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ORIGINAL RESEARCH

Pericoronary Fat Attenuation Index Mediates the Link Between TyG Index and OSA Risk in Type 2 Diabetes

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Objective: The comorbidity of type 2 diabetes mellitus (T2DM) and obstructive sleep apnea (OSA) represents a significant public health challenge. We quantified the mediating role of the coronary fat attenuation index (FAI) in the association between the triglyceride-glucose (TyG) index and OSA risk, characterizing its nonlinear dynamics.

Methods: In this retrospective cross-sectional study, we assessed OSA risk using the STOP-Bang questionnaire in 420 patients with T2DM undergoing coronary computed tomography angiography, classifying scores as low-risk (<3), intermediate-risk (3–4), or high-risk (≥5). We measured pericoronary adipose tissue (PCAT)-FAI in three major epicardial coronary arteries (the right coronary artery, the left anterior descending artery, and the left circumflex artery) and in the culprit vessels. The TyG index was calculated using: ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]. Statistical associations were evaluated using multivariable logistic regression, restricted cubic splines (RCS), and PROCESS macro-mediated analyses.

Results: PCAT-FAI was significantly elevated in LAD, LCX, RCA, and culprit vessels in patients at intermediate or high OSA risk versus the low-risk group (all $p < 0.05$). After adjusting for age, sex, BMI, and medication, each 1-unit TyG increase conferred a 2.3-fold higher OSA risk (adjusted OR = 3.30, 95% CI [1.92, 5.67], $p < 0.01$). RCS revealed threshold effects: OSA risk increased nonlinearly when RCA-FAI exceeded −80 Hounsfield units (HU). RCA-FAI mediated 11.78% of the TyG index–OSA association ($p = 0.03$).

Conclusion: RCA-FAI partially mediates the impact of TyG on OSA severity through nonlinear pathways. These findings elucidate PCAT inflammation as a mechanistic link in T2DM-OSA comorbidity, supporting the use of RCA-FAI ≥ −80 HU screening for precision risk stratification.

Keywords: type 2 diabetes, obstructive sleep apnea, triglyceride-glucose index, fat attenuation index, mediation analysis

Introduction

The coexistence of type 2 diabetes mellitus (T2DM) and obstructive sleep apnea (OSA) poses a major global health challenge. Worldwide, T2DM affects over 537 million people,[1] with T2DM having a significantly higher occurrence of OSA than those without diabetes.[2] Studies suggest a mutual relationship: OSA raises the likelihood of insulin resistance, and T2DM patients with OSA experience increased cardiovascular mortality and coronary heart disease risks.[3–5]

The Stop-Bang questionnaire is a proven tool for screening OSA, offering substantial clinical benefits for individuals with T2DM.[6] This tool quickly detects high-risk individuals by evaluating snoring, daytime sleepiness, high blood pressure, and a body mass index (BMI) over 35 kg/m^2. Significantly, the STOP-Bang score was positively correlated with the apnea-hypopnea index (AHI) among T2DM patients ($P<0.001$), and scores of 5 or more independently indicated severe OSA in this population.[7] Consequently, it facilitates early intervention and enables risk-based management to reduce the risk of cardiovascular disease.

Insulin resistance (IR) is a shared pathophysiological mechanism for OSA, T2DM, and cardiovascular events.[8,9] Quantified as In [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2], the triglyceride-glucose

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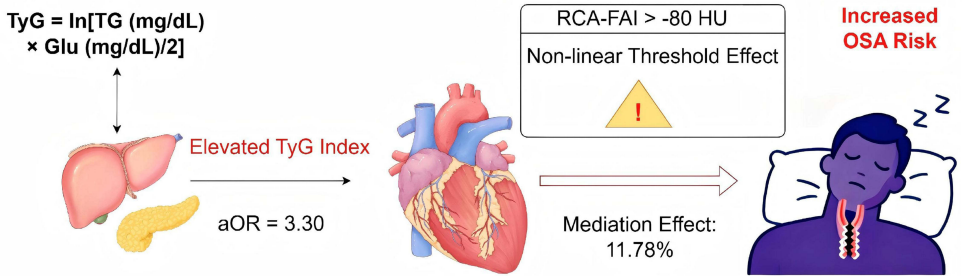
Graphical Abstract



