Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Pituitary-Thyroid Hormones and Related Indices in Euthyroid Type 2 Diabetes: Association With Thyroid Nodules

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Aim: Diabetes is an independent risk factor for thyroid nodules (TNs), however, the influencing factors of TNs have not been fully clarified under the condition of diabetes. Previous studies have shown a connection between pituitary-thyroid hormone (TH) functions and TNs in different populations. However, the potential link in euthyroid patients with diabetes is unclear. We aimed to explore the correlates of TNs in euthyroid type 2 diabetes (T2D) patients.

Methods: This cross-sectional study included 1965 euthyroid adults with T2D. Clinical and biochemical data, including TH and relevant covariates were collected. TNs were evaluated using ultrasound. Univariate and multivariate logistic regression analyses were performed to identify factors associated with TNs, with analyses stratified by sex.

Results: The overall prevalence of TNs was 51.9%. The prevalence of TNs was higher in females. Stratified by sex, the results from univariate and further logistic regression analyses showed that free triiodothyronine (FT3) (OR: 1.381; 95% CI: 1.066–1.790) and thyroid-stimulating hormone index (TSHI) (OR: 0.740; 95% CI: 0.584–0.937) were independently correlated with TNs only in females, while no TH-related indicators entered the regression model in males.

Conclusion: The relationship between TH and related indices with TNs exhibited sex differences. Specifically, FT3 and TSHI were independently associated with TNs in females. These findings underscore the importance of evaluating TH and related indices for early monitoring and management of TNs, particularly in euthyroid female T2D patients.

Keywords: pituitary-thyroid hormone, type 2 diabetes, thyroid nodules, correlates

Introduction

In recent years, the detection rates of thyroid nodules (TNs) have increased rapidly.[1] TNs are more prevalent in type 2 diabetes (T2D) patients compared to the general population,[2,3] suggesting a complex relationship that warrants further investigation. Additionally, TNs are associated with malignancy risk and adverse impacts on mental health.[4,5] Epidemiological and observational studies consistently demonstrate that diabetes is an independent risk factor for TNs,[6–9] with a higher incidence in females than in males.[10–12] Therefore, it is crucial to investigate the risk factors for TNs by sex, specifically in the context of diabetes.

Pituitary-thyroid hormone (TH), including thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4), along with its associated indices—such as the thyroid feedback quantile-based index (TFQI), thyroid-stimulating hormone index (TSHI), thyrotroph T3 resistance index (TT3RI) and thyrotroph T4 resistance index (TT4RI), have been shown to be associated with various diseases, even in euthyroid subjects.[13–17] Recent research showed that the TH axis was related to TNs in euthyroid adults.[18] However, under the condition of diabetes, the relationship between TNs

Received: 7 November 2024
Accepted: 13 February 2025
Published: 27 February 2025

and TH axis and other potential factors affecting TNs is as yet unclear. Therefore, potential correlates of TNs were identified and analyzed among euthyroid patients with T2D in this study.

Materials and Methods

Patients

Medical records of patients with T2D from the Department of Endocrinology, Linyi People's Hospital, were collected for the period between January 2020 and March 2023. The inclusion criteria were as follows: T2D and age ≥ 18 years. The exclusion criteria included: (1) patients with type 1 diabetes and other types of diabetes; (2) patients with thyroid dysfunction and thyroid surgery; (3) patients with missing thyroid ultrasound data. Ultimately, a total of 1965 euthyroid patients with T2D were included in our study.

Physical Examinations

Participants' height and weight were measured. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the in the seated participants' nondominant arm with an automated electronic device. Visceral fat area (VFA) and subcutaneous fat area (SFA) were assessed using bioelectrical impedance analysis (Omron DUALSCAN HDS-2000, Kyoto, Japan).

Laboratory Measurements

Following an overnight fast, blood samples were collected in the morning for analysis. Lipid profiles, including total cholesterol (TC), triglycerides (TG), high density lipoprotein-cholesterol (HDL-c), and low density lipoprotein-cholesterol (LDL-c), were assessed. Liver function markers, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ- glutamyl transpeptidase (GGT); and kidney function markers, including serum creatinine (Scr) and uric acid (UA), were measured. Hemoglobin (Hb); glycosylated haemoglobin (HbA1c, high-performance liquid chromatography), and urinary albumin to creatinine ratio (UACR) was tested by an autoanalyzer (Beckman Coulter AU5821). Thyroid function was assessed by measuring FT3, FT4, TSH, and anti-thyroperoxidase antibody (TPOAb) using a chemiluminescence immunoassay (SIEMENS, USA).

