 adjusted for TPOAb, TGAb; model2: adjusted for sex, age, BMI, duration of diabetes, TPOAb, TGAb; Model3: adjusted for sex, age, BMI, duration of diabetes, TPOAb, TGAb, smoking, drinking, hypertension, MET, SGLT2i, HbA1c, CRP, TC, TG, LDL-C, HDL-C. OR, odds ratio; CI, confidence interval

to thyroid disease varied between males and females, we performed regression models for stratified analyses to understand the independent correlations of UACR and eGFR with thyroid hormones among different sexes. Binary regression analyses were performed with albuminuria, eGFR < 90 mL/min/1.73 m^2, eGFR < 60 mL/min/1.73 m^2 as dependent variables (normal albuminuria with normal eGFR as the control).

As shown in Table 5, after adjusting for age, BMI, duration of diabetes, TPOAb, TGAb, smoking, drinking, hypertension, MET, SGLT2i, HbA1c, CRP, TC, TG, LDL-C, and HDL-C, both albuminuria and eGFR < 90 mL/min/1.73 m^2 significantly correlated with FT3 and TSH in male and female patients. eGFR < 60 mL/min/1.73 m^2 significantly correlated with FT3 in male patients, but not those with TSH. Conversely, eGFR < 60 mL/min/1.73 m^2 significantly correlated with TSH and FT3 levels in female patients.

Diagnostic value of TSH and FT3 in DKD

The predictive values of serum TSH and FT3 levels for DKD were analyzed using ROC curves. As seen in Fig. 3, the AUC of FT3 was the largest at 0.64 (95% CI: 0.61–0.67; $p < 0.001$), with an optimal cut-off value of 2.955, a sensitivity of 39.36%, and a specificity of 83.74%. The AUC of TSH was 0.61 (95% CI: 0.57–0.64; $p < 0.001$),

Table 5 Analysis of the correlation between UACR, eGFR and thyroid-related hormones among different sexes

		Male			Female		
		OR	95% CI	*p* value	OR	95% CI	*p* value
Albuminuria	TSH	1.274	0.162–1.397	< 0.001	1.209	1.088–1.344	< 0.001
	FT3	0.132	0.078–0.226	< 0.001	0.215	0.118–0.393	< 0.001
	FT4	1.237	0.891–1.718	0.204	0.565	0.117–2.734	0.478
	TgAb	0.785	0.318–1.937	0.600	1.249	0.573–2.721	0.576
	TPOAb	0.988	0.421–2.319	0.978	0.596	0.279–1.275	0.182
60 mL/min/1.73 m^2 < eGFR < 90 mL/min/1.73 m^2	TSH	1.198	1.102–1.302	< 0.001	1.328	1.192–1.408	< 0.001
	FT3	0.611	0.416–0.898	0.012	0.479	0.182–0.957	0.006
	FT4	0.929	0.598–1.445	0.744	1.150	0.768–1.722	0.497
	TgAb	1.059	0.457–2.454	0.893	0.993	0.467–2.110	0.986
	TPOAb	0.691	0.301–1.586	0.383	0.898	0.435–1.855	0.771
eGFR < 60 mL/min/1.73 m^2	TSH	0.998	0.843–1.182	0.983	1.287	1.123–1.474	< 0.001
	FT3	0.313	0.132–0.743	0.008	0.407	0.169–0.978	0.044
	FT4	1.261	0.761–2.087	0.368	1.312	0.737–2.336	0.357
	TgAb	1.150	0.210–6.291	0.872	0.822	0.212–3.186	0.777
	TPOAb	0.828	0.123–5.360	0.828	0.833	0.242–2.864	0.772

Adjusted for sex, age, BMI, duration of diabetes, TPOAb, TGAb, smoking, drinking, hypertension, MET, SGLT2i, HbA1c, CRP, TC, TG, LDL-C, HDL-C. OR, odds ratio; CI, confidence interval

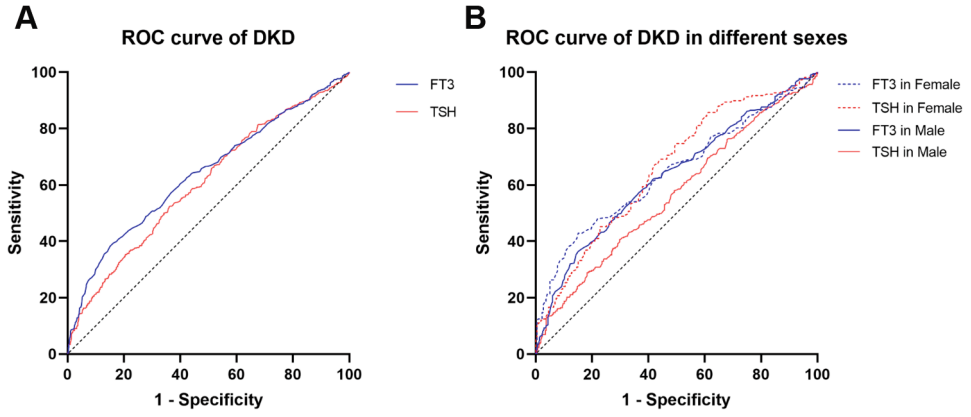

Fig. 3 ROC curve of TSH, FT3 in DKD. **A**, for all individuals; **B**, for different sexes

