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Mediating role of triglyceride-glucose index and its derivatives in the relationship between central obesity and Hashimoto thyroiditis in type 2 diabetes

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Abstract

Background Obesity and insulin resistance (IR) may be risk factors for thyroid disease, but there is no clinical-based consensus on this topic. Therefore, this study aims to evaluate the associations between the triglyceride-glucose index (TyG) and its derivatives and Hashimoto thyroiditis (HT) in type 2 diabetes mellitus (T2DM) patients, and explore the relationships between the central obesity indicators and HT risk to provide a reliable basis for the early prevention of HT.

Methods A total of 1071 T2DM patients aged ≥ 20 years were selected from a tertiary hospital in Tianjin, all of them had normal thyroid function (including free triiodothyronine, free thyroxine, total triiodothyronine, total thyroxine, and thyroid-stimulating hormone). HT was assessed via thyroid-associated antibodies and thyroid colour Doppler ultrasound. TyG and its derivatives were measured via IR. Restricted cubic spline (RCS) models, multivariable logistic regression, and receiver operating characteristic (ROC) curve analysis were used to explore the correlations and predict HT. Mediation analysis explored the mediating role of TyG and its derivatives in the associations between the central obesity indicators and HT.

Results RCS models revealed that increases in waist circumference (WC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR), TyG-WC, TyG-WHR, and TyG-WHtR were associated with increased HT risk. Logistic regression revealed that participants in the fourth quartile of TyG-WC, TyG-WHR, and TyG-WHtR had approximately 3.38 times greater HT risk (odds ratio range: 2.807 to 3.375). ROC analysis revealed that WC, WHtR, WHR, TyG-WC, TyG-WHtR and TyG-WHtR could distinguish the presence of HT. In females, the WHR had the highest predictive power, with an area under the ROC curve of 0.651 (95% confidence interval 0.611–0.691, $P < 0.001$). Mediation analysis revealed that high IR, as assessed by the TyG-body mass index (TyG-BMI), significantly mediated the effects of WC, WHtR, and WHR on the risk of HT. Among them, the TyG-BMI had the highest proportion of mediating effect of WC on HT risk, reaching 74.08%.

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Conclusion IR significantly mediates the increased risk of HT associated with central obesity. In clinical practice, WC, WHtR, WHR, TyG-WC, TyG-WHR, and TyG-WHtR serve as sensitive indicators for predicting HT risk in adult T2DM patients.

Keywords Type 2 diabetes mellitus, Central obesity, Lipid-related index, Triglyceride-glucose, Triglyceride glucose-body mass index, Adult, Hashimoto thyroiditis, Insulin resistance

Introduction

Type 2 diabetes mellitus (T2DM) is a serious chronic metabolic disorder marked by hyperglycaemia and impaired insulin function [1]. In 2021, the global number of adults with diabetes reached 536 million [2], corresponding to a prevalence of 10.5%, with projections suggesting this figure could rise to 783 million by 2045 [3]. China, among the countries with the highest incidence of diabetes, had an estimated 149 million individuals living with diabetes in 2021. Hashimoto's thyroiditis (HT) is a condition where the immune system mistakenly targets the thyroid gland, resulting in the gradual destruction of thyroid cells and the buildup of fibrotic tissue [4]. There is a high prevalence in adults around the world, and the prevalence in women is 4–7 times greater than that in men [5, 6]. Notably, although HT patients may have different thyroid function statuses at different stages, most patients usually have normal thyroid function at the time of diagnosis [7]. Studies show that individuals with T2DM have a 1.9 to 3.5 times higher risk of developing HT compared to nondiabetic individuals [8, 9], Additionally, half of those with HT also have T2DM, often accompanied by elevated insulin resistance (IR) [10]. Diabetes further intensifies the risk of HT [11]. T2DM and HT coexist, altering patients' lifestyle and dietary habits [12], increasing health burdens and socioeconomic costs [13], potentially leading to neuro-psychiatric disorders [14], and even increasing mortality risk [15]. The mechanisms by which diabetes induces HT involve complex neuroendocrine regulatory pathways, which directly induces thyroid hormone (TSH) to hypoxia-inducible factor alpha through the phosphoinositide 3-kinase/extracellular signal-regulated kinase pathway and regulates the glucose metabolism factors [16]. An increase in leptin affects the regulation of TSH, and the core role of TSH in T2DM with HT promotes the occurrence of HT.

Obesity and IR have been identified as key risk factors for T2DM [17]. Furthermore, increased obesity and visceral fat area (VFA) are closely associated with a heightened risk of HT and hypothyroidism [18, 19]. The lipid accumulation product (LAP) and VFA outperform traditional obesity indices in predicting metabolic disease risk and differentiating visceral fat from subcutaneous fat [20, 21]. The triglyceride-glucose (TyG) index, a novel IR marker, also demonstrates high effectiveness in assessing IR [22]. Research shows that IR is closely linked to the onset and progression of thyroid diseases in individuals with T2DM [23]. Additionally, the TyG index is positively linked to the risk of both hypothyroidism and subclinical hypothyroidism [13]. When combined with waist circumference (WC), waist-to-height ratio (WHtR), waist-to-hip ratio (WHR), and body mass index (BMI), the TyG index provides enhanced diagnostic value for assessing IR [24, 25]. Thus, the early detection and management of IR may demonstrate a crucial impact on preventing thyroid diseases [26]. Unfortunately, most of the current studies focus on the separate relationships between T2DM and HT [13, 27] and lack an in-depth discussion of the combined effects of the two, which leaves an important gap in the study of the relationship between T2DM and HT. Furthermore, while studies have indicated that obesity indicators and the IR index can serve as predictors of thyroid disease risk [19, 26], there is still no consensus on the most reliable indicators for predicting the risk of HT in patients. In contrast to earlier research, this study is the first to systematically compare the use of IR indicators alongside obesity indicators to predict HT risk in individuals with T2DM. This study primarily aims to evaluate the association between obesity, lipid indicators (BMI, WC, WHtR, WHR, LAP, and VFA), TyG and its associated indicators, and HT risk in patients with T2DM. Additionally, the study explores the potential mediating effects of TyG and its associated indicators on HT risk in relation to central obesity indicators (WC, WHtR, WHR). Through these analyses, the study aims to provide a solid foundation for the early prevention of HT and offer new insights into clinical prevention and treatment strategies.

Methods

Study population

This cross-sectional study involved individuals who first visited and were admitted to the Department of Endocrinology at Tianjin People's Hospital between July 2020 and January 2024. All participants provided written informed consent, and the study received approval from the Ethics Committee of Tianjin People's Hospital following the Declaration of Helsinki guidelines.

The inclusion criteria were diabetes patients aged ≥ 20 years with complete and normal thyroid function data,

including free triiodothyronine, free thyroxine, total triiodothyronine, total thyroxine, and TSH within the normal range [28–30]. Furthermore, to investigate the impact of various thyroid function states on the study results, diabetes patients aged ≥ 20 years with complete but abnormal thyroid function data (including hypothyroidism and subclinical hypothyroidism) were included in the subsequent analyses. The detailed information is provided in Supplementary Material 1. The exclusion criteria were patients with missing thyroid antibody data; patients with type 1 diabetes who were diagnosed before age 20 and treated with insulin only; those with a history of thyroid-related diseases or who had received anti-thyroid treatment; those lacking data on obesity indices, the TyG index, and its derivatives; patients who had used triglyceride-lowering drugs (including statins, fibrates, and niacin), immunosuppressants, or corticosteroids; and those with acute infections, acute diabetes complications, autoimmune diseases, moderate or severe anaemia, haematological diseases, severe hypoglycaemia, or schizophrenia. Additional exclusions included patients with an estimated glomerular filtration rate < 30, those on chronic dialysis, or those with congestive heart failure, severe pulmonary or liver dysfunction, malignancies, or familial hypertriglyceridaemia.