Euthyroidism was defined as FT3 levels ranging from 3.5 to 6.5 pmol/L; FT4 levels ranging from 11.5 to 22.7 pmol/L; and TSH levels ranging from 0.55 to 4.78 uIU/mL.

Definition of Complications and Comorbidities

According to the corresponding criteria, diabetic neuropathy (DN),[19] retinopathy (DR)[20] and peripheral neuropathy (DPN) (assessed by electromyography) were diagnosed. Peripheral atherosclerosis (PAS) including increased intima-media thickness, plaque formation, stenosis and occlusion of the carotid or lower extremity artery, was assessed by vascular ultrasonography. TNs were assessed by thyroid ultrasound. Self-reported current cigarette smoking, alcohol consumption, the age of menarche, and the age of menopause were collected. A smoker was defined as someone smoking at least one cigarette per day in the last month, and a drinker was defined as alcohol consumption ≥ two or more times per week.

Parameter Calculations

1.$\text{Body mass index (BMI)} = \text{weight (kg)} / \text{height}^2\ (\text{m}^2)$;
2.$\text{FT3/FT4 ratio} = \text{FT3 (pmol/L)} / \text{FT4 (pmol/L)}$;
3.$\text{TFQI}_{\text{FT3}} = \text{cdfFT3} - (1 - \text{cdfTSH})$;[21]
4.$\text{TFQI}_{\text{FT4}} = \text{cdfFT4} - (1 - \text{cdfTSH})$;[22]
5.$\text{TSHI} = \text{lnTSH(mIU/L)} + 0.1345 \times \text{FT4(pmol/L)}$;[23]
6.$\text{TT3RI} = \text{FT3(pmol/L)} \times \text{TSH(mIU/L)}$;[24]
7.$\text{TT4RI} = \text{FT4(pmol/L)} \times \text{TSH(mIU/L)}$.[25]

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 (SPSS, Inc, Chicago, USA). Data were presented as mean ± SD for normally distributed variables, and median (interquartile ranges) for non-normally distributed variables. Independent-Samples *t*-test and Mann–Whitney *U*-test were used for comparisons of normally and non-normally distributed continuous variables between two groups. Categorical variables were presented as percentage (%), and were compared by chi-square test. Spearman correlation analysis and logistic regression analysis were used to analyze the independent correlates of TNs. Statistical significance was defined as *p*-value (two-tailed) less than 0.05.

Results

Baseline Clinical and Biochemical Characteristics

The clinical and biochemical characteristics of the participants are shown in Table 1. A total of 1965 euthyroid patients with T2D with a mean age of 57.1 ± 13.3 years were enrolled in this study. The overall prevalence of TNs was 51.9%. Then, the subjects were divided into two groups: female group and male group, and each variable was compared between the two groups (Table 1). Compared with males, the results showed that the age, SBP, TC, LDL-c, HDL-c, UACR, TSH, TT3RI, TT4RI and the percentage of TNs were increased, while BMI, VFA, SFA, DBP, ALT, AST, GGT, UA, Scr, Hb, FT3, FT4, FT3/FT4 ratio and $TFQI_{FT3}$ were lower in females. Additionally, the percentage of smoking, drinking and DN were also lower in females (all *p*-values < 0.05). However, there was no obvious differences in duration of diabetes, TG, HbA1c, TPOAb, $TFQI_{FT4}$, TSHI, and the percentage of DR, DPN and PAS (all *p*-values > 0.05).