index (TyG) is a trustworthy indicator for assessing insulin resistance.[10,11] With each tertile rise in the TyG index, the risk of OSA increased by 3.35 times (odds ratio [OR] = 3.35, 95% confidence interval [CI]: 1.08–10.37).[12] In individuals with T2DM, there was a significant correlation between higher TyG index quartiles and an increased risk of major adverse cardiovascular events (MACE).[13] Individuals in the top quartile exhibited a 4.32 times greater lifetime risk of cardiovascular disease (OR = 4.32, 95% CI 1.19–15.67; P = 0.026) compared to those in the bottom quartile.[14] According to ROC analysis, TyG outperformed HOMA-IR in predicting lifetime CVD risk, as indicated by an AUC of 0.72 versus 0.65, with the difference being statistically significant (P<0.05),[14] highlighting its key role in the pathophysiology of metabolic-sleep disorders.

The fat attenuation index (FAI) measures inflammation in pericoronary adipose tissue (PCAT) using coronary computed tomography angiography (CCTA),[15] offering new perspectives on the interaction between metabolism and inflammation. A multicenter study conducted over time involved 40,091 patients who underwent CCTA at eight hospitals in the UK, with a median follow-up period of 2.7 years. Patients with FAI scores in the highest quartile, as shown by an interquartile range (IQR) of 1.4–5.3, faced a 29.8-fold increase in cardiac mortality risk (hazard ratio [HR] = 29.8, 95% CI: 13.9–63.9; P<0.001) and a 12.6-fold increase in MACE risk (HR=12.6, 95% CI: 8.5–18.6; *P*<0.001).[16] In T2DM patients, increased lesion-specific FAI is an independent predictor of MACE, especially in cases with moderate-to-severe coronary artery calcification.[17] While researchers have identified independent links between the TyG index and cardiovascular risk in T2DM/OSA groups, the connection between FAI and OSA in T2DM, as well as FAI's involvement in the TyG-OSA pathway, has not been defined. Therefore, this study aimed to investigate the correlations among TyG index, PCAT-FAI, and OSA risk, stratifying OSA risk via STOP-Bang scores, to inform preventive strategies for OSA-associated T2DM.

Patients and Methods

Study Design and Population

This retrospective cross-sectional study investigated the interrelationships among OSA, coronary inflammation, and insulin resistance in T2DM cohorts. At Yan'an University Affiliated Hospital, we retrospectively screened consecutive patients with type 2 diabetes mellitus (T2DM) referred for clinically indicated coronary computed tomography angiography (CCTA) between January 2020 to August 2023.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (i) age >18 years; (ii) active antihyperglycemic pharmacotherapy; and (iii) WHO ICD-10-coded T2DM diagnosis (E11). The exclusion criteria were as follows: (i) history of coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), (ii) chronic total occlusion (CTO) lesions, and (iii) non-diagnostic CCTA studies secondary to respiratory motion artifacts or arrhythmias. Following screening, 420 eligible participants comprised the analytical cohort (Figure 1).