A total of 1071 T2DM patients were included in the analysis (as shown in Fig. 1). Patients were categorized into two groups, T2DM without HT ($n=387$) and T2DM with HT ($n=684$), on the basis of the diagnosis of HT. The diagnosis of HT was established using thyroid ultrasound results showing heterogeneous thyroid parenchyma, along with positivity for thyroid peroxidase antibody (TPOAb > 5.61 IU/mL) and/or thyroglobulin antibody (TgAb > 4.11 IU/mL) [7, 31].

Data collection

Based on the pertinent information of diabetic patients, the following clinical data were collected: age, sex, marital status, smoking and alcohol consumption habits, educational attainment, duration of diabetes, regular exercise (≥ 2 h of physical activity per week), diabetes dietary patterns (emphasizing the intake of grains and high-fibre foods), hypertension [32], lipid abnormalities [33], the use of lipid-lowering medications, and antidiabetic medications. Blood pressure for systolic (SBP) and diastolic (DBP) were measured via sphygmomanometer (AC-05C, Ling Qian, China).

After a 10–12 h overnight fast, blood samples were analysed. Fasting plasma glucose (FPG) was measured via the enzymatic colorimetric method, and insulin concentrations were assessed via electrochemiluminescence immunoassay (Roche Cobas 6000 analyser). Automated biochemical analysers (TBA-120FR, Toshiba, Japan) were used to measure uric acid (UA), total cholesterol (TC), triglyceride (TG), high/low-density lipoprotein cholesterol (HDL-C, LDL-C), blood urea nitrogen to creatinine ratio (UREA/CREA), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Glycated haemoglobin (HbA1c) was measured via an automated glycosylated protein analyser (HA-8180, ARKRAY, Japan). Thyroid function and antibody levels were assessed via an immunoluminescence analyser (Cobas-e601, Roche Diagnostics, Switzerland).

Human body measurement data and calculation

Eleven indicators related to obesity and IR were selected on the basis of previous studies [34–36], and their associations with HT risk in T2DM patients were explored. Noninvasive anthropometric measures included WC, BMI, WHtR, WHR, and VFA, whereas invasive measures included LAP and the TyG index, along with TyG combined with WC, BMI, WHtR, and WHR. Weight and height were recorded via an automatic device (DST-600, China East Garden). The VFA was assessed via body composition analyser (InBody770, Biospace, Korea). WC was measured via soft tape at the lowest point between the ribs and the iliac crest during exhalation. Hip circumference was measured at the symphysis pubis anteriorly and the greatest protuberance of the buttocks posteriorly. The specific calculation formulas for the other indices are as follows [37–43]:

$$HOMA-IR=\left[FPG\left(mg/dL\right)\times fasting\ insulin\ \left(\mu U/ml\right)\right]/405$$

$$BMI=body\ weight\left(kg\right)/height^{2}\left(m^{2}\right)$$

$$WHtR=WC(cm)/height(cm)$$

$$WHR=WC(cm)/hip\ circumference(cm)$$

$$LAP_{male}=\left[WC(cm)-65\right]\times TG(mmol/L)$$

$$LAP_{female}=\left[WC(cm)-58\right]\times TG(mmol/L)$$

$$TyG=ln\left[TG\left(mg/dl\right)\times fasting\ glucose\left(mg/dl\right)/2\right]$$

$$TyG-BMI=TyG\times BMI$$

$$TyG-WC=TyG\times WC$$

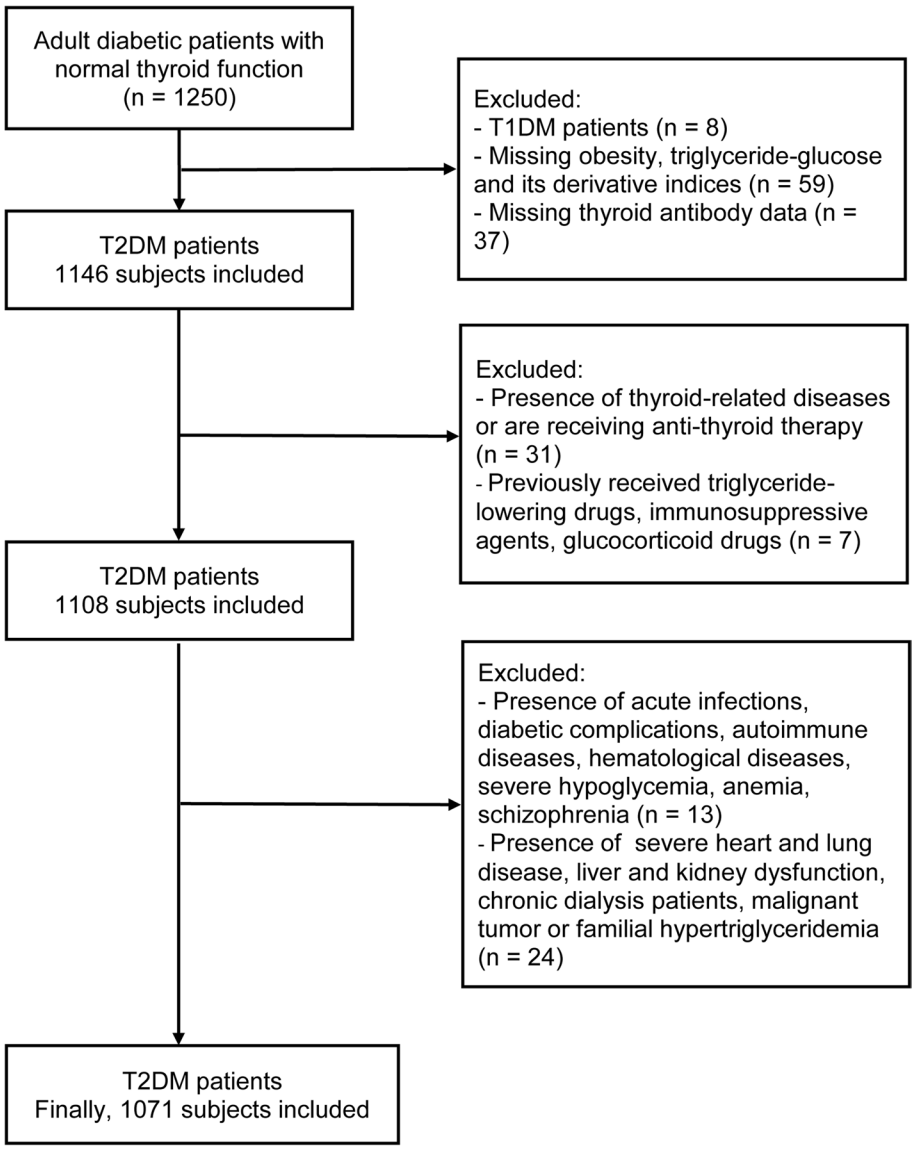

Fig. 1 The flowchart depicting the selection of participants

$$TyG - WHtR = TyG \times WHtR$$

$$TyG - WHR = TyG \times WHR$$

Statistical analysis

Data distribution normality was assessed via the Kolmogorov–Smirnov test. At baseline, continuous variables were described as either mean ± standard deviation or median (interquartile range). Categorical variables were shown as absolute numbers and percentages (%). For normally distributed data, comparisons were conducted via Student's t-test, and nonnormally distributed data were analysed via the Mann–Whitney U test. Categorical data were analyzed using the chi-square test.

To explore the independent associations between the obesity indicators, IR-related indices, and HT risk, binary logistic regression analysis was utilized to establish multiple adjustment models under different thyroid functional states. On the basis of baseline differences and other metabolic risk factors known to affect the occurrence of HT in T2DM patients [34–36, 44], a stepwise adjusted model was established: Model 1 was unadjusted, whereas Model 2 additional adjustments for sex, years of education, age, and marital status; Model 3 further considered HbA1c, diabetes duration, smoking status, alcohol use,

hypertension, dyslipidaemia, lipid-lowering medication, regular exercise, diabetic diet, UA, UREA/CREA, ALT, AST, TSH, and the homeostasis model of IR (HOMA-IR).