Table 1 Clinical and Biochemical Characteristics Stratified by Gender

Variables	All	Female	Male	P
Number	1965	1120	845	
Age (years)	57.1 ± 13.3	58.4 ± 13.2	55.3 ± 13.3	< 0.001
Duration of diabetes (years)	8.0 (2.0 ~ 13.0)	7.0 (2.0 ~ 13.0)	8.0 (2.0 ~ 13.0)	0.325
Smoking (%)	325 (16.5%)	8 (0.7%)	317 (37.5%)	< 0.001
Drinking (%)	272 (13.9%)	3 (0.3%)	269 (31.9%)	< 0.001
BMI (kg/m^2)	25.63 ± 3.72	25.37 ± 3.77	25.97 ± 3.63	0.001
VFA (cm^2)	93.00 (67.00 ~ 121.00)	81.00 (61.00 ~ 105.00)	109.00 (82.00 ~ 135.00)	< 0.001
SFA (cm^2)	182.00 (141.50 ~ 231.50)	179.00 (138.00 ~ 231.00)	189.00 (151.50 ~ 232.00)	< 0.001
SBP (mmHg)	130.3 ± 18.7	131.2 ± 19.6	129.0 ± 17.5	0.008
DBP (mmHg)	80.7 ± 11.5	79.5 ± 11.2	82.3 ± 11.7	< 0.001
Age of menarche (years)	15.0 ± 1.9	15.0 ± 1.9		
Age of menopause (years)	49.8 ± 4.0	49.8 ± 4.0		
TC (mmol/L)	4.83 ± 1.31	4.96 ± 1.22	4.66 ± 1.40	< 0.001
LDL-c (mmol/L)	3.06 ± 1.21	3.15 ± 1.26	2.95 ± 1.12	< 0.001
TG (mmol/L)	1.43 (1.03 ~ 2.11)	1.42 (1.03 ~ 2.04)	1.43 (1.03 ~ 2.23)	0.148
HDL-c (mmol/L)	1.17 ± 0.35	1.24 ± 0.37	1.08 ± 0.28	< 0.001
HbA1c (%)	9.31 ± 2.22	9.24 ± 2.18	9.41 ± 2.26	0.105
ALT (U/L)	17.70 (13.10 ~ 26.60)	16.10 (12.08 ~ 23.90)	20.00 (14.70 ~ 32.00)	< 0.001
AST (U/L)	17.30 (14.10 ~ 22.40)	16.90 (13.80 ~ 21.70)	18.00 (15.00 ~ 23.40)	< 0.001
GGT (U/L)	21.00 (15.00 ~ 32.00)	19.00 (14.00 ~ 27.00)	26.00 (18.00 ~ 40.00)	< 0.001
UA (μmolL)	289.00 ± 93.13	265.99 ± 88.11	319.59 ± 90.83	< 0.001
Scr (μmol/L)	64.35 ± 21.12	57.13 ± 18.11	74.02 ± 21.01	< 0.001
UACR (mg/g)	11.20 (6.00 ~ 37.30)	11.70 (6.50 ~ 33.90)	10.20 (5.00 ~ 42.20)	0.008
Hb (g/L)	141.15 ± 17.92	133.52 ± 14.87	151.19 ± 16.59	< 0.001
FT3 (pmol/L)	4.65 ± 0.57	4.50 ± 0.51	4.84 ± 0.59	< 0.001
FT4 (pmol/L)	16.12 ± 2.19	15.75 ± 2.10	16.60 ± 2.22	< 0.001
FT3/FT4 ratio	0.29 ± 0.05	0.29 ± 0.05	0.29 ± 0.05	0.009

(*Continued*)

Table 1 (Continued).

Variables	All	Female	Male	*P*
TSH (uIU/mL)	1.86 (1.27 ~ 2.64)	1.96 (1.35 ~ 2.83)	1.67 (1.18 ~ 2.38)	< 0.001
TPOAb (IU/mL)	38.10 (32.90 ~ 45.90)	38.60 (32.90 ~ 46.80)	37.60 (32.78 ~ 44.93)	0.064
$TFQI_{FT3}$	0.01 (−0.30 ~ 0.29)	−0.02 (−0.33 ~ 0.25)	0.06 (−0.23 ~ 0.36)	< 0.001
$TFQI_{FT4}$	−0.01 (−0.27 ~ 0.26)	−0.01 (−0.30 ~ 0.24)	−0.01 (−0.24 ~ 0.27)	0.236
TSHI	2.76 (2.38 ~ 3.14)	2.79 (2.38 ~ 3.17)	2.71 (2.39 ~ 3.10)	0.151
TT3RI	8.60 (5.74 ~ 12.17)	8.94 (5.86 ~ 12.68)	8.17 (5.62 ~ 11.40)	0.001
TT4RI	29.35 (20.33 ~ 41.43)	31.06 (21.14 ~ 44.01)	27.54 (19.86 ~ 38.54)	< 0.001
Complications				
DN (%)	490 (24.9%)	239 (21.3%)	251 (29.7%)	< 0.001
DR (%)	719 (36.6%)	412 (36.8%)	307 (36.3%)	0.437
DPN (%)	814 (41.4%)	459 (41.0%)	355 (42.0%)	0.346
PAS (%)	1410 (71.8%)	809 (72.2%)	601 (71.1%)	0.312
TNs (%)	1019 (51.9%)	654 (58.4%)	365 (43.2%)	< 0.001

Notes: Data were presented as mean ± SD for normally distributed variables, and median (interquartile ranges) for abnormal distributions. Independent-Samples *T* test and Mann–Whitney *U*-test were used for comparisons of normally and abnormally distributed continuous variables between TNs and NTNs groups, respectively. Categorical variables were presented as percentage (%), and were compared by chi-square test. Statistical differences were defined by *p*-value (two-tailed) less than 0.05.

