



OPEN

Association between sensitivity to thyroid hormone indices and type 2 diabetic microvascular complications in euthyroid patients

Junping Zhang^{1,2,3,7}, Zhanpeng Luo^{1,5,7}, Jie Zhang^{1,2,3,7}, Ruohao Zhang⁶, Xinnan Liu⁶, Jinying Wang^{1,2,3}, Shasha He^{1,2,3}, Jiao Wang^{1,2,3}, Dandan Chen^{1,2,3}, Cuiyun Chen^{1,2,3}, Jiancheng Wang^{1,2,3}, Shen Chen^{1,4}✉ & Jixiong Xu^{1,2,3}✉

The correlation between thyroid hormone (TH) sensitivity and microvascular complications of type 2 diabetes mellitus (T2DM) remains uncertain. This study aimed to explore the association between TH sensitivity and the risk of diabetic kidney disease (DKD), diabetic retinopathy (DR), and diabetic neuropathy (DNP) in euthyroid T2DM patients. This study included a total of 946 hospitalized T2DM patients and calculated their sensitivity to the TH index, and each patient completed screenings for DKD, DR, and DNP. Multivariate logistic regression, generalized additive modeling, and subgroup analysis were used to assess the association between TH index sensitivity and the risks of DKD, DR, and DNP. After adjusting for confounding factors, a significant linear correlation was observed between the sensitivity of the thyroid feedback quartile index 3 (TFQI3) and DKD risk. However, the sensitivities of thyroid-stimulating hormone index (TSHI), thyrotropin thyroxine resistance index (TT4RI) and partial thyroid feedback quartile index (PTFQI) exhibited nonlinear correlations with the risk of developing DKD. The effect sizes to the left of the inflection point for TSHI, TT4RI and PTFQI were (odd ratio [OR] = 0.53, 95% confidence interval [CI]: 0.288–0.977), (OR = 0.863, 95%CI: 0.751–0.992) and (OR = 0.007, 95%CI: 0–0.724), respectively. However, there was no significant correlation between TH index sensitivity and DR/DNP risk. This study provides valuable insights into the relationship between TH sensitivity and the risks of DKD, DR, and DNP, with substantial clinical implications for individual prediction among T2DM patients.

Keywords Thyroid hormone sensitivity, Type 2 diabetic microvascular complications, Diabetic kidney disease, Diabetic retinopathy, Diabetic neuropathy

Newest data from the International Diabetes Federation indicate that approximately 537 million adults globally are living with diabetes, a number projected to rise to 783 million by 2045¹, and type 2 diabetes mellitus (T2DM) accounts for nearly 90% of the approximately 537 million cases of diabetes worldwide². Notably, China has emerged as the country with the highest number of diabetes patients worldwide³. Patients with T2DM who experience prolonged periods of high blood sugar ultimately possibly face microvascular complications, significantly impacting their health⁴. Microvascular complications in T2DM encompass a range of conditions, primarily including diabetic kidney disease (DKD), diabetic retinopathy (DR), and diabetic neuropathy (DNP)⁵. In the study by An et al., the incidence of microvascular complications in T2DM was investigated among a total of 135,199 T2DM patients. The microvascular complications accounted for more than 16% of the cases,

¹Department of Endocrine and Metabolism, The First Affiliated Hospital, Jiangxi Medical College, Nanchang University, Nanchang, China. ²Jiangxi Clinical Research Center for Endocrine and Metabolic Disease, Nanchang, Jiangxi, China. ³Jiangxi Branch of National Clinical Research Center for Metabolic Disease, Nanchang, Jiangxi, China. ⁴The Key Laboratory of Geriatrics, Beijing Institute of Geriatrics, Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing Hospital, National Center of Gerontology of National Health Commission, Beijing 100730, PR China. ⁵Queen Mary School, Medical College, Nanchang University, Nanchang 330006, China. ⁶The First Clinical Medical College, Jiangxi Medical College of Nanchang University, Nanchang 330006, Jiangxi Province, China. ⁷Junping Zhang, Zhanpeng Luo and Jie Zhang contributed equally to this work. ✉email: Shensen0709@163.com; Jixiong.Xu@ncu.edu.cn

with chronic kidney disease comprising 12.3% of the total cases⁶. The pathology of T2DM microvascular complications requires greater precision, and the study of correlating factors is essential.

A study conducted by Hu et al. found a link between thyroid hormone (TH) levels and microvascular complications in T2DM. Their study indicated that levels of free triiodothyronine (FT3) and free thyroxine (FT4) might be inversely associated with T2DM microvascular complications. Conversely, thyroid stimulating hormone (TSH) levels showed a potential positive correlation with these complications⁷. Hormone levels are regulated by glandular activity, and it is essential to focus on the relationship between hormone levels and diseases. However, the onset and progression of diseases are often dynamic, with the regulatory functions of the secretory glands being closely related to these processes⁸. Understanding the regulatory functions of glands in relation to diseases can better reflect how diseases and glands influence each other.

The thyroid-stimulating hormone index (TSHI), thyrotropin thyroxine resistance index (TT4RI), thyroid feedback quantile-based index (TFQI) and parametric thyroid feedback quantile-based index (PTFQI) were sensitivity to TH indices which were first used to access the relationship between impaired sensitivity to TH and T2DM by Laclastra et al.⁹. These indices are derived from the basal thyroid function indicators FT3, FT4, and TSH through a series of calculations and can reflect the regulatory function of the pituitary-thyroid axis⁹. Previous studies have focused on the correlation between basal thyroid function indicators and microvascular complications of T2DM^{10,11}. Our study aims to utilize indices derived from basic clinical indicators to investigate the relationship between the regulatory function of the pituitary-thyroid axis and the microvascular complications of T2DM.