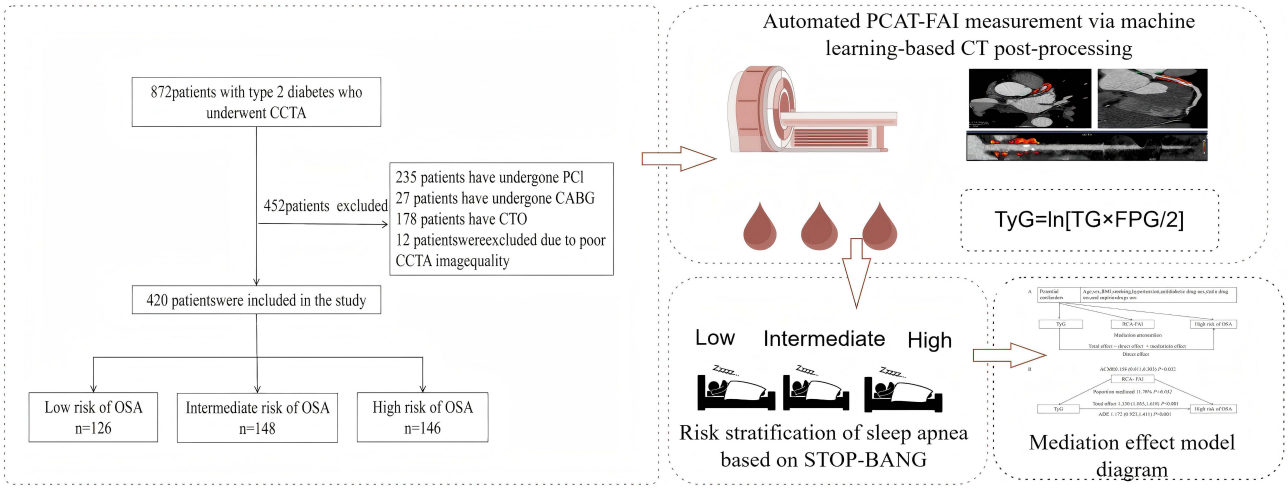


Figure 1 Flowchart of patient recruitment and study design. Patient Flow Diagram Illustrating Cohort Assembly for Analysis of Pericoronary Inflammation (Perivascular Fat Attenuation Index [FAI]) and Obstructive Sleep Apnea (OSA) Risk in Patients with Type 2 Diabetes Mellitus (T2DM) Screening Cohort: Consecutive adults with T2DM who underwent coronary computed tomography angiography (CCTA) (n = 872). Exclusions: Prior history of revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or chronic total occlusion (CTO): n = 440; Unsuccessful FAI quantification: n = 12. Final analytical cohort: n = 420 participants. Core Variables: Pericoronary Inflammation Marker: Perivascular fat attenuation index (FAI) measurements (right coronary artery [RCA], left anterior descending artery [LAD], left circumflex artery [LCX], and culprit vessel). Insulin Resistance Marker: Triglyceride-glucose (TyG) index: ln[fasting triglycerides (TG, mg/dL) × fasting plasma glucose (FPG, mg/dL)/2]. OSA Risk Assessment: Obstructive sleep apnea (OSA) risk assessment using the STOP-Bang questionnaire (cutoff ≥5 for high-risk OSA). Coronary artery bypass grafting (CABG); computed tomography angiography (CTA); chronic total occlusion (CTO); perivascular fat attenuation index (FAI); fasting plasma glucose (FPG); obstructive sleep apnea (OSA); percutaneous coronary intervention (PCI); triglycerides (TG); type 2 diabetes mellitus (T2DM); coronary computed tomography angiography (CCTA).

Ethical Considerations

The Institutional Review Board of Yan'an University Affiliated Hospital approved our study protocol, which adheres to the Declaration of Helsinki (2013 revision), granting exemption from full ethics review and waiving written informed consent requirements under Chinese national regulations for retrospective analyses of anonymized data.

STOP-BANG Risk Stratification

We assessed obstructive sleep apnea (OSA) risk using the validated STOP-Bang questionnaire.[18,19] Consistent with prior research, a STOP-Bang score of 3 or higher demonstrated high diagnostic accuracy (>0.80) for moderate-to-severe OSA (defined as AHI ≥15 events/hour).[18]

CCTA Acquisition and Analysis

Imaging Protocol

We acquired all coronary computed tomography angiography (CCTA) examinations using a 256-slice dual-source CT scanner (SOMATOM Definition Flash; Siemens Healthineers, Forchheim, Germany). Imaging optimization protocols included: patients maintained resting respiration during image acquisition; target heart rate maintained at <70 beats per minute (bpm); patients exceeding threshold received oral metoprolol (25–75 mg) 1 h pre-scan; intravenous access established via 20-gauge cannula in the right antecubital vein; iodinated contrast (iodixanol, 320 mgI/mL; 60–80 mL) injected at 4.5–6.5 mL/s using dual-barrel injector, with contrast volume titrated by body weight (≥75 kg: 80 mL).