Abbreviations: BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ- glutamyl transpeptidase; UA, uric acid; Scr, serum creatinine; Hb, hemoglobin; UACR, urinary albumin to creatinine ratio; Hb, hemoglobin; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TPOAb, anti-thyroperoxidase antibody; $TFQI_{FT3}$, the thyroid feedback quantile-based index calculated by FT3; $TFQI_{FT4}$, the thyroid feedback quantile-based index calculated by FT4; TSHI, TSH index; TT3RI, thyrotroph T3 resistance index; TT4RI, thyrotroph T4 resistance index; DN, diabetic nephropathy; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; PAS, peripheral atherosclerosis; TNs, thyroid nodules; NTNs, without thyroid nodules.

As shown in Table 2, for each sex, patients were divided into NTNs and TNs groups, and each variable was compared. In females, compared with NTNs group, the age, duration of diabetes, and the percentage of DR and PAS were increased, while the UA, TSH, $TFQI_{FT4}$, TSHI, TT3RI and TT4RI were decreased in TNs group (all *p*-values < 0.05). However, there were no statistically significant differences in BMI, VFA, SFA, SBP, DBP, age of menarche, age of

Table 2 Comparison of Clinical and Biochemical Characteristics Between NTNs Group and TNs Group

Variables	Female			Male		
	NTNs Group	TNs Group	*P*	NTNs Group	TNs Group	*P*
Number	466	654		480	365	
Age (years)	56.0 ± 14.5	60.1 ± 12.0	<0.001	52.9 ± 13.5	58.6 ± 12.3	<0.001
Duration of diabetes (years)	6.00 (2.00 ~ 12.00)	8.00 (3.00 ~ 14.00)	<0.001	7.00 (2.00 ~ 12.00)	10.00 (3.00 ~ 15.00)	0.025
Smoking (%)	2 (0.4%)	6 (0.9%)	0.481	203 (42.3%)	114 (31.2%)	0.001
Drinking (%)	1 (0.2%)	2 (0.3%)	1.000	156 (32.6%)	113 (31.1%)	0.655
BMI (kg/m^2)	25.37 ± 4.28	25.37 ± 3.39	0.997	26.06 ± 3.84	25.86 ± 3.34	0.444
VFA (cm^2)	79.00 (56.00 ~ 105.00)	82.00 (63.00 ~ 106.00)	0.073	110.50 (84.00 ~ 137.25)	107.00 (81.00 ~ 130.00)	0.333
SFA (cm^2)	177.00 (129.50 ~ 235.00)	180.00 (140.00 ~ 229.00)	0.555	190.00 (153.00 ~ 235.00)	188.00 (152.00 ~ 229.00)	0.522
SBP (mmHg)	130.0 ± 19.6	132.1 ± 19.5	0.077	128.1 ± 17.0	130.1 ± 18.0	0.095
DBP (mmHg)	79.6 ± 11.9	79.4 ± 10.7	0.684	82.1 ± 11.6	82.5 ± 11.8	0.619
Age of menarche (years)	15.0 ± 1.9	15.0 ± 1.9	0.549			
Age of menopause (years)	49.9 ± 3.6	49.7 ± 4.2	0.571			
TC (mmol/L)	5.00 ± 1.17	4.93 ± 1.25	0.423	4.77 ± 1.53	4.53 ± 1.21	0.017
LDL-c (mmol/L)	3.15 ± 1.01	3.14 ± 1.42	0.208	2.96 ± 1.06	2.93 ± 1.20	0.694
TG (mmol/L)	1.43 (1.03 ~ 2.06)	1.42 (1.03 ~ 2.03)	0.933	1.54 (1.06 ~ 2.41)	1.33 (0.99 ~ 2.09)	0.008
HDL-c (mmol/L)	1.25 ± 0.42	1.24 ± 0.34	0.370	1.06 ± 0.29	1.09 ± 0.27	0.113
HbA1c (%)	9.24 ± 2.32	9.24 ± 2.08	0.950	9.42 ± 2.17	9.40 ± 2.37	0.893
ALT (U/L)	16.05 (11.90 ~ 25.25)	16.20 (12.13 ~ 23.68)	0.660	20.15 (14.70 ~ 33.63)	19.40 (14.60 ~ 29.00)	0.124
AST (U/L)	17.20 (13.40 ~ 22.70)	16.80 (14.00 ~ 20.85)	0.506	18.30 (15.00 ~ 24.50)	17.50 (14.90 ~ 21.75)	0.060

(*Continued*)

Table 2 (Continued).