Sensitivity analysis was performed to account for baseline differences that could confound results and test the reliability of the findings. Initially, categorical stratified analyses were performed for variables such as marital status, drinking status, hypertension, and diabetes dietary control. Owing to the insufficient sample size in the unmarried category, stratification was not performed to ensure adequate statistical power. For continuous variables, including LDL-C, UREA/CREA, AST, and TSH, stratification was done into tertiles. For all stratified analyses, multivariable-adjusted logistic regression models were employed. TyG- and the TyG-derived IR-related indices were categorized into quartiles, and the ORs with 95% CIs for HT were calculated. Two models were employed: Model 1 was unadjusted, whereas Model 2 incorporated further adjustments for demographic characteristics, baseline differences, and other metabolic risk factors, excluding the stratified variables. Additionally, a stratified analysis by sex was conducted to assess the differences in outcomes between the sexes. In this analysis, Model 3 further considered the use of antidiabetic medications.

To explore potential nonlinear relationships between the obesity indicators, IR-related indices, and HT risk, restricted cubic spline (RCS) models were constructed via the rms package in the RCS models on the basis of generalized linear models, with the data fit via smooth curves. The number and positions of the knots were selected on the basis of the Akaike information criterion and data distribution characteristics to optimize model fit and balance complexity. The model adjusts all the above confounding factors.

Receiver operating characteristic (ROC) curves were generated, and areas under the curve (AUCs) computed to assess the predictive ability of obesity and IR indices for HT. Separate ROC curves and AUC values were calculated by sex, where higher AUC values indicate better predictive performance. In addition, to confirm whether obesity and IR-related indicators significantly improved the predictive ability of HT, the DeLong test was utilized to assess the AUCs across various models.

To explore whether IR can explain the effect of abnormal fat metabolism between central obesity and HT, mediation analyses were conducted under different thyroid functional states to assess the potential mediating role of the IR-related indices. On the basis of the binary logistic regression model, the mediation package in R and the bootstrap method of 1000 repetitions were used for mediation analysis. The total effect of the central obesity index on HT was divided into the direct effects of WC, WHtR, and WHR and the indirect effects from TyG and TyG-BMI, with the mediation ratio and significance were calculated. Multivariable adjustment models were established: Model 1 was unadjusted, while Model 2 accounted for all the above confounding factors, and additionally took into account the impact of antidiabetic medications.

Statistical analyses were carried out via SPSS software (V.25) and R (Version 4.3.2). A significance threshold of $P < 0.05$ (two-tailed) was applied for all tests.

Results

Clinical baseline characteristics

This study included 1071 hospitalized patients with T2DM and normal thyroid function were included, among whom 684 (63.9%) were diagnosed with HT (as shown in Table 1). The study population was stratified into a control group and an HT group according to the presence or absence of HT. In terms of demographic characteristics, compared with those in control group, more patients in HT group were married ($P < 0.05$). In terms of clinical indicators and personal life characteristics, the HT group was more likely to drink alcohol and follow a diabetic diet (all <

Table 1 Clinical characteristics of participants

Characteristics	Control group (*n* = 387, 36.1%)	HT group (*n* = 684, 63.9%)	*P* Value
Age (years)	62.27 ± 7.41	62.04 ± 7.92	0.638
Sex-male	215(55.6%)	355(51.9%)	0.249
Married-yes	363(93.8%)	597(87.3%)	< 0.001*
Current smoking-yes	123(31.8%)	214(31.30%)	0.260
Current drinking-yes	88(22.7%)	203(29.7%)	0.023*
Education (years)	10.74 ± 3.27	10.53 ± 2.72	0.295
Duration of diabetes (years)	7(2,15)	7(1,14)	0.165
SBP (mmHg)	131.73 ± 15.85	133.71 ± 12.06	0.033*
DBP (mmHg)	79.23 ± 8.83	79.41 ± 8.63	0.753
Regular exercise-yes	209(54.0%)	554(81.4%)	0.956
Diabetic dietary pattern-yes	276(71.3%)	434(63.8%)	0.004*
Hypertension-yes	263(68%)	465(68%)	0.994
Dyslipidemia-yes	211(54.5%)	361(52.9%)	0.599
Take lipid-lowering drugs-yes	40(10.3%)	77(11%)	0.773
Take hypoglycemic drugs-yes	364(94.1%)	622(90.9%)	0.069
FPG (mmol/L)	8.61 ± 2.83	8.54 ± 3.22	0.742
HbA1C (%)	8.93 ± 1.99	8.83 ± 2.11	0.442
TC (mmol/l)	4.74(4.09,5.53)	4.83(4.14,5.58)	0.429
TG (mmol/l)	1.63(1.16,2.44)	1.52(1.12,2.18)	0.112
HDL-C (mmol/L)	1.20 ± 0.30	1.44 ± 6.73	0.499
LDL-C (mmol/L)	3.11 ± 0.83	2.99 ± 0.87	0.024*
UA (μmol/L)	294.86 ± 82.33	298.33 ± 83.18	0.511
UREA/CREA	22.04 ± 7.05	23.61 ± 11.22	0.013*
ALT (U/L)	19.4(13.7,30.5)	18.2(13.44,27.08)	0.164
AST (U/L)	16(13.1,20.9)	18.4(14.3,2.24)	< 0.001*
Insulin (mU/L)	14.92 ± 18.27	14.25 ± 14.97	0.603
TSH (μIU/mL)	1.79 ± 0.89	2.02 ± 0.98	< 0.001*
HOMA-IR	5.86 ± 6.98	5.69 ± 5.95	0.729
BMI (kg/m^2)	25.77 ± 3.55	26.04 ± 3.50	0.229
WC (cm)	89.10 ± 10.16	93.17 ± 9.58	< 0.001*
WHtR	0.54 ± 0.06	0.56 ± 0.06	< 0.001*
WHR	0.92 ± 0.07	0.95 ± 0.07	< 0.001*
LAP	44.77(27.14,70.00)	48.72(31.50,76.23)	0.008*
VFA	100.71 ± 29.55	104.80 ± 29.14	0.064
TyG	9.32 ± 0.73	9.26 ± 0.77	0.205
TyG-BMI	240.51 ± 39.34	241.72 ± 41.52	0.640
TyG-WC	831.26 ± 118.03	864.47 ± 125.76	< 0.001*
TyG-WHtR	5.00 ± 0.69	5.21 ± 0.74	< 0.001*
TyG-WHR	8.56 ± 0.94	8.85 ± 1.03	< 0.001*

Data are presented as means ± standard deviations or medians (interquartile ranges) for continuous data and numbers (%) for categorical data

Abbreviation: HT Hashimoto thyroiditis, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *HbA1c* hemoglobin A1c, *TC* total cholesterol, *TG* triglycerides, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *UA* uric acid, *UREA/CREA* urea nitrogen related to creatinine, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *TSH* thyroid stimulating hormone, *HOMA-IR* homeostasis model assessment of IR, *BMI* body mass index, *WC* waist circumference, *WHtR* waist to height ratio, *WHR* waist to hip ratio, *LAP* lipid accumulation product, *VFA* visceral fat area, *TyG* triglyceride glucose index

* *P* <0.05

Independent associations between IR, obesity indices and HT risk

The present study employed multivariable adjusted binary logistic regression analysis to explore the independent associations among 11 obesity and IR-related indicators with HT in patients with T2DM, as depicted in Fig. 3. These indicators were split into quartiles, using the first quantile as the reference. In unadjusted model, TyG-WC, TyG-WHtR, TyG-WHR, WC, WHtR, WHR, LAP, and VFA were significantly positively correlated with HT risk when they were in the fourth quantile compared with the first quantile (all $P < 0.05$). In Model 2, demographic factors, including sex, age, marital status, and education level were adjusted. Model 3 made additional adjustments for baseline differences (alcohol consumption, hypertension, diabetic dietary control, dyslipidaemia, UREA/CREA, AST, and TSH) and other metabolic risk factors (HbA1c, diabetes duration, smoking status, use of lipid-lowering drugs, regular exercise, UA, ALT, and HOMA-IR). After these adjustments, the quartiles of TyG-WC, TyG-WHtR, TyG-WHR, WC, WHtR, WHR, and VFA remained significantly associated with an increased HT risk. In Model 3, for TyG-WC (OR = 2.807), TyG-WHtR (OR = 2.535), TyG-WHR (OR = 3.375), WC (OR = 3.011), WHtR (OR = 3.351), WHR (OR = 4.466), and VFA (OR = 1.990), participants in the fourth quartile had a 2 to 4.5 times greater risk of HT than the first quartile. Furthermore, among patients with HT with abnormal thyroid function (including hypothyroidism and subclinical hypothyroidism), when TyG-WC, TyG-WHtR, TyG-WHR, and LAP were in the fourth quartile, they were significantly linked to an increased HT risk ($P < 0.05$, as shown in Figure S1).

