Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Association Between Thyroid Hormone Sensitivity and Peripheral Arterial Disease in Euthyroid Patients with Type 2 Diabetes

Yongjian Ye[1,*], Dandan Liu[2,*], Yu Hang[1], Haitao Qian[3], Junfei Gu[1]

[1]Department of Endocrinology, The Second Affiliated Hospital of Wannan Medical College, Wuhu, Anhui, People's Republic of China; [2]Department of Neurology, the First Affiliated Hospital of Wannan Medical College, Wuhu, Anhui, People's Republic of China; [3]Wannan Medical College, Wuhu, Anhui, People's Republic of China

*These authors contributed equally to this work

Correspondence: Junfei Gu, Department of Endocrinology, The Second Affiliated Hospital of Wannan Medical College, Wuhu, Anhui, 230000, People's Republic of China, Email drgu9999@wnmc.edu.cn

Purpose: This study explored the relationship between thyroid hormone sensitivity and peripheral arterial disease (PAD) in type 2 diabetes mellitus (T2DM) patients with euthyroid, in order to identify potential factors for preventing PAD.

Patients and Methods: A retrospective examination was conducted on 491 type 2 diabetes mellitus patients with euthyroid between October 2021 and June 2024. Based on an ankle-brachial index (ABI) ≤ 1.0, subjects were categorized into two distinct cohorts: PAD group (n = 147) and no peripheral arterial disease (NPAD) group (n = 344). In order to evaluate their responsiveness to thyroid hormone, we calculated several indexes: thyroid feedback quantile-based index (TFQI), thyroid-stimulating hormone index (TSHI), thyrotroph T4 resistance index (TT4RI), and free triiodothyronine/free thyroxine (FT3/FT4). Then we conducted multivariate logistic regression analysis and the analysis of the operating characteristic curve of the subjects to determine the accuracy of these indicators in predicting PAD.

Results: Significant differences were observed in thyroid hormone sensitivity indices across the PAD and NPAD groups. Logistic regression, adjusted for various covariates, identified higher thyroid hormone sensitivity indices (TFQI, TSHI, and TT4RI) and lower FT3/FT4 as predictive of PAD. Moreover, Spearman correlation analysis confirmed these findings, demonstrating positive associations between TFQI, TSHI, TT4RI and PAD, while the FT3/FT4 ratio showed an inverse relationship with the condition. The integrated thyroid sensitivity indices model (covariate-adjusted) achieved a PAD prediction AUC of 0.628 (95% CI 0.575–0.691), featuring 55.5% specificity and 63.9% sensitivity.

Conclusion: Reduced central and peripheral thyroid hormone sensitivity independently predicts PAD risk in T2DM patients with euthyroid.

Keywords: type 2 diabetic, peripheral arterial disease, euthyroid, thyroid hormone sensitivity

Introduction

Diabetes constitutes a critical worldwide health challenge, with incidence rates rising continuously. A comprehensive review of the latest report by the International Diabetes Federation (IDF) reveals an alarming statistic: in 2024, approximately 589 million individuals aged 20–79 globally had diabetes. This staggering figure points to an even more dire future scenario, with estimates projecting an increase to 852.5 million by 2050.[1] Type 2 diabetes mellitus (T2DM) constitutes approximately 90% of these cases. Peripheral arterial disease (PAD) represents a major vascular complication in diabetic patients, and its primary causes are atherosclerosis and thrombosis.[2] In clinical practice, the ankle–brachial index (ABI), a simple, non-invasive, and reproducible test, has become the cornerstone technique for diagnosing and assessing PAD.[3] According to established guidelines, an ABI value ≤ 0.90 is considered diagnostic for hemodynamically significant PAD, with high specificity.[4] However, in high-risk populations, such as patients with

https://doi.org/10.2147/DMSO.S571291
Received: 14 November 2025
Accepted: 9 March 2026
Published: 23 March 2026

diabetes, a stricter cutoff may be warranted for screening and early risk stratification. A pivotal diagnostic performance study by Clairotte et al demonstrated that, using ultrasonography as the gold standard, an ABI cutoff of 1.00 provided an optimal balance in diabetic patients, with a sensitivity of 66.2%, a specificity of 96.8%, and a high positive likelihood ratio (PLR) of 20.7.[5] This suggests that the ≤ 1.00 threshold is particularly effective in identifying hemodynamically significant stenosis in this population. Furthermore, from a prognostic perspective, an ABI below 1.00 has been independently associated with an increased risk of future cardiovascular events and diabetic foot ulcers in Asian patients with T2DM.[6] Therefore, to better capture the spectrum of early yet prognostically relevant arterial compromise associated with novel risk factors, the present study defined PAD using an ABI threshold of ≤ 1.00.

The pathophysiology of PAD is complex and multifactorial, involving vascular inflammatory responses, endothelial dysfunction, abnormal smooth muscle cell proliferation, platelet activation, and dysregulation of coagulation cascades. These mechanisms are further aggravated by metabolic disturbances, ultimately leading to progressive arterial stenosis and impaired blood flow to the lower extremities.[7] Thyroid hormones occupy a central position in the regulation of energy metabolism and growth processes. Their metabolic control is closely associated with the onset and progression of conditions such as diabetes, obesity, and hyperuricemia. In a hyperthyroid state, increased gastrointestinal glucose absorption and hepatic glucose output can lead to insulin resistance and hyperglycemia.[8] In contrast, hypothyroidism may induce chronic low-grade inflammatory responses by activating pro-inflammatory factors and inhibiting anti-inflammatory mediators, thereby increasing the risk of diabetes.[9] Regarding lipid metabolism, thyroid hormones promote the clearance of low-density lipoprotein cholesterol (LDL-C) and the synthesis of high-density lipoprotein cholesterol (HDL-C) by stimulating LDL receptors. Consequently, marked dyslipidemia can be observed in states of thyroid dysfunction: hypothyroidism is associated with elevated total cholesterol (TC), LDL-C, and triglycerides (TG), whereas hyperthyroidism tends to reduce these lipid parameters.[10]