Variables	Female			Male		
	NTNs Group	TNs Group	*P*	NTNs Group	TNs Group	*P*
GGT (U/L)	19.00 (14.00 ~ 29.00)	19.00 (14.00 ~ 26.00)	0.230	26.30 (17.53 ~ 42.00)	25.00 (18.00 ~ 37.00)	0.352
UA (μmolL)	275.24 ± 96.70	259.40 ± 80.88	0.004	328.14 ± 97.06	308.41 ± 80.74	0.002
Scr (μmol/L)	57.72 ± 21.54	56.71 ± 15.23	0.392	73.45 ± 20.65	74.77 ± 21.48	0.375
UACR (mg/g)	11.70 (6.70 ~ 39.50)	11.75 (6.48 ~ 33.45)	0.686	10.80 (4.90 ~ 44.60)	9.60 (5.35 ~ 40.50)	0.834
Hb (g/L)	133.77 ± 15.22	133.34 ± 14.62	0.638	152.52 ± 16.18	149.46 ± 16.98	0.008
FT3 (pmol/L)	4.47 ± 0.52	4.53 ± 0.50	0.052	4.85 ± 0.59	4.84 ± 0.59	0.832
FT4 (pmol/L)	15.82 ± 2.14	15.70 ± 2.06	0.356	16.68 ± 2.21	16.49 ± 2.22	0.220
FT3/FT4 ratio	0.29 ± 0.05	0.29 ± 0.04	0.060	0.29 ± 0.05	0.30 ± 0.05	0.362
TSH (ulU/mL)	2.07 (1.43 ~ 2.93)	1.89 (1.30 ~ 2.77)	0.008	1.70 (1.15 ~ 2.32)	1.63 (1.19 ~ 2.45)	0.835
TPOAb (IU/mL)	39.00 (33.48 ~ 48.63)	38.10 (32.80 ~ 45.80)	0.282	37.60 (32.30 ~ 46.60)	37.50 (33.20 ~ 43.50)	0.357
$TFQI_{FT3}$	−0.01 (−0.32 ~ 0.25)	−0.04 (−0.34 ~ 0.24)	0.400	0.05 (−0.21 ~ 0.35)	0.07 (−0.27 ~ 0.36)	0.932
$TFQI_{FT4}$	0.01 (−0.23 ~ 0.27)	−0.03 (−0.34 ~ 0.23)	0.013	−0.02 (−0.25 ~ 0.29)	−0.01 (−0.23 ~ 0.24)	0.665
TSHI	2.82 (2.48 ~ 3.21)	2.74 (2.32 ~ 3.13)	0.008	2.75 (2.38 ~ 3.12)	2.73 (2.40 ~ 3.08)	0.835
TT3RI	9.53 (6.22 ~ 13.12)	8.50 (5.52 ~ 12.28)	0.024	8.46 (5.59 ~ 11.29)	7.72 (5.62 ~ 12.09)	0.872
TT4RI	32.02 (22.43 ~ 45.66)	29.50 (19.92 ~ 42.69)	0.006	27.74 (19.74 ~ 38.05)	27.21 (19.86 ~ 38.88)	0.922
Complications						
DN (%)	102 (27.9%)	137 (20.9%)	0.712	149 (31.0%)	102 (27.9%)	0.362
DR (%)	147 (31.5%)	265 (40.5%)	0.003	156 (32.5%)	151 (41.4%)	0.009
DPN (%)	178 (38.2%)	281 (43.0%)	0.109	192 (40.0%)	163 (44.7%)	0.182
PAS (%)	292 (62.7%)	517 (79.1%)	<0.001	307 (64.0%)	294 (80.5%)	<0.001

Notes: Data were presented as mean ± SD for normally distributed variables, and median (interquartile ranges) for abnormal distributions. Independent-Samples *T* test and Mann–Whitney *U*-test were used for comparisons of normally and abnormally distributed continuous variables between TNs and NTNs groups, respectively. Categorical variables were presented as percentage (%), and were compared by chi-square test. Statistical differences were defined by *p*-value (two-tailed) less than 0.05.

Abbreviations: BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ- glutamyl transpeptidase; UA, uric acid; Scr, serum creatinine; Hb, hemoglobin; UACR, urinary albumin to creatinine ratio; Hb, hemoglobin; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TPOAb, anti-thyroperoxidase antibody; $TFQI_{FT3}$, the thyroid feedback quantile-based index calculated by FT3; $TFQI_{FT4}$, the thyroid feedback quantile-based index calculated by FT4; TSHI, TSH index; TT3RI, thyrotroph T3 resistance index; TT4RI, thyrotroph T4 resistance index; DN, diabetic nephropathy; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; PAS, peripheral atherosclerosis; TNs, thyroid nodules; NTNs, without thyroid nodules.