A sensitivity stratified analysis was conducted to account for potential confounding effects from the baseline differences and to evaluate the robustness of the results (as shown in Supplementary Material 1). The findings show that among married participants, nondrinkers, diabetic participants, and those with or without hypertension, as well as across different tertiles of LDL-C, UREA/CREA, AST, and TSH levels, the correlations between IR-related indices and HT remained significant after model adjustments (all $P < 0.05$). These findings indicate that the connection between the IR-related indices and increased HT risk remained consistent and robust across different participant subgroups, and were not significantly influenced by these baseline characteristics. Notably, the sensitivity analysis stratified by sex revealed that in both males and females, regardless of whether Model 2 (which accounted for demographic characteristics and metabolic risk factors) or Model 3 (which was further adjusted for antidiabetic

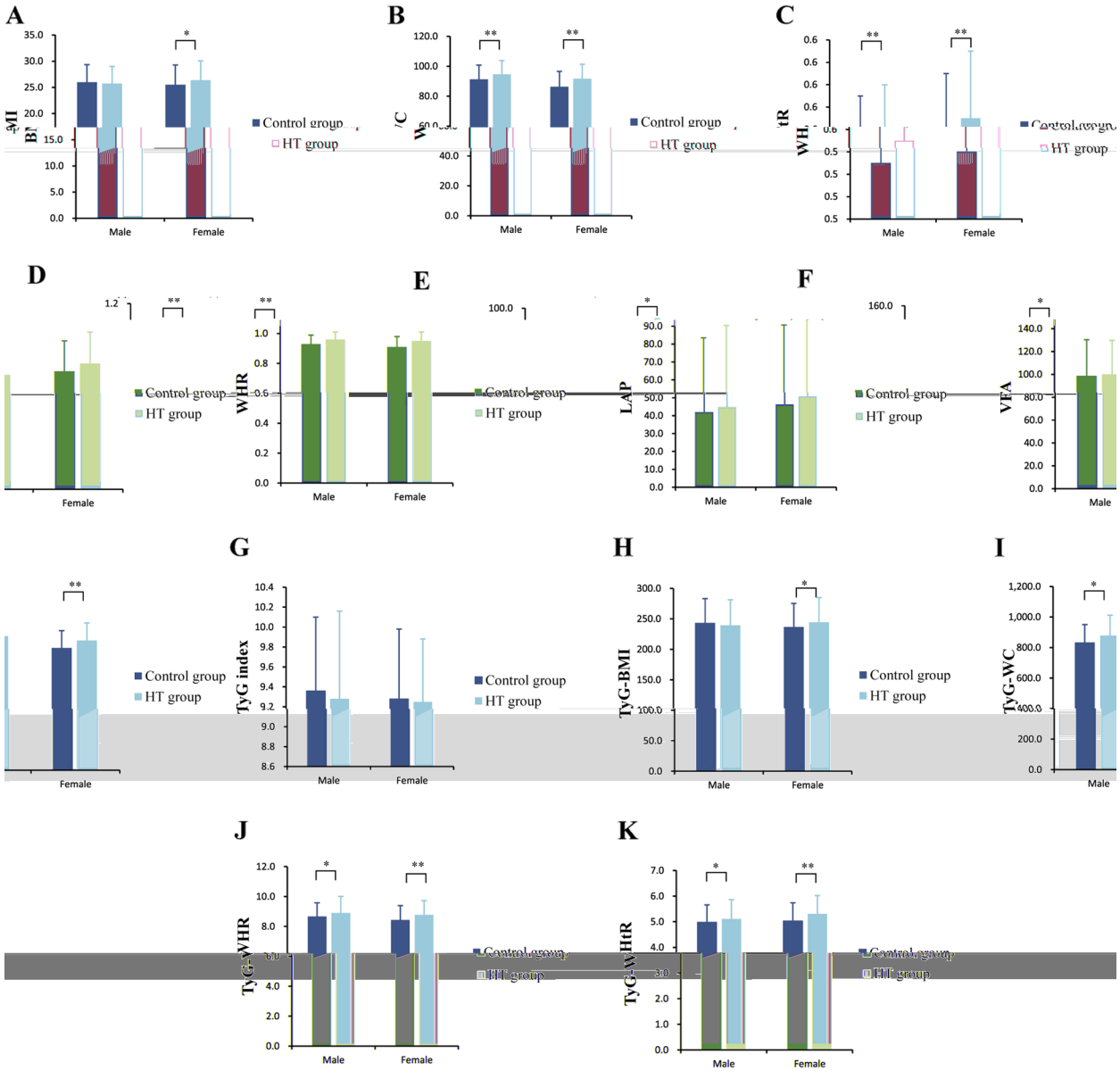

Fig. 2 Comparison of obesity, triglyceride-glucose and its derivative indices between the two groups by sex stratification. NC, normal cognitive; CI, cognitive impairment; SD, standard deviation. **A** BMI, body mass index; **B** WC, waist circumference; **C** WHtR, waist-to-height; **D** WHR, waist to hip ratio; **E** LAP, lipid accumulation product; **F** VFA, visceral fat area; **G** TyG index, triglyceride glucose index; **H** TyG-BMI = TyG × BMI; **I** TyG-WC = TyG × WC; **J** TyG-WHR = TyG × WHR; **K** TyG-WHtR = TyG × WHtR; Column graph with error bar: top of the column represents the mean (**A**, **B**, **C**, **D**, **F**, **G**, **H**, **I**, **J**, **K**) or median **E**; the error bar represents SD (**A**, **B**, **C**, **D**, **F**, **G**, **H**, **I**, **J**, **K**) or interquartile range (**E**). * $P < 0.05$, ** $P < 0.001$; all P values for Student's t-test

medications) was used, the fourth quartile of the IR-related indices was significantly linked to a higher HT risk compared to the first quartile (all $P < 0.05$).

Nonlinear associations between obesity indices, IR-related indices, and HT risk

This study employed the RCS model to investigate the potential nonlinear associations between obesity, the IR indices, and HT in T2DM patients, adjusting for covariates, including demographic factors, baseline differences, and other metabolic risk factors, as illustrated in Fig. 4. Consistent with the logistic regression findings, the RCS model's dose–response relationships indicated significant positive correlations between the obesity-related indices (WC, WHtR, WHR, VFA) and the IR indices with HT risk. As WC, WHtR, WHR, VFA, TyG-WC, TyG-WHR, and TyG-WHtR increased, there was a notable linear increase in HT risk (all P overall ≤ 0.05). Slightly diverging from