Currently, the potential contribution of thyroid dysfunction to diabetic peripheral vascular disease is still inconclusive.[11,12] This may be partly due to differences in thyroid function assessment methods or individual differences in vascular sensitivity to thyroid hormone. Recently, some researchers have coined the term "thyroid hormone sensitivity" to describe the individual variation in how effectively target tissues respond to thyroid hormones. In the euthyroid zone, a heightened sensitivity to thyroid hormones is strongly linked to an increased risk of negative metabolic consequences, such as obesity, metabolic syndrome, and diabetes.[13–16] Nevertheless, Thyroid hormone sensitivity's relationship with diabetic macrovascular complications, particularly PAD, requires further examination. This research aims to leverage the ABI as a metric for identifying PAD in T2DM. This study aimed to elucidate the association of thyroid hormone sensitivity with the risk of PAD. The assessment of sensitivity was based on specific indices, including the thyroid feedback quantile index (TFQI), thyroid hormone sensitivity index (TSHI), thyrotroph T4 resistance index (TT4RI), and the free triiodothyronine/free thyroxine (FT3/FT4). The findings are expected to facilitate earlier detection and more targeted interventions, ultimately mitigating the burden of vascular complications among individuals with diabetes.

Materials and Methods

Research Subjects

This retrospective cohort included 491 T2DM inpatients from the Department of Endocrinology at the Second Affiliated Hospital of Wannan Medical College, enrolled between October 2021 and June 2024.

Inclusion criteria: (1) Qualified subjects were 18 years of age and above, diagnosed with T2DM according to the 1999 World Health Organization (WHO) diagnostic guidelines; (2) Euthyroid status; (3) Availability of ABI measurement data. Conversely, individuals were excluded from participation if they fell into any of these categories: (1) Individuals suffering from gestational diabetes, type 1 diabetes, or other nuanced diabetes forms; (2) Missing or irregular thyroid hormone (TH) test outcomes; (3) Ongoing use of drugs that could alter serum TH concentrations; (4) Presence of acute conditions, including diabetic complications, acute heart failure, severe infection, malignancy, severe hepatic or renal insufficiency, or other systemic illnesses that could interfere with thyroid function. A flow chart of patient selection and exclusion is shown in Figure 1.

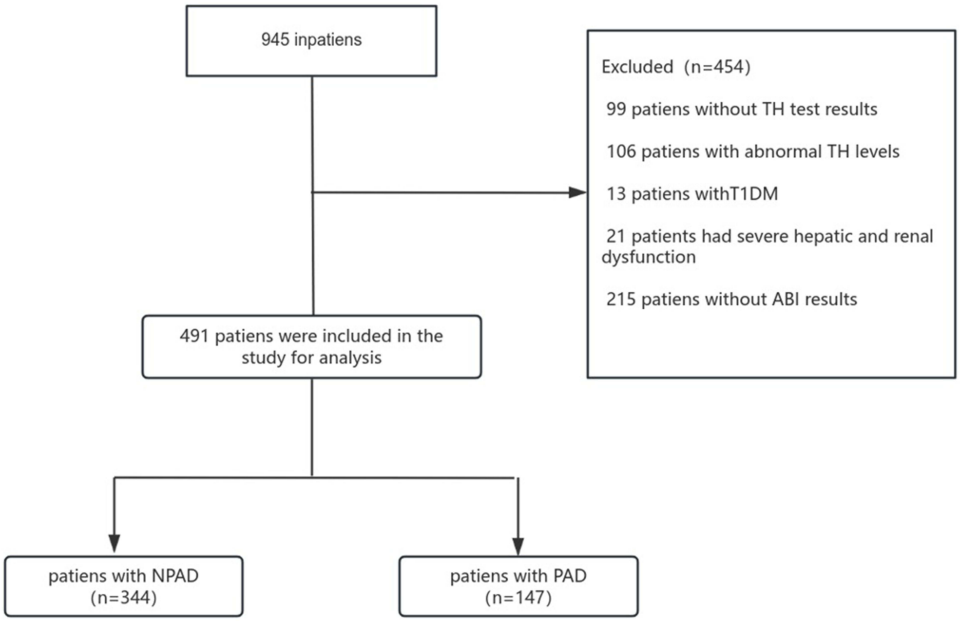

Figure 1 Patient Screening Flowchart.
Abbreviation: TH, thyroid hormone.

Data Collection

Electronic medical records provided demographic and clinical information. All participants underwent blood collection via venipuncture following a standardized fasting period of 8 hours. We then quantified glycated hemoglobin (HbA1c), fasting blood glucose (FBG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), triglycerides (TG), serum creatinine (Scr), and uric acid (UA) levels using the Beckman Coulter AU5800 automated biochemical analyzer from the United States. The CKD-EPI formula was used to calculate the estimated glomerular filtration rate (eGFR). After morning urine collection, albumin and creatinine were measured via automated biochemical analysis (Beckman Coulter AU5800, USA) to calculate the urine albumin/creatinine ratio (UACR). Serum levels of thyrotropin (TSH), free thyroxine (FT4) and free triiodothyronine (FT3) were concurrently assessed using electrochemiluminescence analysis from Abbott Laboratories in the United States.

ABI Measurement and PAD Grouping

The patient should lie supine for 5 to 10 minutes before the examination. Systolic blood pressure of the bilateral brachial arteries and lower limbs is measured using a Doppler diagnostic system from Summit Doppler Systems (USA). Clinically, the ABI for the left and right lower limbs is typically calculated separately. The ABI for each leg is determined by taking the highest systolic reading from either the dorsalis pedis or posterior tibial artery at the ankle and dividing it by the greater of the systolic pressures recorded from both arms' brachial arteries. The lower of the two lower limb ABI values is then used as the patient's ABI result. According to major guidelines, a normal ABI is generally defined as 1.0–1.4, with values ≤ 0.90 indicating PAD. Values between 0.91 and 1.00 are often considered borderline or in a "gray zone". However, for the present study, PAD was defined as ABI ≤ 1.0. Therefore, in our study, we used ABI ≤ 1.0 as the cutoff point and divided the enrolled patients into PAD group (n = 147) and no peripheral arterial disease (NPAD) group (n = 344).