menopause, TC, LDL-c, TG, HDL-c, ALT, AST, GGT, Scr, HbA1c, UACR, Hb, FT3, FT4, FT3/FT4 ratio, TPOAb, $TFQI_{FT3}$, and the percentage of smoking, drinking, DN and DPN (all p-value < 0.05). In males, compared with NTNs group, the age, duration of diabetes, and the percentage of smoking, DR and PAS were increased, while the TC, TG, UA and Hb were lower in the TNs group (all p-values < 0.05). However, there was no obvious differences in BMI, VFA, SFA, SBP, DBP, LDL-c, HDL-c, HbA1c, ALT, AST, GGT, Scr, UACR, FT3, FT4, FT3/FT4 ratio, TSH, TPOAb, $TFQI_{FT3}$, $TFQI_{FT4}$, TSHI, TT3RI, TT4RI, and the percentage of drinking, DN and DPN (all p-values < 0.05).

Correlation Between TNs and All Variables by Univariate Analysis

As shown in Table 3, for each sex, a Spearman correlation analysis was performed to examine the relationship between TNs and each variable. For females, the results showed that TNs were related positively to age, duration of diabetes, FT3, DR and PAS, while negatively to UA, TSH, $TFQI_{FT4}$, TSHI, TT3RI and TT4RI (all p-values < 0.05). However, there was no significant association between TNs and smoking, drinking, BMI, VFA, SFA, SBP, DBP, age of menarche, age of menopause, TC, LDL-c, TG, HDL-c, HbA1c, ALT, AST, GGT, Scr, UACR, Hb, FT4, FT3/FT4 ratio, TPOAb, $TFQI_{FT4}$, DN and DPN in both groups (all p-value > 0.05). For males, the results showed that TNs were related positively to age, duration of diabetes, smoking, drinking, HDL-c, DR and PAS, while negatively to TG, UA and Hb (all p-values < 0.05). However, there was no statistically significant association between TNs and BMI, VFA, SFA, SBP, DBP, TC, LDL-c, HbA1c, ALT, AST, GGT, Scr, UACR, FT3, FT4, FT3/FT4 ratio, TSH, TPOAb, $TFQI_{FT3}$, $TFQI_{FT4}$, TSHI, TT3RI, TT4RI, DN and DPN (all p-values > 0.05).

Table 3 The Correlation Between TNs and Different Variables by Univariate Analysis

Variables	Female		Male	
	Correlation Coefficient	*p*	Correlation Coefficient	*p*
Age	0.130	< 0.001	0.211	< 0.001
Duration of diabetes	0.118	< 0.001	0.082	0.025
Smoking	0.029	0.338	−0.133	0.001
Drinking	0.009	0.770	−0.028	0.431
BMI	0.020	0.513	−0.052	0.165
VFA	0.059	0.073	−0.037	0.334
SFA	0.019	0.555	−0.024	0.552
SBP	0.042	0.158	0.067	0.051
DBP	−0.003	0.922	0.030	0.385
Age of menarche	0.037	0.234		
Age of menopause	−0.028	0.443		
TC	−0.033	0.271	−0.061	0.079
LDL-c	−0.028	0.348	−0.025	0.475
TG	−0.003	0.933	−0.092	0.008
HDL-c	0.007	0.823	0.072	0.038
HbA1c	0.006	0.836	−0.010	0.775
ALT	−0.013	0.660	−0.054	0.124
AST	−0.020	0.506	−0.065	0.060
GGT	−0.036	0.230	−0.032	0.352
UA	−0.073	0.016	−0.105	0.002
Scr	0.014	0.647	0.012	0.729
UACR	−0.012	0.686	0.007	0.834
Hb	−0.021	0.497	−0.106	0.002
FT3	0.062	0.039	−0.004	0.911
FT4	−0.023	0.450	−0.040	0.246
FT3/FT4 ratio	0.055	0.067	0.022	0.521
TSH	−0.080	0.008	0.007	0.835
TPOAb	−0.041	0.283	−0.040	0.357
$TFQI_{FT3}$	−0.025	0.400	0.003	0.932
$TFQI_{FT4}$	−0.074	0.013	−0.015	0.666
TSHI	−0.081	0.007	−0.006	0.862
TT3RI	−0.067	0.024	0.006	0.873
TT4RI	−0.082	0.006	−0.003	0.922
Complications				
DN	−0.011	0.705	−0.034	0.330
DR	0.092	0.002	0.091	0.008
DPN	0.050	0.095	0.047	0.175
PAS	0.180	< 0.001	0.181	< 0.001

Notes: Correlation coefficients between TNs and different variables were determined by Spearman correlation analysis.