with an optimal cut-off 3.075, a sensitivity of 52.48%, and a specificity of 63.65%. In male patients, FT3 had a greater predictive value with an AUC of 0.63 (95% CI: 0.59–0.67, $p<0.001$), an optimal cut-off of 2.955, sensitivity of 36.21%, and specificity of 84.99%, TSH had a low predictive value with an AUC of 0.56 (95% CI: 0.52–0.60, $p=0.002$), an optimal cut-off of 3.265, sensitivity of 40.63%, and specificity of 70.21%. However, for female patients, both TSH and FT3 had a high predictive value (TSH: AUC 0.66, 95% CI: 0.61–0.71, $p<0.001$, optimal cut-off value of 2.72, sensitivity of 74.65%, and specificity of 50.23%; FT3: AUC 0.64, 95% CI: 0.59–0.70, $p<0.001$, optimal cut-off of value 2.94, sensitivity of 42.86%, and specificity of 84.93%).

Discussion

In this cross-sectional study, we analyzed the relationship between thyroid-related hormones and DKD and found that the UACR correlated positively with TSH and negatively with FT3, whereas the eGFR correlated negatively with TSH and positively with FT3. This trend was especially apparent in normal or reduced FT levels and in normal or increased TSH levels.

DM and its complications involve complex interactions with the thyroid gland. Hyperinsulinemia and high leptin levels, which are common in T2DM patients, can stimulate the synthesis of TSH [15, 16], whereas excessive or reduced thyroid-related hormones can exacerbate glucose metabolism disorders [17]. The prevalence of thyroid function disorders in T2DM patients is reportedly higher than that in the normal population [18], and DKD, a major complication of DM, is also closely related to thyroid dysfunction. Our study also confirmed that

T2DM patients with thyroid dysfunction have a higher prevalence of abnormal renal function than that in the normal population. Our study showed a greater probability of abnormal renal function in T2DM patients with higher TSH levels than in those with lower TSH levels. This is consistent with the results reported by Han et al. This study, which included 61 meta-studies, concluded that the prevalence of subclinical hypothyroidism was higher in T2DM patients, and that subclinical hypothyroidism increased the prevalence of diabetic nephropathy (odds ratio [OR] 1.74, 95% CI: 1.34–2.28) [19]. In addition, similar results were found in clinical studies, where two cross-sections of 414 T2DM patients with no prior history of thyroid disease and 8418 normoglycemic individuals found that higher UACR ratios were positively associated with subclinical hypothyroidism (OR, 3.51, 95% CI: 1.10–10.0), and increased TSH was negatively correlates with eGFR independently of age, body mass index, and glucose [20, 21]. A Japanese longitudinal study that included 7609 health-screened members of the general population showed that those with above-normal TSH levels had a significantly higher risk of developing chronic kidney disease within 3 years than the risk in those with below-normal TSH levels (OR 1.58, 95% CI: 1.02–2.45) [22].

We found that FT3 was associated with abnormal renal function in all sexes. The ROC curve analysis showed that the AUC value of FT3 was greater than that of TSH, i.e., a low FT3 level may be more strongly associated with DKD than a high TSH level. The results of the METAL study also showed that the AUC of FT3 with decreased eGFR, higher UACR, and higher UACR and/or decreased eGFR was much higher than those of any other hormone [23]. While some studies have shown that TSH does not predict decreased renal function in T2DM patients, FT3 or the FT3/FT4 ratio seems to be independently associated with the development of DKD [24–26], and a lower FT3 within the normal range still increases the risk of DKD in T2DM [27]. Our study also found that the prevalence of an abnormal UACR and eGFR tended to decrease with reduced FT3 levels, which is consistent with our results. Several studies have found improvements in renal function after thyroxine supplementation [28, 29]; however, a meta-analysis by Meuwese et al. incorporating 16 cohort studies showed that hypothyroidism (especially subclinical hypothyroidism) was not associated with renal function deterioration, and the authors hypothesized that several of the cross-sectional studies may have been affected by renal dysfunction [30]. A Mendelian randomization analysis by Chen et al. showed no causal relationship between genetically elevated TSH levels and eGFR [31]. Thus, we hypothesize that changes in FT3 may be more valuable as a predictor of DKD progression, even if it is within the normal range.