Methods

Study design and participants

This is a retrospective study that included 946 T2DM patients who were hospitalized in the Department of Endocrinology at Nanchang University First Affiliated Hospital due to poor glycemic control between August 2020 and March 2022. Patients included in the study met the following criteria: (1) diagnosed as adults with T2DM according to the 1999 World Health Organization standards; (2) diagnosis with any of the three types of microvascular complications of diabetes (DKD, DR, or DNP); (3) normal thyroid function. Patients were excluded from the study if they met any of the following criteria: (1) incomplete data; (2) type 1 Diabetes Mellitus or diabetes secondary to other diseases; (3) history of thyroid disease or thyroid surgery; (4) previous treatment with medications that could alter thyroid hormone concentrations (Iodine, lithium, amiodarone, phenytoin sodium); (5) history of pituitary disease; (6) severe chronic liver disease, cancer, acute diabetes complications, and other serious circulatory, respiratory, or digestive system diseases; (7) pregnancy. The study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University, and the study was conducted in accordance with the Declaration of Helsinki (Ethics number: 2022-3-031).

Clinical information and chemistry measurements

Clinical data of study participants were gathered from electronic medical records, including information such as sex, age, systolic blood pressure (SBP), diastolic blood pressure (DBP), duration of diabetes, smoking and drinking status, as well as height and weight measurements. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2).

Blood samples were obtained from all patients following a minimum 8-hour fasting period. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured using an automated biochemistry analyzer (AU5421, Olympus, Shizuoka, Japan). Additionally, levels of free triiodothyronine (FT3), free tetraiodothyronine (FT4), and thyrotropin were determined via electrochemiluminescence analysis (Cobas e601, Roche, Basel, Switzerland). Glycated hemoglobin (HbA1c) levels were assessed using an HbA1c analyzer (D-10, Bio-Rad, Hercules, CA, USA).

Definition of DKD, DR and DNP

The urinary albumin/creatinine ratio (UACR) was assessed using an automated biochemical analyzer (Biosystems A25, Spain), utilizing the first urine sample collected from each patient alternate morning. The estimated glomerular filtration rate (eGFR) was determined employing the Chronic Kidney Disease Epidemiology Collaboration formula¹². DKD was defined by $\text{UACR} \geq 30 \text{ mg/g}$ or reduced eGFR ($\text{eGFR} < 60 \text{ mL/min}/1.73 \text{ m}^2$).

All patients underwent fundus photography and lower limb nerve electromyography examination, and DR and DNP were identified according to the definition outlined in the American Diabetes Association¹³.

TH sensitivity indices formulas

TSHI, TT4RI, and TFQI were used to evaluate the central sensitivity of TH. The calculation formulas for TSHI and TT4RI were derived from previous research by Mehran et al.¹⁴, and their values were negatively correlated with central TH sensitivity. The calculation method for TFQI was developed by Laclastra et al.⁹, and further refined and expanded into TFQI3, TFQI4, and PTFQI. The lower the values, the higher the central TH sensitivity. The specific calculation formulas are as follows:

- [1]: $\text{TSHI} = \ln \text{TSH} (\text{mIU/L}) + 0.1345 \times \text{fT4} (\text{pmol/L})^{15}$;
- [2]: $\text{TT4RI} = \text{fT4} (\text{pmol/L}) \times \text{TSH} (\text{mIU/L})^{16}$;
- [3]: $\text{TFQI3} = \text{cdfFT3} - (1 - \text{cdfTSI})^{9,17}$; cdf: cumulative distribution function^{15,18};
- [4]: $\text{TFQI4} = \text{cdfFT4} - (1 - \text{cdfTSI})^{9,17}$;
- [5]: $\text{PTFQI} = \text{NORM.DIST}(\text{fT4_cell}, 10.075, 2.155, \text{TRUE}) + \text{NORM.DIST}(\text{LN} (\text{TSH_ cell}), 0.4654, 0.7744, \text{TRUE}) - 1^{9}$;

Statistical analysis

Continuous variables with normal distribution were presented as mean \pm standard deviation ($X \pm S$) and compared using the independent-samples t-test. Non-normally distributed continuous data were expressed as median and interquartile range and compared using the Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages and analyzed using the chi-square test or Fisher's exact probability method.

All the statistical analyses were conducted in R (<http://www.R-project.org>, The R Foundation), and $P < 0.05$ was considered statistically significant. We analyzed the PTFQI, TT4RI, TFQI3, TFQI4, and TSHI. Our endpoints are DNP, DR, and DKD. Initially, a crude model was applied using a two-piece logistic regression with the R package 'segmented'. Subsequently, we constructed an adjusted model that accounted for potential confounders, including Age, BMI, LDL, TG, diabetes duration, and HbA1c. Additionally, we performed subgroup analyses separately for males and females.

Results

Patient characteristics

A total of 946 patients were included in the study, with a DKD prevalence of 40.2%. As depicted in Table 1, patients in the DKD group were characterized by older age, longer diabetes duration, and elevated SBP levels, along with lower levels of FT3 and TFQI3, compared to the non-DKD group ($P < 0.05$). Conversely, there were no significant differences between the two groups regarding gender, smoking or drinking history, BMI, DBP, HbA1c, TC, TG, LDL-C, HDL-C, FT4, TSH, TT4RI, TFQI4, and PTFQI levels ($P > 0.05$).

The prevalence of DR and DNP among the patients in this study was 42.5% and 84.9%, respectively. Detailed patient characteristics were provided in supplementary Tables 1 and 2.