Abbreviations: BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ- glutamyl transpeptidase; UA, uric acid; Scr, serum creatinine; Hb, hemoglobin; UACR, urinary albumin to creatinine ratio; Hb, hemoglobin; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TPOAb, antithyroperoxidase antibody; $TFQI_{FT3}$, the thyroid feedback quantile-based index calculated by FT3; $TFQI_{FT4}$, the thyroid feedback quantile-based index calculated by FT4; TSHI, TSH index; TT3RI, thyrotroph T3 resistance index; TT4RI, thyrotroph T4 resistance index; DN, diabetic nephropathy; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; PAS, peripheral atherosclerosis; TNs, thyroid nodules.

Table 4 The Relative Risks for TNs by Logistic Regression Analysis

Variables	B	SE	Wals	*p*-value	OR	95.0% CI for OR
In all						
PAS	0.500	0.129	14.948	< 0.001	1.649	1.280–2.124
Female	0.251	0.122	4.270	0.039	1.286	1.013–1.632
DR	0.228	0.106	4.639	0.031	1.256	1.021–1.544
Age	0.012	0.005	6.826	0.009	1.012	1.003–1.021
UA	−0.002	0.001	7.301	0.007	0.998	0.997–1.000
Smoking	−0.432	0.161	7.245	0.007	0.649	0.474–0.889
In female						
PAS	0.612	0.145	17.789	<0.001	1.845	1.388–2.452
FT3	0.323	0.132	5.978	0.014	1.381	1.066–1.790
DR	0.294	0.136	4.720	0.030	1.342	1.029–1.751
UA	−0.002	0.001	4.851	0.028	0.998	0.997–1.000
TSHI	−0.032	0.121	6.259	0.012	0.740	0.584–0.937
In male						
PAS	0.547	0.201	7.436	0.006	1.729	1.166–2.562
Age	0.024	0.007	12.346	< 0.001	1.025	1.011–1.039
Smoking	−0.430	0.164	6.897	0.009	0.651	0.472–0.897

Abbreviations: PAS, peripheral atherosclerosis; DR, diabetic retinopathy; UA, uric acid; FT3, free triiodothyronine; TSHI, thyroid-stimulating hormone index; TNs, thyroid nodules; CI, confidence interval; OR, odd ratio; SE, standard error.

Independent Correlates of TNs by Logistic Regression Analysis

For females, TNs were served as the dependent variable including the age, duration of diabetes, FT3, UA, TSH, $TFQI_{FT4}$, TSHI, TT3RI, TT4RI, DR and PAS were considered as the independent variables according to the results of univariate analysis (Table 3). A logistic regression analysis was performed to identify the independent correlates of TNs (Table 4). After adjusting for the other variables, the analysis revealed that PAS (OR: 1.845; 95% CI: 1.388–2.452), FT3 (OR: 1.381; 95% CI: 1.066–1.790), and DR (OR: 1.342; 95% CI: 1.029–1.751) were independently related to TNs. Additionally, UA (OR: 0.998; 95% CI: 0.997–1.000) and TSHI (OR: 0.740; 95% CI: 0.584–0.937) were also independently correlates of TNs.

For males, adjusting for the age, duration of diabetes, smoking, drinking, HDL-c, TG, UA, Hb, DR and PAS, the results showed that the PAS (OR: 1.729; 95% CI: 1.166–2.562), age (OR: 1.025; 95% CI: 1.011–1.039) and smoking (OR: 0.651; 95% CI: 0.472–0.897) were independently related to TNs.

Discussion

This study demonstrated a high prevalence of TNs in euthyroid T2D patients, with a prevalence of 51.9% among the study population. This finding is consistent with previous studies reporting a prevalence of approximately 60% among T2D patients.[2] The data underscore the importance of investigating factors that influence TNs in the T2D population. A deeper understanding of these complex relationships is essential for identifying potential risk factors and developing targeted strategies for managing TNs in T2D patients.

There might be an exist association between the function of pituitary-thyroid axis and TNs, but it has not been fully clarified. Some studies showed a positive association between TSH level and TNs, as well as cancer in adults,[26] but others displayed that TSH measurement may not serve as a single effective tool to detect or exclude TNs.[27] In our study, a difference in TSH levels between TNs and NTNs groups was observed only in females. However, after adjusting for other confounding factors, this difference was no longer significant. Additionally, in contrast to previous studies,[28,29] we found that FT3 rather than FT4 was positively correlated with TNs in patients with T2D in females. The composite indices were better to reflect the dynamic variability between THS and TH than a single index. Research on the relationship between TNs and TH related indices, such as $TFQI_{FT3}$, $TFQI_{FT4}$, TSHI, TT3RI and TT4RI, has been limited in euthyroid T2D. A recent study found that $TFQI_{FT3}$ and $TFQI_{FT4}$ showed sex differences in euthyroid adults,

https://doi.org/10.2147/DMSO.S503444

and were related negatively to TNs in females.[18] Similarly, in our study, we found a significant association between low levels of $TFQI_{FT4}$, TSHI, TT3RI and TT4RI and the presence of TNs in females. However, after adjusting for other confounding factors, we observed that only TSHI, which reflected pituitary thyrotroph function, remained independently correlated with the presence of TNs. This discrepancy in results might be attribute to the different physiological states. Thus, further research should be carried out to explore the roles of the pituitary-thyroid axis function on the occurrence and progression of TNs.