Indices of Thyroid Hormone Sensitivity

TFQI = cdfFT4 − (1 − cdfTSH). This index, which ranges from −1 to 1, serves as a metric for HPT axis sensitivity: values below zero suggest enhanced sensitivity, those above zero imply diminished sensitivity. TSHI = lnTSH (mIU/

https://doi.org/10.2147/DMSO.S571291

L) + 0.1345 × FT4 (pmol/L); TT4RI = FT4 (pmol/L) × TSH (mIU/L). The higher values of TSHI and TT4RI impaired sensitivity to thyroid hormone action. The three indices above represent central thyroid hormone sensitivity.

Peripheral thyroid hormone sensitivity was quantified by the FT3/FT4, with an increased level suggesting a heightened peripheral response to thyroid hormone.

Statistical Analyses

Counts (percentages) represented categorical variables, while mean ± standard deviation or median (interquartile range) characterized continuous ones. The Shapiro–Wilk test assessed data normality. Intergroup comparisons employed the chi-square, Mann–Whitney U, or independent *t*-tests as appropriate. Variable associations were assessed via Spearman correlation. To identify risk factors and outcomes, we utilized both single and multiple logistic regression analyses. Clinically relevant covariates were selected a priori based on established evidence, including age, sex, hypertension, smoking, alcohol drinking, duration of diabetes, HbA1c, LDL-C, and eGFR-the latter was included given the well-established link between chronic kidney disease(CKD), reduced renal function, and PAD in T2DM. Results are reported as odds ratios (ORs) with 95% confidence intervals (CIs) and visualized using forest plots. Receiver operating characteristic (ROC) curves were constructed to evaluate the discriminatory performance of the models by calculating the area under the curve (AUC). To integrate the predictive information from the four significant thyroid hormone sensitivity indices (TFQI, TSHI, TT4RI, and FT3/FT4), a composite thyroid hormone sensitivity score was calculated for each participant by summing their standardized z-scores, weighted by the respective beta coefficients derived from the final multivariate logistic regression model. Internal validation of the final multivariable model was conducted using bootstrap resampling with 1000 iterations to evaluate model stability and potential overfitting. Sensitivity analyses were performed to test the robustness of the primary findings by sequentially replacing LDL-C with other lipid parameters (HDL-C, TG or TC) in the multivariable logistic regression models. All statistical tests used a two-tailed significance threshold of $p < 0.05$. We conducted the data analysis with SPSS 24.0 and R 4.5.1.

Results

Demographics and Laboratory Metrics of Research Subjects

Compared with the NPAD cohort, the PAD group had a demographic and biochemical profile characterized by more advanced age, elevated TSH, TFQI, TSHI, and TT4RI levels, along with markedly reduced FT3 and FT3/FT4—achieving statistical significance ($P < 0.05$). A complete rundown of these baseline characteristics across both groups can be found in Table 1. These differences in thyroid hormone sensitivity indices suggest reduced central and peripheral thyroid hormone responsiveness in PAD patients compared with NPAD patients.

Association of Thyroid Hormone Sensitivity with the Risk of PAD

Unadjusted variable model revealed the risk of PAD increased significantly with each standard deviation (SD) increase in TFQI (OR=1.286, 95% CI: 1.055–1.566, p=0.013), TSHI (OR=1.305, 95% CI: 1.068–1.594, p=0.009), and TT4RI (OR=1.288, 95% CI: 1.066–1.557, p=0.009), while FT3/FT4 showed a negative association (OR=0.738, 95% CI: 0.602–0.904, p=0.003). Following multivariate adjustment for sex, age, hypertension, smoking, alcohol drinking, duration, HbA1c, LDL-C, and eGFR, the thyroid hormone sensitivity indices TFQI, TSHI, TT4RI, and FT3/FT4 remained significantly associated with PAD, with adjusted odds ratios of 1.296 (95% CI: 1.058–1.587), 1.297 (95% CI: 1.058–1.590), 1.275 (95% CI: 1.049–1.550), and 0.766 (95% CI: 0.622–0.944), respectively (all $P < 0.05$). The forest plot visually demonstrated the correlation, and the 95% confidence intervals of all indicators did not overlap, further verifying the statistical significance of the above association (Figure 2).

Quartile-based trend analysis demonstrated a significant increasing trend in PAD prevalence with ascending quartiles of TFQI, TSHI, and TT4RI, and a decreasing trend across FT3/FT4 quartiles. The significant dose-response trend persisted following comprehensive adjustment for potential confounding factors ($P < 0.05$) (Table 2).