	Total	Non-DKD	DKD	<i>p</i>
N (%)	946	598	348	
Age (years)	56 (48, 64)	55 (47, 63)	59 (51.75, 67)	< 0.001
Sex (n (%))				0.474
Male	584 (61.73)	364 (60.87)	220 (63.22)	
Female	362 (38.27)	234 (39.13)	128 (36.78)	
Smoking, n (%)				0.591
No	700 (74)	439 (73.41)	261 (75)	
Yes	246 (26)	159 (26.59)	87 (25)	
Drinking, n (%)				0.741
No	761 (80.44)	483 (80.77)	278 (79.89)	
Yes	185 (19.56)	115 (19.23)	70 (20.11)	
BMI (kg/m^2)	24.38 (21.95, 26.88)	24.22 (21.89, 26.56)	24.56 (22.04, 27.16)	0.116
Duration of diabetes (years)	5 (1, 10)	3 (1, 9)	8 (2, 13)	< 0.001
SBP (mmHg)	130 (118, 143)	127 (116, 138)	135 (123, 149)	< 0.001
DBP (mmHg)	76 (67, 84)	75 (67, 83)	76 (67, 85)	0.082
HbA1c (%)	8.65 (7.1, 10.8)	8.6 (6.95, 10.8)	8.9 (7.2, 10.7)	0.248
TC (mmol/L)	4.53 (3.88, 5.32)	4.53 (3.91, 5.32)	4.52 (3.79, 5.33)	0.911
TG (mmol/L)	1.57 (1.04, 2.44)	1.5 (1.01, 2.35)	1.61 (1.08, 2.62)	0.077
LDL-C (mmol/L)	2.55 (1.94, 3.17)	2.58 (2, 3.19)	2.54 (1.86, 3.16)	0.24
HDL-C (mmol/L)	1.06 (0.9, 1.28)	1.08 (0.92, 1.28)	1.01 (0.87, 1.27)	0.126
FT3 (pmol/L)	4.53 (4.1, 5)	4.64 (4.19, 5.05)	4.39 (3.91, 4.91)	< 0.001
FT4 (pmol/L)	17.03 (15.34, 18.59)	17.03 (15.47, 18.72)	17.03 (15.21, 18.46)	0.357
TSH (uIU/mL)	1.76 (1.22, 2.45)	1.74 (1.24, 2.44)	1.81 (1.17, 2.53)	0.987
TSHI	2.84 (2.47, 3.21)	2.85 (2.49, 3.22)	2.83 (2.42, 3.2)	0.39
TT4RI	29.4 (20.42, 41.53)	29.4 (20.79, 41.28)	29.38 (19.81, 41.91)	0.736
TFQI3	0.01 \pm 0.41	0.04 \pm 0.4	-0.06 \pm 0.42	< 0.001
TFQI4	0.01 (-0.26, 0.27)	0.02 (-0.23, 0.27)	-0.02 (-0.3, 0.27)	0.395
PTFQI	0.54 (0.35, 0.7)	0.54 (0.36, 0.7)	0.55 (0.33, 0.71)	0.931

Table 1. Baseline characteristics when grouped by DKD. Data for continuous variables are presented as median and interquartile range, categorical variables are presented as percentages. Abbreviations: DKD: diabetic kidney disease, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HbA1c: glycated hemoglobin, TC: total cholesterol, TG: triglyceride, LDL-C: low density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TSHI, TSH Index; TT4RI, thyroid feedback quartile index 4; TFQI, Thyroid Feedback Quantile-based Index (TFQI3 was calculated using FT3 and TFQI4 was calculated using FT4). P value < 0.05 was considered significant.

Association between sensitivity to thyroid hormones and DKD in T2DM

The association between sensitivity to thyroid hormones and DKD in T2DM are presented in Fig. 1A-E, the adjusted association was the next Fig. 1F-J, adjust factors including Age, BMI, LDL, TG, diabetes duration, and HbA1c. Worth noting that TFQI3 and DKD showed significant liner associations, with $OR=0.549$, $95\%CI = (0.394, 0.763)$, $P < 0.01$, the adjusted outcome still significant with $OR=0.565$, $95\%CI = (0.39, 0.816)$, $P < 0.01$.