Mechanistically, thyroid hormones and DKD can influence each other. Firstly, diabetes affects thyroid function. Hyperglycemia-induced inflammation can inhibit 5'-deiodinase activity to reduce peripheral T4 to T3 deiodination [32], FT3 decreased, affecting the hypothalamic–pituitary–thyroid axis [33]. In the context of metabolic disorders and with the development of DKD, damage to glomerular structures can cause protein loss, which further reduces FT3, leading to hypothyroidism [34, 35]. And the kidney, as an important organ for iodine metabolism, can experience iodine accumulation, elevated thyroxine, and negative feedback to elevated TSH levels in pathological conditions, which also affects thyroid function [36]. Secondly, thyroid dysfunction can also affect kidney function. Elevated TSH levels can cause increased peripheral vascular resistance, decreased cardiac output and eGFR [37–39]. Low FT3 levels can consequently aggravate impaired tubular concentrating and diluting functions [40], reduce renal plasma flow and glomerular transcapillary hydrostatic pressure [41], and deteriorate renal function. As mentioned above, the more severe the development of DKD, the lower the FT3 level will be and the more it will affect the thyroid function, and the thyroid dysfunction in turn will aggravate the development of DKD, and both of these interactions will contribute to the development of the disease on both sides.

We found an interesting phenomenon in the different sex analyses, TSH was significantly associated with decreased eGFR in those with eGFR < 90 mL/min/1.73 m^2, while eGFR < 60 mL/min/1.73 m^2 significantly correlated with FT3 but not TSH in male patients, whereas these exhibited correlations in all patients, although the AUC for FT3 was higher. Previous studies have also shown that the prevalence of chronic kidney disease and decreased eGFR is higher in female patients than in male patients. There are several possible reasons regarding this difference: firstly, the mean age of female in our included participants was greater than 60 years, higher than that of male, with lower TSH in female compared to male (3. 32 (3.26) vs. 2.48 (2.29)). This is consistent with previous studies that found that the proportion of hypothyroidism in T2DM was 1.7-fold higher in female patients than in male patients, and that the risk was higher in patients older than 60 years [42]. Differences in age and TSH levels may have combined to influence eGFR levels, contributing to the correlation between TSH and lower eGFR in female [43, 44]. Secondly, estrogen affects the hypothalamo-hypophyseal-thyroidal axis, Increased estrogen lead to increased amounts of T3 and TRH receptors in the anterior pituitary, an increased thyroxine-5′-deiodinase activity, and an induction of the conversion of T4 to T3, but an increase in androgens may mildly suppress 5′-deiodinase activity [45, 46]. Differences in thyroid

hormone levels caused by this difference in physiologic environment can also affect renal function. In addition, considering that the thyroid antibody positivity rate is generally higher in female patients than in male patients, logistic regression analysis was performed, and neither TPOAb nor TGAb were found to be associated with DKD among the different sexes, which is consistent with a study by Suher et al., suggesting that thyroid autoimmunity is not strongly associated with renal dysfunction in patients with low TSH levels [47]. However, because additional biological or sociocultural factors (e.g., sex hormones) were not collected in our study, which is a limitation of this study. Whether increased TSH levels in female patients exacerbate the increased prevalence of DKD compared with that in male patients requires verification via further research.

Conclusion

T2DM patients with subclinical hypothyroidism had a higher prevalence of DKD than that in patients with normal thyroid function. TSH correlated positively with UACR and negatively with eGFR, with the prevalence of renal abnormalities increasing as TSH increased. FT3 correlated negatively with UACR and positively with eGFR, with the prevalence of renal abnormalities increasing as FT3 decreased. Both albuminuria and eGFR < 90 mL/min/1.73 m^2 significantly correlated with FT3 and TSH in male and female patients. In male patients, eGFR < 60 mL/min/1.73 m2 significantly correlated with FT3 in male patients, but not those with TSH. FT3 has a higher predictive value for DKD than that of TSH. Potentially, the early assessment of FT3 can be used to predict or further treat kidney injury in T2DM patients.

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None.

Author contributions
Jingfang Liu contributed to the study conception and design. Data collection and analysis were performed by Jie Gao. The first draft and revisions of the manuscript was written by Jie Gao. All authors discussed the results and approved the final manuscript.

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Data availability
The data and materials involved in the study are not publicly available due to the containing information that could compromise research participant privacy/consent but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved and informed consent from all subjects of our study was waived by the Ethics Committee of First Hospital of Lanzhou University, China. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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