Table 1 General Characteristics and Biochemical Indices Between the Two Groups

	NPAD (n=344)	PAD (n=147)	P value
Sex (male%)	193 (56.105)	73 (49.660)	0.225
Age (years)	60 (53, 68)	65 (56, 73)	0.005*
Hypertension (%)	180 (52.326)	74 (50.340)	0.761
Smoking (%)	107 (31.105)	49 (33.333)	0.704
Alcohol drinking (%)	52 (15.116)	20 (13.605)	0.769
Duration (years)	7 (2, 10)	10 (2.5, 14.5)	0.118
UACR (mg/g)	33.16 (13.40, 91.872)	26.82 (13.70, 96.03)	0.744
HbA1c (%)	9.6 (7.6, 11.4)	9.6 (7.7, 11.3)	0.977
FBG (mmol/L)	7.420 (5.508, 10.543)	7.890 (5.755, 10.795)	0.383
LDL-C (mmol/L)	2.750 (2.062, 3.380)	2.730 (2.005, 3.250)	0.971
HDL-C (mmol/L)	1.050 (0.870, 1.280)	1.050 (0.840, 1.330)	0.688
TG (mmol/L)	1.425 (0.998, 2.072)	1.230 (0.975, 1.955)	0.261
TC (mmol/L)	4.440 (3.610, 5.162)	4.300 (3.550, 5.075)	0.545
Scr (umol/L)	65 (54, 78.25)	66 (52, 84.5)	0.795
UA (umol/L)	315.5 (261.75, 372.25)	303 (247.5, 368)	0.252
eGFR (mL/min/1.73m2)	102.05 (81.3, 125.35)	97.1 (69.25, 119.9)	0.092
TSH (ulU/mL)	1.590 (1.108, 2.358)	1.752 (1.267, 2.430)	0.028*
FT4 (pmol/L)	13.528 ±1.535	13.766 ±1.629	0.123
FT3 (pmol/L)	3.875 (3.520, 4.272)	3.810 (3.230, 4.160)	0.010*
TFQI	−0.023 (−0.344, 0.211)	0.043 (−0.258, 0.301)	0.022*
TSHI	2.302 (1.903, 2.659)	2.439 (2.054, 2.784)	0.010*
TT4RI	21.248 (14.856, 30.995)	24.460 (17.614, 33.510)	0.014*
FT3/FT4	0.286 (0.253, 0.319)	0.275 (0.239, 0.320)	0.018*

Notes: Data are expressed as the mean ± standard deviations or medians (interquartile ranges) or numbers (%); *P<0.05 was considered statistically significant.

Abbreviations: NPAD, no peripheral arterial disease; PAD, peripheral arterial disease; UACR, urine albumin/creatinine ratio; HbA1c, glycated hemoglobin; FBG, fasting blood glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein. Cholesterol; TG, triglycerides; TC, total cholesterol; Scr, serum creatinine; UA, uric acid; eGFR, estimated glomerular filtration rate; TSH, thyroid stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; TT4RI, thyrotropin thyroxine resistance index; FT3/FT4, free triiodothyronine/free thyroxine.

Consistent with the above group differences, Spearman analysis identified significant associations of PAD with TFQI (rs = 0.103, P = 0.022), TSHI (rs = 0.116, P = 0.010), TT4RI (rs = 0.111, P = 0.014), and an inverse association with FT3/FT4 (rs = −0.107, P = 0.017) (Table 3).

https://doi.org/10.2147/DMSO.S571291

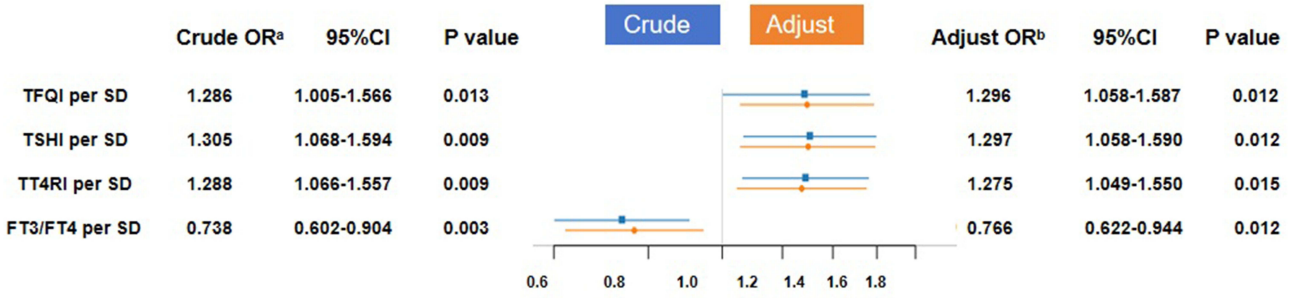

Figure 2 Forest plot of the association between thyroid hormone sensitivity and PAD.
Notes: [a]Unadjusted; [b]Adjusted for sex, age, hypertension, smoking, alcohol drinking, duration, HbA1c, LDL-C, and eGFR.
Abbreviations: SD, standard deviation; TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; TT4RI, thyrotropin thyroxine resistance index; FT3/FT4, free triiodothyronine/free thyroxine.

In age-stratified analyses (≤ 60 vs > 60 years), the associations between thyroid hormone sensitivity indices and PAD were broadly similar across age groups, and no statistically significant interactions with age were observed for any index (all P for interaction > 0.05; Supplementary Table S1).

ROC Curve of Thyroid Hormone Sensitivity for Predicting PAD

ROC curve assessed thyroid hormone sensitivity's predictive ability fo PAD. In the unadjusted model, the AUC was 0.565 for the TFQI, 0.573 for the TSHI, 0.570 for the TT4RI, and 0.432 for the FT3/FT4 (Figure 3). After combining these thyroid hormone sensitivity indicators and multivariate adjustment (sex, age, hypertension, smoking, alcohol

Table 2 Quartile Analysis of Thyroid Hormone Sensitivity and PAD

		Crude OR[a]	95% CI	P value	Adjust OR[b]	95% CI	P value
TFQI							
	Q1	1			1		
	Q2	1.289	0.729–2.294	0.384	1.272	0.708–2.299	0.422
	Q3	1.395	0.792–2.472	0.251	1.431	0.799–2.583	0.222
	Q4	1.962	1.132–3.442	0.017*	1.959	1.116–3.484	0.022*
TSHI							
	Q1	1			1		
	Q2	1.46	0.827–2.600	0.194	1.502	0.842–2.704	0.170
	Q3	1.296	0.728–2.321	0.379	1.281	0.709–2.328	0.412
	Q4	2.201	1.269–3.873	0.005*	2.095	1.194–3.726	0.011*
TT4RI							
	Q1	1			1		
	Q2	1.544	0.866–2.782	0.143	1.591	0.885–2.891	0.123
	Q3	1.865	1.058–3.336	0.033*	1.922	1.077–3.479	0.029*
	Q4	2.105	1.199–3.754	0.010*	1.979	1.112–3.575	0.022*
FT3/FT4							
	Q1	1			1		
	Q2	0.577	0.336–0.982	0.044*	0.599	0.343–1.036	0.068
	Q3	0.425	0.241–0.783	0.003*	0.434	0.242–0.765	0.004*
	Q4	0.657	0.386–1.113	0.120	0.744	0.427–1.290	0.293

Notes: [a]Unadjusted; [b]Adjusted for sex, age, hypertension, smoking, alcohol drinking, duration, HbA1c, LDL-C, and eGFR; *P < 0.05 was considered statistically significant.
Abbreviations: TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; TT4RI, thyrotropin thyroxine resistance index; FT3/FT4, free triiodothyronine/free thyroxine.