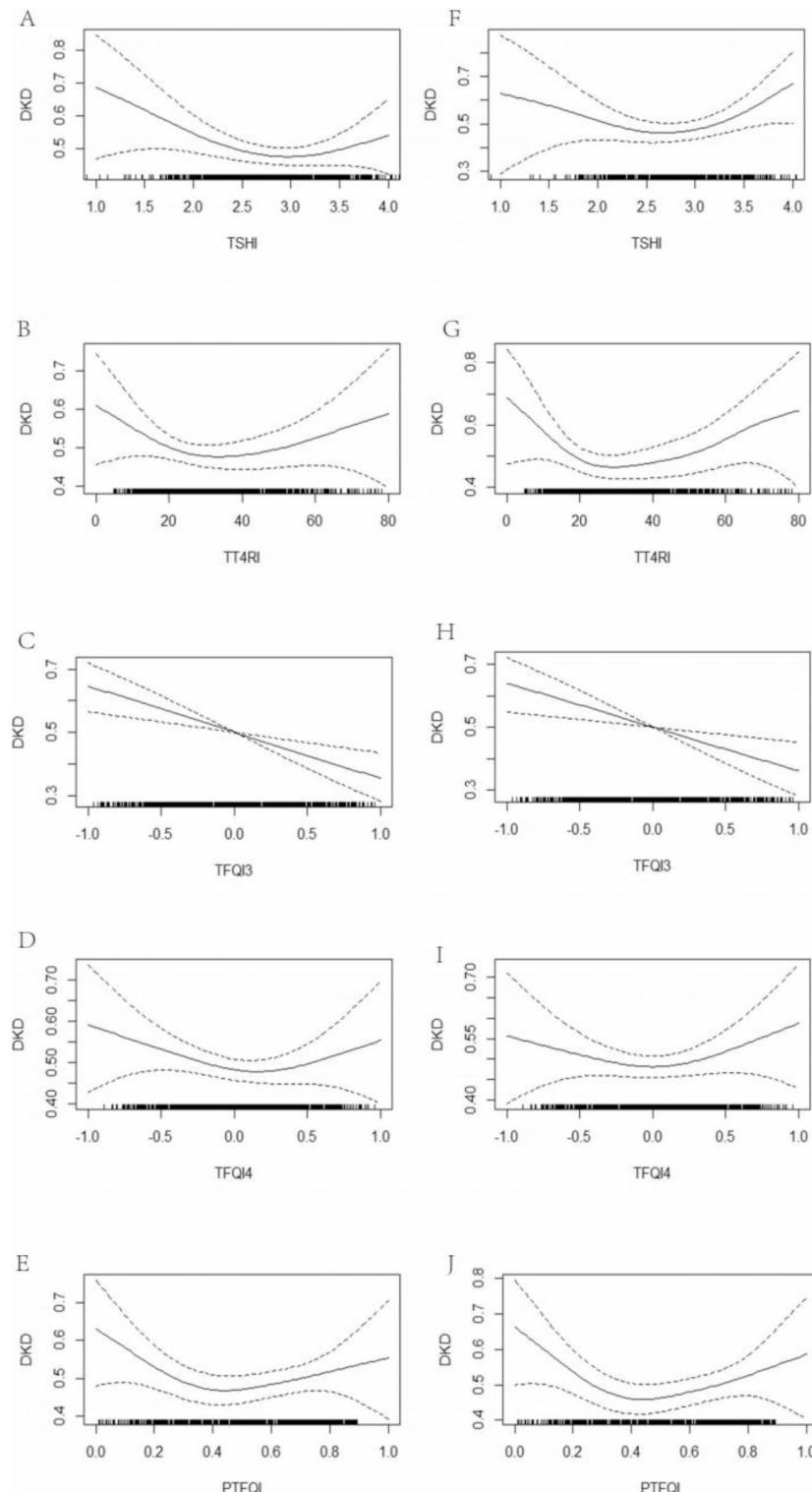


Fig. 1. Association between sensitivity to thyroid hormone indices and type 2 diabetic nephropathy in euthyroid patients in curve model.

Evidence from statistics revealed that there were no liner associations exist between TSHI, TT4RI, TFQI4, PTFQI and DKD in T2DM. Nonlinear association analysis showed that association between TSHI and DKD was significant when the inflection point was less than 3.306 with OR = 0.697, 95%CI = (0.498, 0.975), $P = 0.035$, after adjusting for the factors mentioned above, the association still significant with OR = 0.53, 95%CI = (0.288, 0.977), $P = 0.042$ when the inflection point was less than 2.768. TT4RI is not associated with DKD in T2DM when the inflection point was less than 16.185 in crude mode with OR = 0.878, 95%CI = (0.769, 1.003), $P = 0.056$, however, after adjustment, it is significant with OR = 0.863, 95%CI = (0.751, 0.992), $P = 0.039$ when inflection point was less than 16.146. All analysis results about associations between TFQI4 and DKD in T2DM were getting rid of statistic significant. PTFQI is not associated with DKD in T2DM when the inflection point was less than 0.289 in crude mode with OR = 0.017, 95%CI = (0, 1.127), $P = 0.057$, however, after adjustment, it is significant with OR = 0.007, 95%CI = (0, 0.724), $P = 0.036$ when inflection point was less than 0.036. All of the statistical results between sensitivity to thyroid hormones and DKD in T2DM were presented in Table 2.

Incident DR	Crude (OR, 95%CI, P)	Adjusted (OR, 95%CI, P)
<i>Exposure TSHI</i>		
Fitting model by standard linear regression		
Inflection point of thyroid hormone Index	3.306	2.768
< Inflection point	0.697 (0.498, 0.975) 0.035	0.53 (0.288, 0.977) 0.042
> Inflection point	3.061 (0.721, 13.003) 0.13	1.725 (0.946, 3.148) 0.075
Log likelihood ratio	0.054	0.025
<i>Exposure TT4RI</i>		
Fitting model by standard linear regression		
Inflection point of thyroid hormone Index	16.185	16.146
< Inflection point	0.878 (0.769, 1.003) 0.056	0.863 (0.751, 0.992) 0.039
> Inflection point	1.006 (0.996, 1.017) 0.221	1.009 (0.998, 1.02) 0.094
Log likelihood ratio	0.016	0.007
<i>Exposure TFQI3</i>		
Fitting model by standard linear regression		
Inflection point of thyroid hormone Index	0.549 (0.394, 0.763) < 0.01	0.565 (0.39, 0.816) < 0.01
Fitting model by two-piecewise linear regression		
Inflection point of thyroid hormone Index	-	-
< Inflection point	-	-
> Inflection point	-	-
Log likelihood ratio	-	-
<i>Exposure TFQI4</i>		
Fitting model by standard linear regression		
Inflection point of thyroid hormone Index	0.885 (0.626, 1.251) 0.489	1.045 (0.721, 1.518) 0.815
Fitting model by two-piecewise linear regression		
Inflection point of thyroid hormone Index	0.275	-0.01
< Inflection point	0.597 (0.346, 1.033) 0.065	0.528 (0.213, 1.312) 0.169
> Inflection point	2.926 (0.588, 14.566) 0.19	1.983 (0.848, 4.64) 0.114
Log likelihood ratio	0.095	0.115
<i>Exposure PTFQI</i>		
Fitting model by standard linear regression		
Inflection point of thyroid hormone Index	0.898 (0.493, 1.638) 0.726	0.906 (0.474, 1.735) 0.766
Fitting model by two-piecewise linear regression		
Inflection point of thyroid hormone Index	0.289	0.284
< Inflection point	0.017 (0, 1.127) 0.057	0.007 (0, 0.724) 0.036
> Inflection point	1.87 (0.76, 4.6) 0.173	2.141 (0.833, 5.502) 0.114
Log likelihood ratio	0.027	0.01