Strong evidence demonstrates that females and age are strongly associated with TNs.[6,10–12,30] Our results also supported the conclusion that the prevalence of TNs was significantly increased in females. The mechanism of the sex difference in TNs was unclear, and the underlying reason might be related to the effect of oestrogen in the propagation of thyroid stem/progenitor cells which are probably involved in the origin of non-functioning TNs in females.[31] Additionally, it should be noted that our study suggested that age might have a more significant impact on TNs in male patients. Additionally, studies showed that although the prevalence of TNs increased with advancing age, such nodules had a lower risk of malignancy, whereas identified cancers were more likely to be of high-risk histology.[32,33] Therefore, it is essential to further explore the effect of age on TNs and carefully weigh the risks and benefits of the diagnosis and treatment in older adults.

In addition, there was no consensus on the association between UA and TNs. In the studies by Huang et al[34] and Li et al.[10] UA was an independent risk factor for the formation of TNs. However, in the meta-analysis by Hu et al[35] the data showed no correlation between the incidence of TNs and the presence or absence of hyperuricemia in the overall population, but revealed a bidirectional regulatory effect of UA on TNs in different genders. In the present study, we found that UA was negatively associated with TNs and may serve as protective factor for TNs in females. Therefore, further large sample studies are needed to analyze the relationships and mechanism between UA and TNs by stratified analysis.

Moreover, we found that smoking was a protective factor for TNs in males. Our finding was consistent with Cho et al study,[36] and might be due to smoking can decrease TSH secretion and its anti-estrogenic properties.[37] However, other studies inconsistent with our results, Wan et al observed that smoking was a risk factor for TNs,[38] which might be attribute to the harmful substances in tobacco smoke that could negative impact on thyroid cells.[39] Nevertheless, there is currently no consensus on the relationship between smoking and TNs, and the potential mechanisms needed to be further explored.

Finally, our results showed that the percentage of PAS was significantly higher in the TNs group than in the NTNs group, and a significant relationship existed between PAS and TNs in both females and males. Also, we found DR was an independent risk factor for TNs only in females. Unfortunately, there were few evidence to support our data. A recent study of 4696 patients with T2D showed that eye disorders and peripheral vascular disease were significantly related to TNs.[40] Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins), potent cholesterol-lowering drugs, presented multiple vascular protective actions.[41] Accumulating evidence indicated an antiproliferative effect of statins on TNs.[42–45] Overall, the specific relationship and mechanism between PAS, DR and TNs, and the preventive and therapeutic effects of statins on TNs needed to be further elaborated.

A few limitations of our study should be considered. First, the single-center design means that the study sample is limited to hospitalized euthyroid T2D patients, and thus the findings cannot be directly extrapolated to the entire diabetic population, potentially affecting their generalizability. Second, as a cross-sectional study, this research only identifies an association between thyroid hormone-related indices and TNs without establishing causality. Therefore, longitudinal or experimental studies are needed to further explore the potential pathogenic mechanisms underlying the relationship between these factors and TNs. Additionally, we only conducted a preliminary analysis of correlates of TNs, further studies should be performed to explore the effects of the above correlates on the size, morphology and pathology of TNs.

In conclusion, sex differences are evident in the relationship between TH and related indices with TNs. FT3 and TSHI were independently associated with TNs exclusively in females. These findings underscore the importance of evaluating TH and related indices, particularly in euthyroid female T2D patients, to facilitate early detection and targeted management of TNs.

Ethics Approval and Consent to Participate

All procedures were performed in accordance with ethical standards laid out in the Declaration of Helsinki. Written informed consent was obtained from all patients upon admission, explicitly stating that their medical records could be used for scientific research purposes. No patients objected to this during the study period. Furthermore, the study was approved by the Human Ethics Committee of Linyi People's Hospital (202404-H-018).

Funding

This study was funded by grants from the Postdoctoral Program of Affiliated Hospital of Jining Medical University (JYFY322152), and the Key Research and Development Program of Linyi City (2024YX004).

Disclosure

This paper has been uploaded to ResearchSquare as a preprint: https://www.researchsquare.com/article/rs-3241534/v1. All authors declare that they have no conflicts of interest.

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