Table 3 Spearman Analysis of Thyroid Hormone Sensitivity and PAD

	rs	P value
TFQI	0.103	0.022*
TSHI	0.116	0.010*
TT4RI	0.111	0.014*
FT3/FT4	−0.107	0.017*

Notes: *P<0.05 was considered statistically significant.
Abbreviations: TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; TT4RI, thyrotropin thyroxine resistance index; FT3/FT4, free triiodothyronine/free thyroxine.

drinking, duration, HbA1c, LDL-C, and eGFR), ROC analysis revealed an AUC of 0.628 (95% CI: 0.575–0.691), with specificity at 55.5% and sensitivity at 63.9% (Figure 4).

Internal Validation and Sensitivity Analyses

Internal validation using 1000 bootstrap resamples showed that the bootstrap-derived regression coefficients and odds ratios were highly consistent with the original estimates, indicating that the multivariable model is relatively stable and that the risk of overfitting is limited. The internally validated performance suggested that the model retained a modest discriminative ability for PAD (AUC approximately 0.63). To address concerns about selective lipid adjustment, we further performed sensitivity analyses replacing LDL-C with HDL-C, triglycerides, or total cholesterol in the multivariable models; the associations between thyroid hormone sensitivity indices and PAD were largely unchanged across these models (Supplementary Table S2).

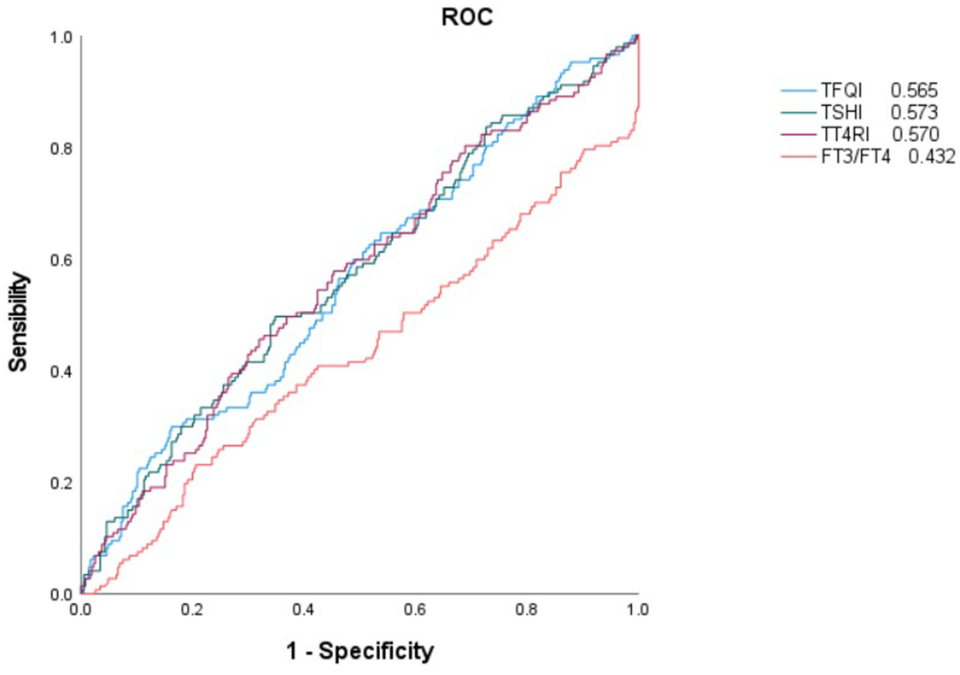

Figure 3 The overall predictive accuracy of Univariate predictive model for the risk of PAD.
Abbreviations: TFQI, thyroid feedback quantile-based index; TSHI, thyroid stimulating hormone index; TT4RI, thyrotropin thyroxine resistance index; FT3/FT4, free triiodothyronine/free thyroxine.