Table 2. Threshold effect analysis of sensitivity to thyroid hormone indices on DKD using the two-Piecewise linear regression model. Notes: Crude model was not adjusted, adjusted model was adjusted for: Age, BMI, LDL, TG, diabetes duration, and HbA1c. P value < 0.05 was considered significant. Abbreviations: OR Odds ratios; CI Confidence; DKD: diabetic kidney disease, BMI: body mass index; HbA1c: glycated hemoglobin; HDL-C: high density lipoprotein cholesterol, FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TSHI, TSH Index; TT4RI, thyroid feedback quartile index 4; TFQI, Thyroid Feedback Quantile-based Index (TFQI3 was calculated using FT3 and TFQI4 was calculated using FT4). P value < 0.05 was considered significant.

It is worth noting that due to significant differences in blood pressure between patients with DKD and those without, we further adjusted for SBP and DBP. The results are shown in Supplementary Table 3. Interestingly, after adjusting for blood pressure, we found that this had no significant effect on the outcomes.

Association between sensitivity to thyroid hormones and DR in T2DM

The association between sensitivity to thyroid hormones and DR in T2DM are presented in Figure S1 A-E, the adjusted association was in the Figure S1 F-J, adjust factors including Age, BMI, LDL, TG, diabetes duration, and HbA1c. In the linear analysis, association between TFQI3 and DR is significant in the crude mode with $OR = 0.674$, 95%CI = (0.489, 0.926), $P = 0.015$, however it turns out nonsignificant after adjustment with $OR = 0.754$, 95%CI = (0.531, 1.068), $P = 0.112$. In the nonlinear analysis, association between TFQI3 and DR is significant when the inflection point was greater than -0.692 with $OR = 0.604$, 95%CI = (0.421, 0.867) $P = 0.006$, however it turns out nonsignificant after adjustment with $OR = 0.67$, 95%CI = (0.441, 1.019) $P = 0.061$. Association between TSHI, TT4RI, TFQI4, PTFQI and DR in T2DM were all nonsignificant before and after adjustment in linear or nonlinear analysis, all of the statistics results were presented in supplementary Table 4.

Association between sensitivity to thyroid hormones and DNP in T2DM

The association between sensitivity to thyroid hormones and DNP in T2DM are presented in Figure S1 K-O, the adjusted association was in the supplementary Fig. 1P-T, adjust factors including Age, BMI, LDL, TG, diabetes duration, and HbA1c. In the nonlinear analysis, association between TFQI3 and DNP is significant in the crude mode with $OR = 0.402$, 95%CI = (0.163, 0.992), $P = 0.048$ when inflection point was greater than -0.04 , however it turns out nonsignificant after adjustment with $OR = 0.626$, 95%CI = (0.236, 1.657), $P = 0.345$ when inflection point was greater than -0.039 . Association between TSHI, TT4RI, TFQI4, PTFQI and DNP in T2DM were all nonsignificant before and after adjustment in linear or nonlinear analysis, all of the statistics results were presented in supplementary Table 5.

Subgroup analysis of sex in three groups

In order to have a further understanding of how the association between sensitivity to thyroid hormone indices and type 2 diabetes microvascular complications in different sex, subgroup analysis conducted.

In the male subgroup, after adjusting for age, BMI, LDL, TG, diabetes duration, and HbA1c, TT4RI was associated with DKD when the inflection point exceeded 18.94 (OR: 1.019, 95% CI: 1.004–1.035, $P = 0.014$). Similarly, PTFQI was associated with DKD when the inflection point surpassed 0.392 (OR: 6.03, 95% CI: 1.223–29.722, $P = 0.027$). However, no significant associations were found between TSHI, TFQI3, and TFQI4 and DKD. These findings are detailed in Table 3. Additionally, we further adjusted for SBP and DBP, as shown in Supplementary Table 6. Interestingly, after adjusting for blood pressure, there was no significant effect on the outcomes. Furthermore, within the male subgroups, no significant associations were detected between the sensitivity of the thyroid hormone index and either DR or DNP, as illustrated in supplementary Tables 7 and 8.

In the female subgroup, after adjusting for Age, BMI, LDL, TG, diabetes duration, and HbA1c, it was found that TFQI3 was associated with diabetic kidney disease (OR: 0.354, 95% CI: 0.187–0.657, $P = 0.001$), while TSHI, TT4RI, TFQI4, and PTFQI were not significantly related to DKD after adjustment. Similarly, after further adjusting for SBP and DBP, we found that the results remained unchanged (Supplementary Table 6). In addition, no significant association was found between the sensitivity of thyroid hormone indices and DR or DNP, as all detailed in supplementary Tables 7 and 8.

Discussion

Based on data from 946 hospital patients, we explored the relationship between TH sensitivity and the risk of DKD, DR, and DNP. The results showed that in euthyroid T2DM patients, the sensitivity of TH index TFQI3 was linearly associated with the risk of DKD, while TSHI, TT4RI, and PTFQI were non-linearly associated. Further subgroup analysis stratified by gender showed that TT4RI, and PTFQI were non-linearly associated with the prevalence of DKD in males, while TFQI3 was linearly associated with the risk of DKD in females. There was no significant correlation between TH sensitivity index and the risk of DR/DNP.

TSHI was first developed by Jostel et al., it provides an accurate estimate of the severity of pituitary dysfunction in hypopituitary patients based on simple thyroid function tests, and more severe degrees of hypopituitarism were associated with relatively lower TSHI¹⁵. In our study, we found that, in the initial segment of the non-linear relationship between TSHI and DKD, an increase in TSHI is associated with a reduced risk of DKD. This suggests that in a certain condition, lower TSHI values are more likely to be related to DKD in T2DM.