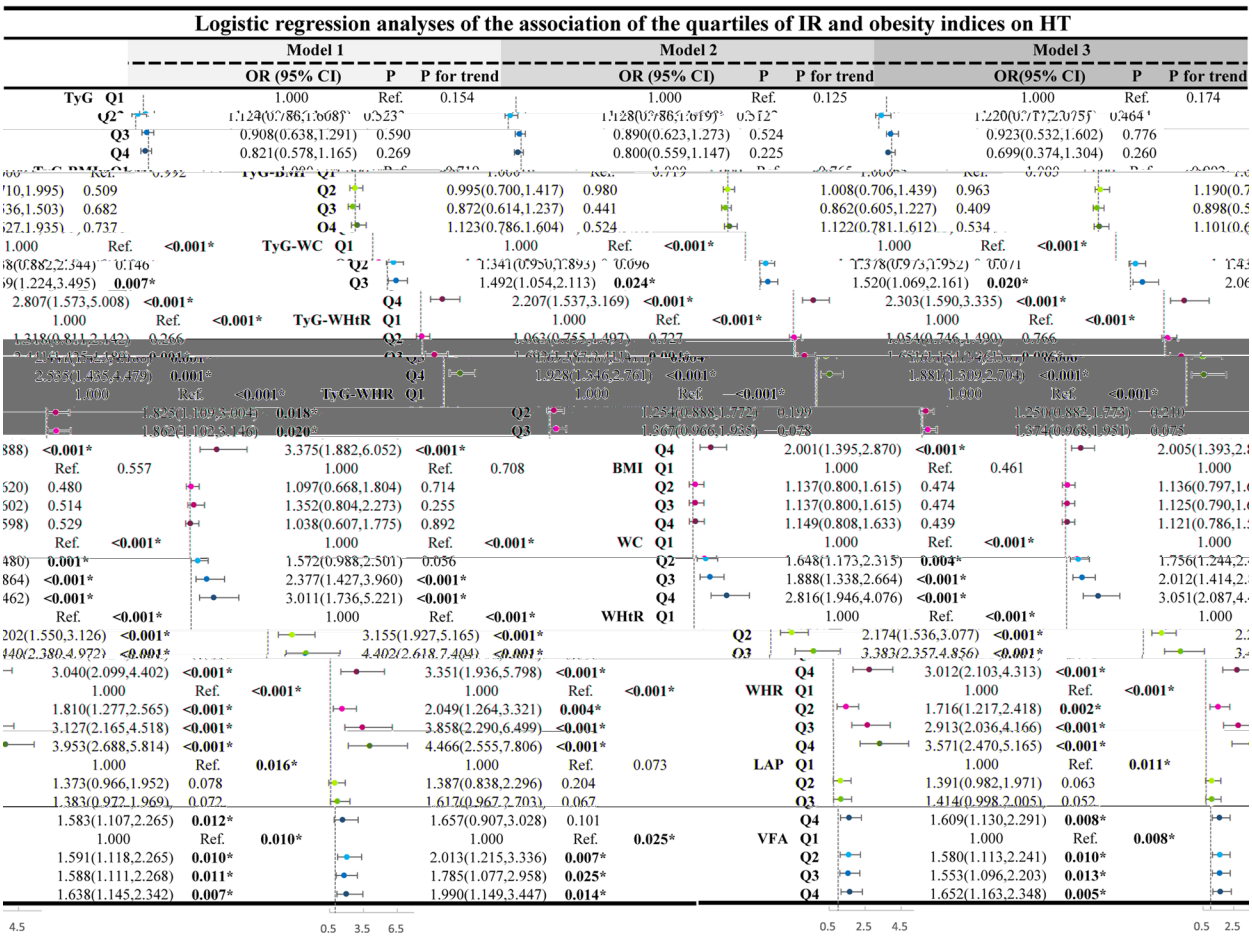

Fig. 3 Logistic regression analysis of quartiles of IR and obesity indices on HT risk. OR, Odds ratio; 95%CI, 95% confidence interval; BMI, body mass index; WC, waist circumference; WHtR, waist-to-height; WHR, waist to hip ratio; LAP, lipid accumulation product; VFA, visceral fat area; TyG, triglyceride glucose index; TyG-BMI = TyG × BMI; TyG-WC = TyG × WC; TyG-WHR = TyG × WHR; TyG-WHtR = TyG × WHtR; Model 1 were not adjusted. Model 2 were adjusted for age, sex, years of education and married. Model 3 were further adjusted for current smoking, current drinking, hemoglobin A1c, duration of diabetes, dyslipidemia, hypertension, take lipid-lowering drugs, regular exercise, diabetic dietary pattern, uric acid, urea nitrogen related to creatinine, alanine aminotransferase, aspartate aminotransferase, thyroid stimulating hormone, homeostasis model assessment of IR. * $P < 0.05$

the logistic regression results, the WHtR exhibited an "S"-shaped association with HT risk among T2DM patients (P nonlinear = 0.007). When the WHtR was < 0.55, HT risk rose as the TyG index increased; however, when the WHtR exceeded 0.55, the rate of increase decreased, indicating a relatively stable level of risk.

Evaluation of the predictive capacity of IR and the obesity indicators for HT risk

This research evaluated the predictive capacity of eleven obesity and IR indicators for HT among patients with T2DM stratified by sex (as shown in Fig. 5 and Table 2). Among female participants, BMI, WC, WHtR, WHR, LAP, VFA, TyG-WC, TyG-WHR, and TyG-WHtR were predictive of HT ($P < 0.05$), with AUCs ranging from 0.562 to 0.650. The WHR had the highest AUC (AUC: 0.650; $P < 0.001$) and had a cut-off value of 0.91 determined by maximizing the Youden index (0.271). In male participants, WC, WHtR, WHR, and their associated indicators of TyG were predictive of T2DM-associated HT (all $P < 0.05$), with AUCs ranging from 0.560 to 0.651. Similar to females, WHR had the highest AUC (0.651). Importantly, when predicting HT in male and female T2DM patients, WC, WHtR, and WHR presented higher AUC values than did the other IR indices.

Mediating role of the IR-related indices on the impact of the central obesity indices on HT risk

To further explore the pathogenic mechanisms and potential cascading effects of IR on the relationship