https://doi.org/10.2147/DMSO.S571291

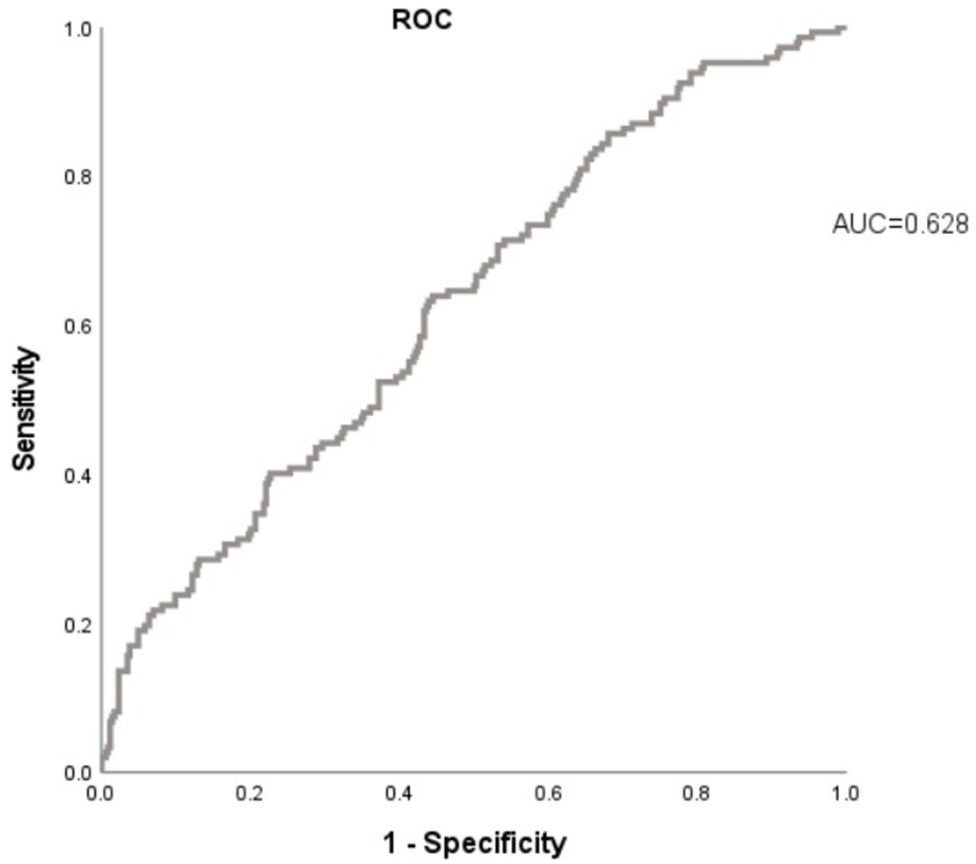

Figure 4 The overall predictive accuracy of a multivariate predictive model for the risk of PAD.
Notes: Adjusted for sex, age, hypertension, smoking, alcohol drinking, duration, HbA1c, LDL-C, and eGFR.

Discussion

This study investigated the association between thyroid hormone sensitivity and peripheral artery disease (PAD) through a retrospective analysis of 491 patients with type 2 diabetes mellitus (T2DM) and normal thyroid function. Our findings indicate that among T2DM patients with normal thyroid function, a state of reduced central thyroid hormone sensitivity, as reflected by higher TFQI, TSHI, and TT4RI, confers a significantly greater risk for PAD. Conversely, a higher FT3/FT4, indicating increased peripheral sensitivity, was negatively associated with PAD. Remarkably, the correlations retained statistical significance post-multiple adjustments accounting for gender, age, hypertension, tobacco use, alcohol consumption, duration, HbA1c, LDL-C levels, and eGFR. Furthermore, the ROC curve analysis revealed that a composite index of these thyroid hormone sensitivity parameters, after the same multivariate adjustments, demonstrated a moderate predictive value for PAD, with an AUC of 0.628, a specificity of 55.5%, and a sensitivity of 63.9%. Aggregate evidence suggests that lower thyroid hormone responsiveness is a standalone risk indicator for PAD in T2DM, showing predictive power regarding its development.

Afflicting roughly one in four individuals with diabetes, PAD stands as a frequent macrovascular complication, with a prevalence rate 2 to 4 times that observed in the non-diabetic population. PAD is closely associated with lower limb amputation and potential cardiovascular and cerebrovascular fatalities.[17,18] The pathological mechanisms of diabetes combined with PAD are complex and diverse. Peripheral vascular changes associated with diabetes include vascular inflammatory response, endothelial cell dysfunction, abnormal smooth muscle cell proliferation, and changes in platelets and coagulation factors.[19]

Building on this concept, in addition to macrovascular disease, several recent studies have explored the relationship between thyroid hormone sensitivity indices and diabetic microvascular complications. A retrospective study conducted in euthyroid hospitalized patients with T2DM in China reported that higher TFQI, TSHI, and TT4RI were independently

associated with an increased risk of diabetic retinopathy(DR), and that both central and peripheral thyroid hormone sensitivity indices had predictive value for the presence of DR.[20] Another study on diabetic retinopathy further demonstrated a non-linear association between TSHI, TFQI and the risk of adverse DR; importantly, the non-linear relationship for TFQI remained significant even after adjustment for multiple covariates.[21] Moreover, in a cohort of elderly patients with T2DM, a lower FT3/FT4 ratio, indicating reduced peripheral thyroid hormone sensitivity, was significantly related to a higher prevalence of diabetic peripheral neuropathy(DPN) after controlling for age, sex, and diabetes duration.[22] Taken together, these findings suggest that impaired thyroid hormone sensitivity, even within the euthyroid range, may be involved in the pathogenesis of both microvascular (DR and DPN) and macrovascular complications in diabetes. Our results extend this evidence by demonstrating that altered central and peripheral thyroid hormone sensitivity indices are also closely associated with PAD in euthyroid patients with T2DM.

Owing to their unique actions, thyroid hormones modulate both glucose and lipid metabolism and maintain overall energy balance. Several studies have pinpointed a notable link between thyroid hormone responsiveness and peripheral vascular disorders. A large-scale cross-sectional analysis of nearly 20,000 people provided compelling evidence that diminished thyroid hormone sensitivity constitutes a robust and independent risk factor for carotid artery plaque development.[23] In an epidemiological study of the general population, Wang et al observed that lower FT3/FT4 levels were associated with a higher incidence of peripheral artery disease[24] However, an independent association between thyroid hormone sensitivity and PAD within the normal thyroid function range has not been established, particularly in a population specific to diabetes. Our study hopes to provide some preliminary data in this specific area.