TT4RI was first developed by Yagi et al., in their study this index was used to quantitate the sensitivity of the thyrotrophs to the feedback regulation by thyroid hormone, TT4RI in normal individuals were significantly lower than it in subjects with resistance to thyroid hormone¹⁶. Our study demonstrated statistically significant negative correlations in the initial half of the non-linear relationship post-adjustment, indicating that an increase in TSHI correlates with a reduced risk of DKD. However, according to Laclaustra et al.'s research, no significant statistical relationship was found between TT4RI and T2DM⁹. In our study as well, the relationship between TT4RI and DKD was not significant before adjustment, suggesting that the significant correlations observed might be unstable and potentially influenced by remaining confounding factors.

TFQI and PTFQI were indices developed by Laclaustra et al., compared with TSHI and TT4RI, TFQI was more stable and without extreme values, PTFQI, as the parametric mode of TFQI, can be applied into other different populations than US⁹. In our study, TFQI3 was found significant negatively associated with DKD in a linear relationship before and after adjustment, the value of TFQI ranges from -1 to 1 , with positive values representing a poor sensitivity to thyroid hormones, while negative values reflect a good sensitivity, and 0 indicate a normal sensitivity to thyroid hormone¹⁹. In the study conducted by Schultheiss et al., lower FT3 levels

Sex	Male (OR,95%CI, P)	Female (OR, 95%CI, P)
<i>Exposure TSHI</i>		
Fitting model by standard linear regression	1.14 (0.816, 1.597) 0.443	0.721 (0.476, 1.088) 0.12
Fitting model by two-piecewise linear regression		
Inflection point of thyroid hormone Index	3.392	2.715
< Inflection point	0.828 (0.529, 1.295) 0.408	0.449 (0.166, 1.212) 0.114
> Inflection point	13.377 (0.969, 184.62) 0.053	1.159 (0.468, 2.871) 0.75
Log likelihood ratio	0.03	0.377
<i>Exposure TT4RI</i>		
Fitting model by standard linear regression	1.009 (0.997, 1.021) 0.137	0.992 (0.976, 1.007) 0.281
Fitting model by two-piecewise linear regression		
Inflection point of thyroid hormone Index	18.94	11.793
< Inflection point	0.904 (0.798, 1.024) 0.112	0.677 (0.38, 1.207) 0.186
> Inflection point	1.019 (1.004, 1.035) 0.014	0.997 (0.981, 1.014) 0.738
Log likelihood ratio	0.035	0.07
<i>Exposure TFQI3</i>		
Fitting model by standard linear regression	0.713 (0.445, 1.138) 0.157	0.354 (0.187, 0.657) 0.001
Fitting model by two-piecewise linear regression		
Inflection point of thyroid hormone Index	-	-
< Inflection point	-	-
> Inflection point	-	-
Log likelihood ratio	-	-
<i>Exposure TFQI4</i>		
Fitting model by standard linear regression	1.293 (0.801, 2.096) 0.295	0.748 (0.407, 1.367) 0.347
Fitting model by two-piecewise linear regression		
Inflection point of thyroid hormone Index	0.656	-0.151
< Inflection point	1.012 (0.592, 1.731) 0.964	0.36 (0.046, 2.788) 0.328
> Inflection point	83951.959 (0.116, 60869617770.942) 0.1	1.164 (0.394, 3.438) 0.784
Log likelihood ratio	0.033	0.541
<i>Exposure PTFQI</i>		
Fitting model by standard linear regression	1.375 (0.592, 3.207) 0.46	0.518 (0.183, 1.464) 0.214
Fitting model by two-piecewise linear regression		
Inflection point of thyroid hormone Index	0.392	0.195
< Inflection point	0.052 (0.002, 1.581) 0.09	0 (0, 155.337) 0.205
> Inflection point	6.03 (1.223, 29.722) 0.027	0.997 (0.267, 3.718) 0.996
Log likelihood ratio	0.025	0.153

Table 3. Threshold effect analysis of sensitivity to thyroid hormone indices on DKD using the two-piecewise linear regression model with sex differences. Notes: Crude model was not adjusted, adjusted model was adjusted for: Age, BMI, LDL, TG, diabetes duration, and HbA1c. P value < 0.05 was considered significant. Abbreviations: OR Odds ratios; CI Confidence; DKD: diabetic kidney disease, BMI: body mass index; HbA1c: glycated hemoglobin; HDL-C: high density lipoprotein cholesterol, FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid stimulating hormone; TSHI, TSH Index; TT4RI, thyroid feedback quartile index 4; TFQI, Thyroid Feedback Quantile-based Index (TFQI3 was calculated using FT3 and TFQI4 was calculated using FT4). P value < 0.05 was considered significant.

were significantly associated with a higher risk of all-cause mortality in chronic kidney disease²⁰. Referring to the TFQI3 calculating formula, a lower FT3 may indicate a lower cdfFT3 and ultimately a low TFQI3 value. Although our main focus is on the association between the incidence of DKD and TFQI3, it is evident that lower FT3 and lower TFQI3 are associated with adverse events in kidney disease. Additionally, in their study, continuous FT3 levels alone showed a significant positive association with eGFR²⁰. eGFR is a crucial indicator for DKD in clinical practice. However, in the progression of DKD, eGFR levels do not remain stable but ultimately decrease. This finding implies that in DKD patients, a lower FT3 level would eventually correspond to a low eGFR, aligning with our study results. In our study, there was no significant relationship between TFQI4 and DKD. The discrepancy between TFQI3 and TFQI4 may be due to the reduced activity of peripheral deiodinases in (patients with) diabetes, which can hinder the conversion of T4 to T3, potentially leading to lower T3 levels while T4 levels may remain normal or slightly increased^{21,22}. Therefore, to account for the effects of disease states on thyroid function, future research should include a general outpatient population to further investigate the association between different thyroid hormone sensitivities and DKD.