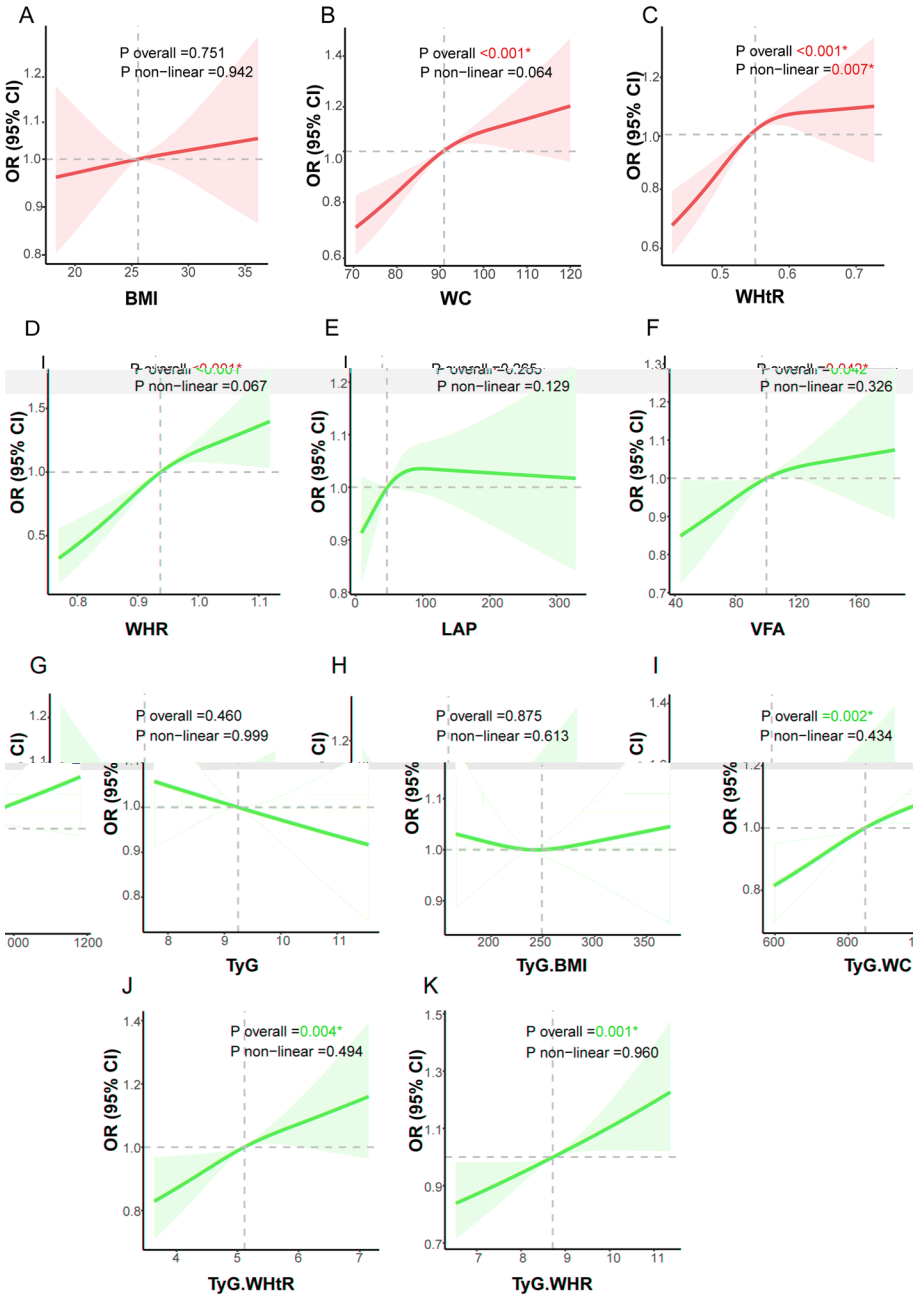

Fig. 4 Nonlinear analysis of IR and obesity indices with HT risk in T2DM patients. Nonlinear associations obesity, triglyceride-glucose and its derivative indices with Hashimoto thyroiditis risk in T2DM patients were explored using restricted cubic spline (RCS) models and fitted with smooth curves. **A** BMI, body mass index; **B** WC, waist circumference; **C** WHtR, waist-to-height; **D** WHR, waist to hip ratio; **E** LAP, lipid accumulation product; **F** VFA, visceral fat area; **G** TyG index, triglyceride glucose index; **H** TyG-BMI = TyG × BMI; **I** TyG-WC = TyG × WC; **J** TyG-WHR = TyG × WHR; **K** TyG-WHtR = TyG × WHtR. The models were adjusted for age, sex, years of education, married, current smoking, current drinking, hemoglobin A1c, duration of diabetes, dyslipidemia, hypertension, take lipid-lowering drugs, regular exercise, diabetic dietary pattern, uric acid, urea nitrogen related to creatinine, alanine aminotransferase, aspartate aminotransferase, thyroid stimulating hormone, homeostasis model assessment of IR.* $P < 0.05$

between obesity and HT, mediation analyses were conducted under different thyroid functional states, as depicted in Fig. 6. IR-related indices were utilized as mediators, distinguishing the total effects of the central obesity indices on HT into direct effects and the mediating effects of IR indices. In patients with normal thyroid function and HT, a significant mediating effect of TyG-BMI on the relationship between central obesity indices

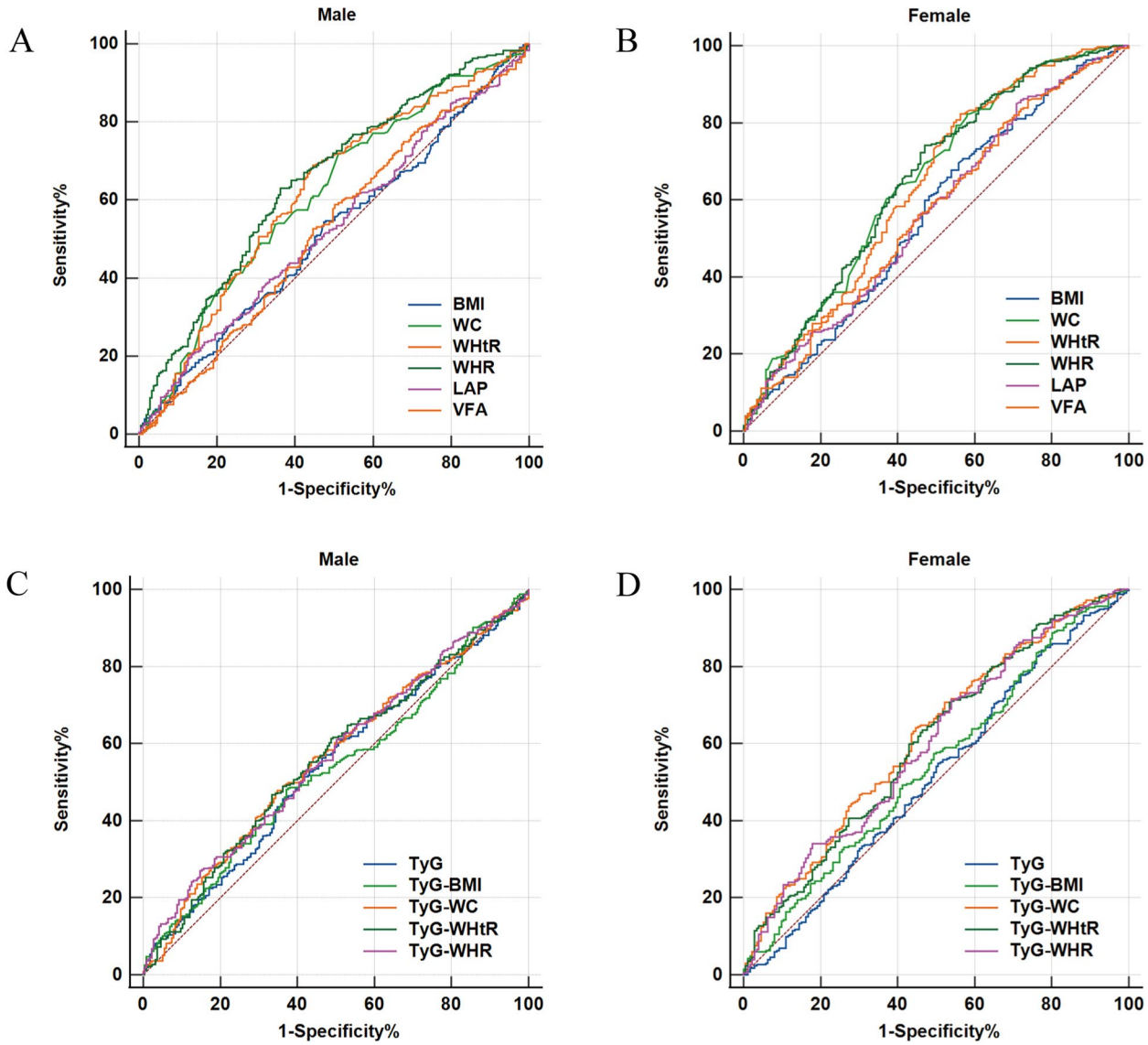

Fig. 5 ROC curves of IR and obesity indices for predicting HT in T2DM by sex. A ROC curves of obesity and lipid-related indices in males; B ROC curves of obesity and lipid-related in females. C ROC curves of the triglyceride-glucose and its derivative indices in males; D ROC curves of the triglyceride-glucose and its derivative indices in females. BMI, body mass index; WC, waist circumference; WHtR, waist-to-height; WHR, waist to hip ratio; LAP, lipid accumulation product; VFA, visceral fat area; TyG, triglyceride glucose index; TyG-BMI = TyG × BMI; TyG-WC = TyG × WC; TyG-WHR = TyG × WHR; TyG-WHtR = TyG × WHtR

on HT was observed, regardless of whether Model 1 (without adjustment for confounders) or Model 2 (which accounted for demographic variables, antidiabetic medications, and other metabolic risk factors) was used, with all mediation effect *P* values < 0.05. The adjusted mediation proportions ranged from 2.98% to 74.08%, with the highest mediation proportion of TyG-BMI noted in the relationship between WC and HT, reaching 74.08%. Additionally, in both Model 1 and Model 2, when the IR-related indices were considered as mediators, WC, WHtR, and WHR had a significant positive total effect on HT (all total effect *P* values < 0.001), which was primarily mediated by their direct effects (all direct effect *P* values < 0.001). Notably, in HT patients with abnormal thyroid function (including those with hypothyroidism and subclinical hypothyroidism), similar results were also observed. Regardless of whether the model was adjusted, the TyG-BMI demonstrated a significant mediating impact on how central obesity indices relate to HT (all mediation effect *P* values < 0.05).