The biological pathways linking impaired thyroid hormone sensitivity to PAD pathogenesis are likely multifactorial and warrant further investigation. Mehran L et al demonstrated that decreased thyroid hormone sensitivity contributes to arteriosclerosis, as evidenced by lessened relaxation in arterial smooth muscle, higher systemic vascular resistance, and a decrease in endothelium-mediated vasodilation and nitric oxide synthesis[25] Cyrielle Billon et al found the absence of thyroid hormone receptors in ApoE (-/-) male mice can lead to abnormal cholesterol accumulation, increase the inflammatory response of macrophages, and thus accelerate the formation of plaques[26] Studies have shown that adipocyte fatty acid binding protein (A-FABP) is an important risk factor for subclinical atherosclerosis.[27] Nie et al reported that in euthyroid patients, increased A-FABP levels are closely related to decreased thyroid hormone sensitivity (TFQI and other indices), which may be one of the pathways mediating atherosclerosis.[28]

The robustness of our primary findings is supported by several supplementary analyses. Further subgroup analyses in this study revealed that the associations between thyroid hormone sensitivity indices and PAD were consistent across different age groups ($\leq$ 60 years and > 60 years), with no significant age interaction observed (all interaction $P > 0.05$). This strengthens the generalizability of our conclusions across age groups in T2DM patients. It is noteworthy that some conventional risk factors for PAD, such as smoking history and lipid profiles, did not show significant intergroup differences in our cohort. This is likely attributable to the relatively homogeneous nature of our study population, which consisted exclusively of patients with type 2 diabetes under standardized and intensive management in a specialized center. Under such conditions, the variance in these traditional risk factors may be attenuated, thereby limiting the statistical power to detect their effects. Importantly, this finding does not challenge their established etiological role nor does it diminish the robustness of our primary conclusion regarding the independent association between thyroid hormone sensitivity and PAD. To further ensure the rigor of our analysis, we specifically adjusted for eGFR in our models. This adjustment is critical given the strong, independent link between CKD and PAD, which share pathogenic mechanisms like accelerated atherosclerosis and vascular calcification. This adjustment was intended to minimize potential confounding by renal impairment. Concurrently, to address concerns regarding covariate selection, we performed sensitivity analyses by replacing LDL-C in the model with other lipid parameters (HDL-C, TG, or TC). The associations between thyroid hormone sensitivity indices and PAD remained materially unchanged in all analyses. These findings collectively support the robustness of our core results.

There are several limitations in our study. First, this study permits the identification of associations but cannot establish causality between thyroid hormone sensitivity and PAD. Second, diagnosis of PAD relied on ABI, a screening tool with known limitations in sensitivity for non-occlusive atherosclerosis and in certain patient populations, potentially leading to false negatives. The severity of PAD was not further validated with complementary imaging modalities. Third, our analysis

focused on clinical correlations and did not investigate the specific molecular mechanisms, through which thyroid hormone sensitivity may influence PAD pathogenesis. Nonetheless, the research confirms a notable independent link between reduced thyroid hormone sensitivity and PAD in euthyroid T2DM. These findings highlight a potential novel pathway and call for larger prospective studies to confirm the relationship and elucidate the underlying mechanisms.

Conclusion

In summary, our results reveal a distinct link between diminished thyroid hormone sensitivity and PAD in T2DM. Furthermore, a composite index of thyroid hormone sensitivity showed predictive value for the presence of PAD. The results offer compelling clinical data that highlight thyroid hormone responsiveness as a key player in the development of large-vessel complications associated with diabetes, pointing to thyroid sensitivity evaluation as a promising approach for identifying PAD risk factors among T2DM.

Data Sharing Statement

Study data can be obtained from primary author Yongjian Ye.

Ethics Statement

The research gained ethical clearance from the Second Affiliated Hospital of Wannan Medical College's Ethics Committee (Approval No. WYEFYLS2025047), and adhered to the principles outlined in the Helsinki Declaration. As a retrospective analysis of clinical data that involved no patient intervention, this retrospective clinical data analysis received ethics committee approval for written informed consent exemption.

Acknowledgments

We sincerely thank all study participants and staff members for their essential contributions.

Author Contributions

Yongjian Ye: Conceptualization, Methodology, Funding Acquisition, Writing – Original Draft. Dandan Liu: Conceptualization, Formal Analysis, Visualization, Validation, Writing – Original Draft. Yongjian Ye and Dandan Liu contributed equally to this work as co-first authors. Yu Hang: Resources, Data Curation, Supervision, Project Administration, Writing – Review & Editing. Haitao Qian: Investigation, Data Curation, Validation, Writing – Review & Editing. Junfei Gu: Conceptualization, Supervision, Funding Acquisition, Writing – Review & Editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Clinical and Translational Research Project of Anhui Province (202427b10020110) and Youth Project of Anhui Provincial Natural Science Foundation (2308085QH260).

Disclosure

The authors declared no competing interests.

References

1. Duncan BB, Magliano DJ, Boyko EJ. IDF diabetes atlas 11th edition 2025: global prevalence and projections for 2050. *Nephrol Dial Transplant*. 2025;41(1):7–9. doi:10.1093/ndt/gfaf177
2. Barnes JA, Eid MA, Creager MA, Goodney PP. Epidemiology and risk of amputation in patients with diabetes mellitus and peripheral artery disease. *Arterioscler Thromb Vasc Biol*. 2020;40(8):1808–1817. doi:10.1161/ATVBAHA.120.314595
3. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2017;69(11):1465–1508. doi:10.1016/j.jacc.2016.11.008
4. Aboyans V, Criqui MH, Abraham P, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. *Circulation*. 2012;126(24):2890–2909. doi:10.1161/CIR.0b013e318276fbcb