In the subgroup analysis, the association between TFQI3 and DKD was reserved in female not male, the reason why may attributed to that women's thyroid function is more active compared to men's. The impact of the thyroid on the body might be more pronounced in women than in men²³. Firstly, correlates with sex hormone levels. Studies have shown that estrogen regulates the synthesis and secretion of thyroid hormones, not only by increasing levels of thyroid hormone-binding protein, which raises the total amount of thyroid hormones in the blood, but also indirectly by affecting the hypothalamus-pituitary-thyroid axis, which may regulate thyroid function²⁴. In addition, estrogen levels may influence the development of diabetes, especially in patients over the age of 60²⁵. In contrast, testosterone in men has less of an effect on thyroid function. However, since sex hormone levels were not examined in this study, further research is needed to explore this hypothesis. Secondly, gender differences in the immune system are also significant, with women's immune systems typically being more active^{26,27}. Numerous studies have found that women's immune systems tend to be more sensitive in response to infections and other stimuli, making them more susceptible to developing autoimmune diseases such as thyroiditis and Hashimoto's thyroiditis^{28,29}. These autoimmune diseases can affect the functioning of the thyroid gland, leading to abnormal levels of thyroid hormones²⁹. Furthermore, variations in lifestyle and environmental factors may also contribute to differences in thyroid function between genders³⁰⁻³².

The association between sensitivity to TH indices and DR, DNP appears not significant in our study. Previous studies have investigated the relationship between sensitivity to TH indices and DR. In Yang et al.'s study, they discovered a non-linear relationship between TFQI4 and DR, rather than a linear one²⁵. Zhao et al.'s study found that higher levels of TFQI4 and TSHI were associated with DR³³. However, in our study, we did not observe a linear or non-linear relationship between these indices and DR. This discrepancy may be due to variations in sample size and potential differences in clinical measurements. Larger sample size studies or meta-analyses may be necessary to confirm these findings. Our study was the first to investigate the association between sensitivity to TH indices and T2DM neuropathy. However, the results were not significant. Further research involving larger samples and diverse populations is required to explore this issue more thoroughly.

However, our study has several limitations. Firstly, as a cross-sectional study, it cannot establish causality; future prospective research is needed to assess the relative risk between TH sensitivity in T2DM patients and the risk of DKD. Secondly, despite including over 900 cases, the sample size remains insufficient, and all data are derived from a single center, which limits generalizability. Thirdly, since all included patients were euthyroid T2DM patients and thyroid function was tested only once during hospitalization, this could introduce statistical errors. Additionally, we did not collect data on diabetes treatments, which is a significant oversight. The occurrence of microvascular complications is closely related to blood glucose control, and different diabetes treatment regimens are crucial for effective management and control. Finally, although we described the reason for hospital admission as "poor glycemic control," there is considerable variation in HbA1c levels. Therefore, further clarification of the specific reasons for patient admission would be beneficial. However, the inability to perform a retrospective evaluation represents a major limitation of our study.

Conclusion

In our study, we found a significant correlation between elevated levels of TH indices (TSHI, TT4RI, TFQI3, and PTFQI) based on population data and increased risk of DKD. Through further subgroup analysis by gender, we found that TFQI3 primarily increases the risk in female DKD patients, while TT4RI, and PTFQI increase the risk in male DKD patients. This finding is of important clinical significance for further understanding the pathogenesis of DKD. Furthermore, the estimated values of thyroid indicators can be obtained through simple calculations without additional cost. Therefore, it is expected to be widely applied in the early identification of high-risk DKD patients in clinical practice.

Data availability

All data in this study are available from the corresponding authors upon reasonable request.

Received: 1 July 2024; Accepted: 2 December 2024

Published online: 28 December 2024

References

1. Sun, H. et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res. Clin. Pract.* **183**, 109119 (2022).
2. Ahmad, E. et al. Type 2 diabetes. *Lancet* **400**(10365), 1803–1820 (2022).
3. Magliano, D. J., Boyko, E. J. & committee IDFDates. IDF Diabetes Atlas. Idf diabetes atlas. Brussels: International Diabetes Federation © International Diabetes Federation, 2021 (2021).
4. Kosiborod, M. et al. Vascular complications in patients with type 2 diabetes: Prevalence and associated factors in 38 countries (the DISCOVER study program). *Cardiovasc. Diabetol.* **17**(1), 150 (2018).
5. Faselis, C. et al. Microvascular complications of type 2 diabetes mellitus. *Curr. Vasc Pharmacol.* **18**(2), 117–124 (2020).
6. An, J. et al. Prevalence and incidence of microvascular and macrovascular complications over 15 years among patients with incident type 2 diabetes. *BMJ Open. Diabetes Res. Care* **9**(1) (2021).
7. Hu, Y. et al. Association of thyroid hormone levels with microvascular complications in euthyroid type 2 diabetes mellitus patients. *Diabetes Metab. Syndr. Obes.* **15**, 2467–2477 (2022).
8. Baksi, S. & Pradhan, A. Thyroid hormone: Sex-dependent role in nervous system regulation and disease. *Biol. Sex. Differ.* **12**(1), 25 (2021).
9. Laclaustra, M. et al. Impaired sensitivity to thyroid hormones is associated with diabetes and metabolic syndrome. *Diabetes Care* **42**(2), 303–310 (2019).
10. Qi, Q. et al. Association of thyroid-stimulating hormone levels with microvascular complications in type 2 diabetes patients. *Med. Sci. Monit.* **23**, 2715–2720 (2017).