Table 2 ROC analysis of IR and obesity indices for predicting HT

Indices	AUC (95% CI)	Cut-off	Sens. (%)	Spec. (%)	Youden Index	*P* value
Male						
BMI	0.518(0.476,0.559)	25.45	54.37	52.56	0.069	0.473
WC	0.615(0.574,0.655)	89.80	71.83	48.84	0.207	< 0.001*
WHtR	0.619(0.578,0.659)	0.53	69.01	55.35	0.244	< 0.001*
WHR	0.651(0.611,0.691)	0.94	63.10	63.72	0.268	< 0.001*
[a]LAP	0.530(0.488,0.571)	85.25	20.56	86.51	0.071	0.231
[a]VFA	0.526(0.484,0.568)	92.74	58.87	49.77	0.086	0.303
TyG	0.541(0.499,0.583)	9.19	51.55	58.60	0.102	0.095
TyG-BMI	0.532(0.490,0.573)	231.85	48.17	62.79	0.110	0.194
TyG-WC	0.562(0.520,0.603)	882.65	47.89	65.12	0.130	0.012*
TyG-WHtR	0.560(0.518,0.601)	5.18	46.76	66.51	0.133	0.015*
TyG-WHR	0.565(0.523,0.606)	9.50	27.04	85.12	0.122	0.007*
Female						
BMI	0.562(0.517,0.606)	24.39	70.82	43.02	0.138	0.025*
WC	0.649(0.605,0.691)	83.30	82.37	41.86	0.242	< 0.001*
WHtR	0.635(0.591,0.677)	0.52	82.37	43.60	0.260	< 0.001*
WHR	0.650(0.607,0.692)	0.91	74.16	52.91	0.271	< 0.001*
[a]LAP	0.567(0.523,0.611)	29.76	85.11	29.07	0.142	0.014*
[a]VFA	0.569(0.524,0.612)	88.41	79.94	32.56	0.125	0.012*
TyG	0.514(0.470,0.559)	9.83	84.19	22.67	0.069	0.603
[b]TyG-BMI	0.544(0.500,0.589)	202.28	88.75	19.77	0.085	0.104
TyG-WC	0.617(0.573,0.660)	804.98	64.13	55.23	0.194	< 0.001*
TyG-WHtR	0.604(0.560,0.647)	4.92	70.82	46.51	0.17	< 0.001*
TyG-WHR	0.600(0.556,0.644)	8.22	71.43	45.93	0.174	< 0.001*

ROC receiver operating characteristic, *AUC* areas under the ROC curve, *CI* confidence interval, *Sens* sensitivity, *Spec* specificity, *BMI* body mass index, *WC* waist circumference, *WHtR* waist-to-height, *WHR* waist to hip ratio, *LAP* lipid accumulation product, *VFA* visceral fat area, *TyG* triglyceride glucose index, *TyG-BMI* TyG × BMI, *TyG-WC* TyG × WC, *TyG-WHR* TyG × WHR, *TyG-WHtR* TyG × WHtR

[a] Statistically significant differences were observed between the AUC of obesity-related indicators and LAP, VFA

[b] Statistically significant differences were observed between the AUC of the triglyceride-glucose derivative indices and TyG-BMI

(*P* values for the DeLong test were < 0.05) * *P* < 0.05

Discussion

This study employed various models to analyze the associations between obesity indices (WC, WHtR, WHR, BMI), lipid-related indices (LAP, VFA), and IR-related indices with HT risk in patients with T2DM. Multivariable-adjusted logistic regression and nonlinear analysis revealed a linear increase in HT risk with increasing WC, WHtR, WHR, VFA, TyG-WC, TyG-WHtR, and TyG-WHR. Sensitivity analysis confirmed the robustness of these associations across various subgroups. ROC curve analysis indicated that obesity-related indices (WC, WHtR, WHR) were better predictors of HT risk than the TyG-derived indices were, with the WHR achieving the highest AUC of 0.651. These results suggest that visceral fat accumulation significantly increases HT risk in T2DM patients. Mediation analysis further revealed that the TyG-BMI significantly mediated the effects of the central obesity indices (WC, WHtR, WHR) on HT risk. These findings emphasize the critical role of IR in connecting abnormal adipose metabolism to the risk of HT.

Previous studies have explored the relationships among obesity, IR, and HT, primarily focusing on distinct thyroid disease cohorts. For instance, Song et al.'s meta-analysis emphasized that obesity is a major factor in increasing HT risk [45]. Similarly, a cross-sectional study conducted in Turkey found a strong association between IR and HT [46]. Additionally, a study involving 47,710 participants reported a substantial increase in hypothyroidism risk with increased TyG index values [44]. This study focused on a T2DM population with a relatively high risk of HT. These findings reveal a notable association between obesity indices (WC, WHtR, WHR) and novel IR metrics (TyG-WC, TyG-WHtR, TyG-WHR), which correlate with a heightened risk of HT across varying thyroid function statuses. These results align with previous research indicating that obesity and IR disrupt glucose metabolism

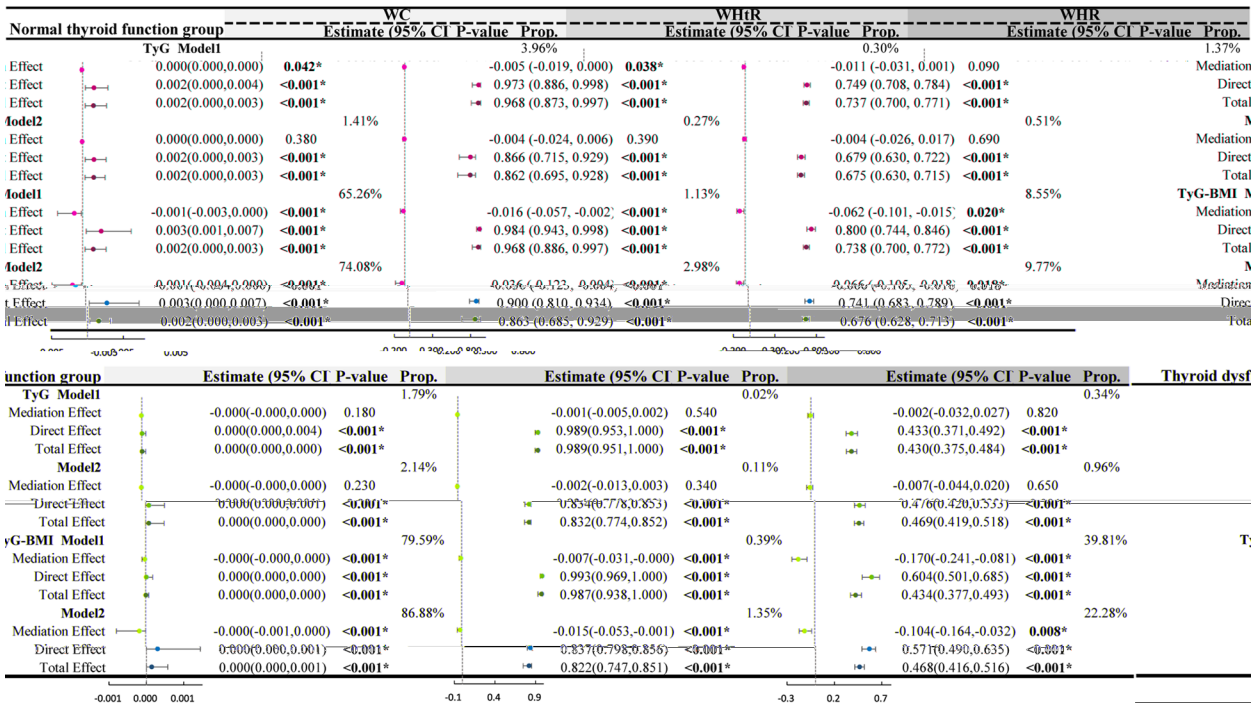

Fig. 6 Mediating role of IR-related indices in the impact of central obesity indices on HT risk. BMI, body mass index; WC, waist circumference; WHtR, waist-to-height; WHR, waist to hip ratio; LAP, lipid accumulation product; VFA, visceral fat area; TyG, triglyceride glucose index; TyG-BMI = TyG × BMI; TyG-WC = TyG × WC; TyG-WHR = TyG × WHR; TyG-WHtR = TyG × WHtR. Mediation analysis was conducted using the triglyceride -glucose and its four derivative indices—TyG, TyG-BMI, TyG-WC, TyG-WHR, TyG-WHtR—as mediators. The total effect of central obesity-related indices (WC, WHtR and WHR) on Hashimoto thyroiditis was divided into direct effects and mediation effects through the triglyceride-glucose and its derivative indices. The mediation proportion and statistical significance were calculated. Model 1 was unadjusted. Model 2 was adjusted for age, sex, years of education, married, current smoking, current drinking, hemoglobin A1c, duration of diabetes, dyslipidemia, hypertension, take lipid-lowering drugs, regular exercise, diabetic dietary pattern, uric acid, urea nitrogen related to creatinine, alanine aminotransferase, aspartate aminotransferase, thyroid stimulating hormone, homeostasis model assessment of IR, take hypoglycemic drugs. * $P < 0.05$, ** $P < 0.001$