5. Clairotte C, Retout S, Potier L, Roussel R, Escoubet B. Automated ankle-brachial pressure index measurement by clinical staff for peripheral arterial disease diagnosis in nondiabetic and diabetic patients. *Diabetes Care*. 2009;32(7):1231–1236. doi:10.2337/dc08-2230
6. Yang MC, Huang YY, Hsieh SH, Sun JH, Wang CC, Lin CH. Ankle-brachial index is independently associated with cardiovascular outcomes and foot ulcers in asian patients with type 2 diabetes mellitus. *Front Endocrinol*. 2021;12:752995. doi:10.3389/fendo.2021.752995
7. Shah AJ, Pavlatos N, Kalra DK. Preventive therapies in peripheral arterial disease. *Biomedicines*. 2023;11(12):3157. doi:10.3390/biomedicines11123157
8. Kalra S, Aggarwal S, Khandelwal D. Thyroid dysfunction and type 2 diabetes mellitus: screening strategies and implications for management. *Diabetes Ther*. 2019;10(6):2035–2044. doi:10.1007/s13300-019-00700-4
9. Rong F, Dai H, Wu Y, et al. Association between thyroid dysfunction and type 2 diabetes: a meta-analysis of prospective observational studies. *BMC Med*. 2021;19(1):257. doi:10.1186/s12916-021-02121-2
10. Sun H, Zhu W, Liu J, An Y, Wang Y, Wang G. Reduced sensitivity to thyroid hormones is associated with high remnant cholesterol levels in Chinese euthyroid adults. *J Clin Endocrinol Metab*. 2022;108(1):166–174. doi:10.1210/clinem/dgac523
11. Patel PR, Maitra A, Ashok A, Jose J, Ragav Y, Novalene Paul N. Evaluation of thyroid dysfunction in type 2 diabetes mellitus patients and its association with diabetic complications: a cross-sectional study. *Cureus*. 2025;17(2):e78871. doi:10.7759/cureus.78871
12. Ittermann T, Lorbeer R, Tiller D, et al. Serum thyrotropin concentrations are not associated with the ankle-brachial index: results from three population-based studies. *Eur Thyroid J*. 2015;4(Suppl 1):101–107. doi:10.1159/000381309
13. Yagi H, Pohlenz J, Hayashi Y, Sakurai A, Refetoff S. 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'-triiodothyroinine binding affinity. *J Clin Endocrinol Metab*. 1997;82(5):1608–1614. doi:10.1210/jcem.82.5.3945
14. Jostel A, Ryder WD, Shalet SM. The use of thyroid function tests in the diagnosis of hypopituitarism: definition and evaluation of the TSH Index. *Clin Endocrinol*. 2009;71(4):529–534. doi:10.1111/j.1365-2265.2009.03534.x
15. Laclaustra M, Moreno-Franco B, Lou-Bonafonte JM, et al. Impaired sensitivity to thyroid hormones is associated with diabetes and metabolic syndrome. *Diabetes Care*. 2019;42(2):303–310. doi:10.2337/dc18-1410
16. Park SY, Park SE, Jung SW, et al. Free triiodothyronine/free thyroxine ratio rather than thyrotropin is more associated with metabolic parameters in healthy euthyroid adult subjects. *Clin Endocrinol*. 2017;87(1):87–96. doi:10.1111/cen.13345
17. Campia U, Gerhard-Herman M, Piazza G, Goldhaber SZ. Peripheral artery disease: past, present, and future. *Am J Med*. 2019;132(10):1133–1141. doi:10.1016/j.amjmed.2019.04.043
18. Ghimire MR, Acharya S, Pandey S, et al. Screening of peripheral arterial disease in patients with diabetes. *J Nepal Health Res Counc*. 2023;21(1):46–49. doi:10.33314/jnhrc.v21i1.4402
19. Liarakos AL, Tentolouris A, Kokkinos A, Eleftheriadou I, Tentolouris N. Impact of glucagon-like peptide 1 receptor agonists on peripheral arterial disease in people with diabetes mellitus: a narrative review. *J Diabetes Complications*. 2023;37(2):108390. doi:10.1016/j.jdiacomp.2022.108390
20. Zhao X, Sun J, Xu X, Xin S, Zhang X. The effect of Central and peripheral thyroid resistance indices on diabetic retinopathy: a study of hospitalized euthyroid patients with T2DM in China. *Ann Med*. 2023;55(2):2249017. doi:10.1080/07853890.2023.2249017
21. Yang J, Ding W, Wang H, Shi Y. Association between sensitivity to thyroid hormone indices and diabetic retinopathy in euthyroid patients with type 2 diabetes mellitus. *Diabetes Metab Syndr Obes*. 2023;16:535–545. doi:10.2147/DMSO.S39991
22. Fei SJ, Luo JY, Wang WH, Guo LX, Pan Q. Correlation between diabetic peripheral neuropathy and thyroid hormone sensitivity in elderly patients with type 2 diabetes mellitus. *World J Diabetes*. 2025;16(2):98897. doi:10.4239/wjd.v16.i2.98897
23. Wang J, Yang L, Liu W, Wei C, Shen J. Impaired sensitivity to thyroid hormone and risk of carotid plaque development in a chinese health check-up population: a large sample cross-sectional study. *Diabetes Metab Syndr Obes*. 2024;17:1013–1024. doi:10.2147/DMSO.S454023
24. Wang P, Rui DU, Lin L, et al. Association between free triiodothyronine levels and peripheral arterial disease in euthyroid participants. *Biomed Environ Sci*. 2017;30(2):128–133. doi:10.3967/bes2017.016
25. Mehran L, Delbari N, Amouzegar A, Hasheminia M, Tohidi M, Azizi F. Reduced sensitivity to thyroid hormone is associated with diabetes and hypertension. *J Clin Endocrinol Metab*. 2022;107(1):167–176. doi:10.1210/clinem/dgab646
26. Billon C, Canaple L, Fleury S, et al. TRα protects against atherosclerosis in male mice: identification of a novel anti-inflammatory property for TRα in mice. *Endocrinology*. 2014;155(7):2735–2745. doi:10.1210/en.2014-1098
27. Xiao Y, Xiao X, Xu A, Chen X, Tang W, Zhou Z. Circulating adipocyte fatty acid-binding protein levels predict the development of subclinical atherosclerosis in type 2 diabetes. *J Diabetes Complications*. 2018;32(12):1100–1104. doi:10.1016/j.jdiacomp.2018.09.001
28. Nie X, Ma X, Xu Y, Shen Y, Wang Y, Bao Y. Increased serum adipocyte fatty acid-binding protein levels are associated with decreased sensitivity to thyroid hormones in the euthyroid population. *Thyroid*. 2020;30(12):1718–1723. doi:10.1089/thy.2020.0011