11. Li, H. et al. Assessment of the association between genetic factors regulating thyroid function and microvascular complications in diabetes: A two-sample mendelian randomization study in the European population. *Front. Endocrinol. (Lausanne)* **14**, 1126339 (2023).
12. Levey, A. S. et al. A new equation to estimate glomerular filtration rate. *Ann. Intern. Med.* **150**(9), 604–612 (2009).
13. Retinopathy, neuropathy, and foot care: standards of care in diabetes-2024. *Diabetes Care* **47**(Suppl 1), S231–s243 (2024).
14. Mehran, L. et al. Reduced sensitivity to thyroid hormone is associated with diabetes and hypertension. *J. Clin. Endocrinol. Metab.* **107**(1), 167–176 (2022).
15. Jostel, A., Ryder, W. D. & Shalet, S. M. The use of thyroid function tests in the diagnosis of hypopituitarism: Definition and evaluation of the TSH Index. *Clin. Endocrinol. (Oxf)* **71**(4), 529–534 (2009).
16. Yagi, H. et al. Resistance to thyroid hormone caused by two mutant thyroid hormone receptors beta, R243Q and R243W, with marked impairment of function that cannot be explained by altered in vitro 3,5,3'-triiodothyronine binding affinity. *J. Clin. Endocrinol. Metab.* **82**(5), 1608–1614 (1997).
17. Lai, S. et al. Sensitivity to thyroid hormone indices are closely associated with NAFLD. *Front. Endocrinol. (Lausanne)* **12**, 766419 (2021).
18. Hassan-Smith, Z., Hewison, M. & Gittoes, N. Vitamin D supplementation and prevention of type 2 diabetes. *N Engl. J. Med.* **381**(18), 1784–1785 (2019).
19. Xie, H. et al. The association between the thyroid feedback quantile-based index and serum uric acid in U.S. adults. *Eur. J. Med. Res.* **28**(1), 259 (2023).
20. Schultheiss, U. T. et al. Thyroid function, renal events and mortality in chronic kidney disease patients: The German chronic kidney Disease study. *Clin. Kidney J.* **14**(3), 959–968 (2021).
21. Liu, X. et al. Thyroid function and thyroid homeostasis parameters are associated with increased urinary albumin excretion in euthyroid individuals over 60 years old from NHANES. *Front. Endocrinol. (Lausanne)* **14**, 1285249 (2023).
22. Bianco, A. C. & Kim, B. S. Pathophysiological relevance of deiodinase polymorphism. *Curr. Opin. Endocrinol. Diabetes Obes.* **25**(5), 341–346 (2018).
23. Taylor, P. N. et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat. Rev. Endocrinol.* **14**(5), 301–316 (2018).
24. Mauvais-Jarvis, F., Clegg, D. J. & Hevener, A. L. The role of estrogens in control of energy balance and glucose homeostasis. *Endocr. Rev.* **34**(3), 309–338 (2013).
25. Yang, J. et al. Association between sensitivity to thyroid hormone indices and diabetic retinopathy in euthyroid patients with type 2 diabetes mellitus. *Diabetes Metab. Syndr. Obes.* **16**, 535–545 (2023).
26. Markle, J. G. & Fish, E. N. SeXX matters in immunity. *Trends Immunol.* **35**(3), 97–104 (2014).
27. Klein, S. L. & Flanagan, K. L. Sex differences in immune responses. *Nat. Rev. Immunol.* **16**(10), 626–638 (2016).
28. Billi, A. C., Kahlenberg, J. M. & Gudjonsson, J. E. Sex bias in autoimmunity. *Curr. Opin. Rheumatol.* **31**(1), 53–61 (2019).
29. Ragusa, F. et al. Hashimoto's thyroiditis: Epidemiology, pathogenesis, clinic and therapy. *Best Pract. Res. Clin. Endocrinol. Metab.* **33**(6), 101367 (2019).
30. Bauer, M. et al. Gender differences in thyroid system function: Relevance to bipolar disorder and its treatment. *Bipolar Disord* **16**(1), 58–71 (2014).
31. Kim, J. M. et al. The relationship between thyroid function and different obesity phenotypes in Korean Euthyroid adults. *Diabetes Metab. J.* **43**(6), 867–878 (2019).
32. Suzuki, S. et al. Gender-specific regulation of response to thyroid hormone in aging. *Thyroid Res.* **5**(1), 1 (2012).
33. Zhao, X. et al. The effect of Central and peripheral thyroid resistance indices on diabetic retinopathy: A study of hospitalized euthyroid patients with T2DM in China. *Ann. Med.* **55**(2), 2249017 (2023).

Author contributions

Data analysis S.C.; manuscript writing J.Z. and Z.L.; article design J.Z. and S.C.; data collection, Z.L. Z.R. and X.L.; table making J.W. S.H. and J.W.; figure creation and article layout D.C. C.C. and J.W.; review and revise manuscripts, J.X.; All authors contributed to the article and approved the final manuscript.

Funding

This work was supported by the Jiangxi Provincial Science and Technology Innovation Base Plan - Provincial Clinical Medical Research Center (2020BCG74001); Jiangxi Provincial Science and Technology Innovation Base Construction - Clinical Medical Research Center (20221ZDG02011); Jiangxi Provincial Natural Science Foundation (20224ACB206010).

Declarations

Competing interests

The authors declare no competing interests.

Consent for publication

Not applicable.

Ethical approval and consent to participate

Our study protocol was approved by the research committee of the First Affiliated Hospital of Nanchang University (no. 2022-3-031). The ethics committee granted approval for the utilization of anonymized historical data in the study and waived the requirement for informed consent from patients.

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-024-82028-z>.

Correspondence and requests for materials should be addressed to S.C. or J.X.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

© The Author(s) 2024