and haemodynamics, impair the physiological insulin response, affect thyroid hormone regulation, and ultimately contribute to HT [16]. Recent studies further indicate that patients with hypothyroidism typically present elevated levels of inflammatory markers associated with insulin IR. Moreover, obesity can worsen thyroid dysfunction through mechanisms such as elevated leptin levels and reduced adiponectin levels, which may, in turn, contribute to the development of IR [47, 48]. This study further substantiates the impact of obesity and IR on HT in T2DM patients, emphasizing the critical importance of long-term interventions for this high-risk population.

BMI reflects overall obesity, while WC, WHtR, and WHR are indicators of abdominal obesity. Previous studies have established an independent link between higher WC, WHtR, and WHR and an increased risk of thyroid disease, particularly hypothyroidism [49, 50]. Consistent with these findings, this study observed that patients with HT exhibited higher WC, WHtR, and WHR. Multivariable-adjusted analyses using the RCS model further revealed a linear relationship between increases in WC, WHtR, and WHR and the heightened risk of HT in patients with T2DM. Thus, abdominal obesity indices (WC, WHtR, WHR) may serve as important markers for assessing HT risk in T2DM patients.

The pathogenesis of obesity is closely related to the total fat content and distribution, particularly the correlation between visceral fat and IR [51], which is widely acknowledged as a major risk factor for obesity-related complications [52]. The TyG index is increasingly recognized as a novel marker for evaluating IR and related disease risks [22], showing strong associations with nonalcoholic fatty liver disease (NAFLD), diabetes, and thyroid disorders [53, 54]. Studies by Zhang and Kim et al. indicate a significant association between the TyG index and hypothyroidism, identifying it as a risk factor for thyroid dysfunction [44, 55]. Given the pivotal role of IR in obesity pathophysiology, combining TyG with obesity indicators offers notable advantages for disease risk assessment [24, 25]. This study demonstrated that in T2DM patients, elevated levels of TyG-WC, TyG-WHR, and TyG-WHtR are linearly correlated with a greater risk

of HT. Additionally, TyG-BMI acts as a pivotal mediator in connecting central obesity and HT risk. Furthermore, extensive meta-analyses, along with multiple longitudinal and cross-sectional studies, suggest that assessing IR using the TyG index and HOMA-IR may be linked to increased risks of hypothyroidism, thyroid dysfunction, and HT [44, 56, 57]. Therefore, IR may provide a potential explanation for the abnormal fat metabolism associated with obesity and the heightened risk of HT in patients with T2DM.

Previous studies have traditionally focused on the relationships among individual TyG indices, obesity markers, and the risk of thyroid diseases, yet comparative analyses of the ability of multiple TyG indices and obesity markers to predict outcomes have been limited. ROC curve analyses revealed the significant predictive efficacy of the central obesity indicators (WC, WHtR, WHR) and TyG-derived indices (TyG-WC, TyG-WHR, TyG-WHtR) for assessing HT risk in T2DM patients. This finding aligns with previous research. For example, Malek et al. found that TyG-WHtR is a key predictor of NAFLD [34], whereas Zhou et al. demonstrated that WC, WHtR, TyG-WC, and TyG-WHtR effectively predict hyperuricaemia risk in young adults [58]. This study is the pioneering investigation into the predictive capability of obesity markers and TyG-derived indices for assessing HT risk in patients with T2DM. The results revealed that obesity-related indicators, especially the WHtR, significantly improved the predictive ability. These findings indicate that visceral fat accumulation could be a key factor contributing to the heightened risk of HT in T2DM patients, especially in the presence of IR and abnormal fat distribution.

Several studies have shown that impaired insulin signalling in diabetes mellitus often leads to reduced glucose metabolism in adipocytes and muscles [59], as well as a downregulation of glucose transporter type 4 expression in fat cells, thereby exacerbating IR and obesity risk [60]. Furthermore, adipose tissue functions as an endocrine organ, releasing multiple molecules that influence energy balance and glucose homeostasis, further complicating the regulation of insulin sensitivity in diabetic patients [61]. This study underscores the importance of employing obesity and IR-related indicators for a thorough prediction of HT risk in T2DM patients. The findings further suggest that effective diabetes management should take into account both obesity and IR factors to help reduce the risk of HT.

Study strengths and limitations

This study provides important insights into the links between IR, central obesity, and HT risk in patients with T2DM, deepening our understanding of how metabolic factors impact HT status in this group. However, the study has certain limitations. Primarily, being a single-center cross-sectional study restricts its ability to draw causal inferences. Second, since the sample was derived from a specific population in northern China, the results may not be universally applicable. Although the focus was on T2DM patients with normal thyroid function, the relationship between IR and HT risk could be evaluated more comprehensively through supplementary analysis of patients with hypothyroidism and subclinical hypothyroidism. Future long-term intervention studies and multicentre cohort studies are essential to develop more effective intervention strategies.

Conclusion

This study found that central obesity indices (WC, WHtR, WHR) and IR-related indices (TyG-WC, TyG-WHtR, TyG-WHR) are independently linked to an elevated HT risk in patients with T2DM. Notably, the IR and central obesity-related indices demonstrated higher sensitivity and accuracy in identifying HT risk. Additionally, the TyG-BMI mediates the relationship between central obesity and HT risk. The clinical relevance of this study lies in identifying IR and central obesity assessments as important risk prediction tools for patients with HT, particularly those with T2DM. This finding will support risk stratification and the development of personalized management strategies in clinical practice.

Abbreviations

TyG	Triglyceride glucose
BMI	Body mass index
WC	Waist circumference
WHtR	Waist-to-height
WHR	Waist to hip ratio
LAP	Lipid accumulation product
VFA	Visceral fat area
IR	Insulin resistance
HOMA-IR	Homeostasis Model Assessment
HT	Hashimoto thyroiditis
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c
TC	Total cholesterol
TG	Triglycerides
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
UA	Uric acid
UREA/CREA	Urea nitrogen related to creatinine
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
TSH	Thyroid stimulating hormone

Supplementary Information

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Supplementary Material 1.

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Not applicable.

Authors' contributions
The project was jointly conceptualized by Y-LW and J-NL, who also made significant contributions to the project reported by the project. The research design, statistical analysis, data visualization and majority of the writing was performed by Y-JZ and C-YL. The interpretation of results and revised of the manuscript was undertaken by J-BL and H-NQ. FW, J-BL and H-NQ perform data extraction, collection and management. All authors have read and approved the published version of the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study followed the ethical principles stipulated in the 'Helsinki Declaration 'and was approved by the institution. All protocols involving human subjects were reviewed by the Tianjin Union Medical Center Council. Before the study began, all subjects signed informed consent.

Consent for publication
All authors have agreed to submit the final manuscript and take responsibility for all aspects of the work. This manuscript has not been published elsewhere or is under consideration for publication.

Competing interests
The authors declare no competing interests.

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