Scan Parameters

We employed retrospective electrocardiographic (ECG) gating with the following optimized parameters: tube voltage, 120 kV; tube current, 250–800 mA (automated dose modulation via CARE Dose4D); rotation time, 270 ms; collimation, 128×0.625 mm; reconstruction, 0.75 mm slice thickness at 0.5 mm increments; matrix size, 512×512 pixels.[20,21]

PCAT Analysis

PCAT attenuation was quantified using deep learning-based software (CT-FAI V1.2, ShuKun Technology Co., Ltd., Beijing, China).[21] Vessel segments analyzed: left anterior descending (LAD) and left circumflex (LCX) arteries: proximal

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40-mm segments; right coronary artery (RCA): proximal 10–50 mm segments. The Segment Technical workflow included: 1. Bolus tracking in the ascending aorta (trigger threshold: 120 Hounsfield units [HU]);2. Automated vessel segmentation via centerline extraction; 3. PCAT definition: adipose tissue within a radial distance ≤3 Mm from the vessel wall;4. Attenuation measurement: mean HU values within the −190 to −30 HU range. Two board-certified cardiovascular radiologists, blinded to the clinical and OSA statuses, independently analyzed all CCTA datasets.

TyG Index Calculation and Covariate Definitions

TyG Index Derivation

The TyG index (TyG) was derived using the following validated formula: TyG = ln[fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2]. We converted all original laboratory measurements from mmol/L to mg/dL using standardized international conversion factors: fasting plasma glucose at 1 mmol/L = 18.018 mg/dL and triglycerides at 1 mmol/L = 88.57 mg/dL.

Diagnostic Criteria

T2DM was diagnosed according to American Diabetes Association (ADA) criteria, requiring fulfillment of ≥1 diagnostic criterion: Fasting plasma glucose ≥7.0 mmol/L;2-hour oral glucose tolerance test ≥11.1 mmol/L; Glycated hemoglobin (HbA1c) ≥6.5%;[22] Current glucose-lowering pharmacotherapy; Documented physician diagnosis. ②We classified hypertension (HTN) according to the 2024 Chinese Guidelines for Hypertension Management (CGH-2024), defining it as systolic blood pressure (SBP) ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or current use of prescribed antihypertensive medication.[23] We defined smoking status based on cumulative tobacco exposure exceeding five pack-years, equivalent to at least six months of sustained smoking at ≥20 cigarettes per day.

Statistical Analysis

We utilized SPSS software, version 26.0, from IBM Corp. in Armonk, NY, USA, to conduct all statistical analyses. According to Shapiro–Wilk normality tests, continuous variables with a normal distribution were presented as mean ± standard deviation (SD), while those without a normal distribution were displayed as median with interquartile range (IQR). We displayed categorical variables in terms of frequencies and percentages. For analyses with two groups, we used Student's *t*-test for normally distributed data and the Mann–Whitney *U*-test for non-normally distributed data. One-way ANOVA was used to analyze normally distributed data to compare multiple groups, while the Kruskal–Wallis test was applied to non-normally distributed data. We developed multivariable logistic regression models to assess the associations between metabolic markers and OSA risk, taking into account predetermined factors such as age, sex, BMI, and medication history. We used the Akaike information criterion (AIC) to optimize and fit restricted cubic splines (RCS) with four knots to explore potential nonlinear relationships between STOP-Bang scores, RCA-FAI, and the TyG index with high-risk OSA. The TyG index's mediation effects were significant, as assessed using Hayes' PROCESS macro (Model 4), to evaluate the role of RCA-FAI in mediating the TyG-OSA relationship.[24,25] We assessed the statistical significance of indirect mediation effects by generating 95% confidence intervals using 1000 bias-corrected bootstrap resamples. All statistical tests were conducted as two-tailed, with a P-value of less than 0.05 indicating statistical significance.

Study Objectives

The primary objective was to evaluate the exposure-response relationships between OSA severity and coronary inflammation, as quantified by FAI, and insulin resistance, assessed via the TyG index, in T2DM patients. The secondary objective was to evaluate the mediating role of coronary inflammation in the association between the TyG index and the severity of OSA.

Results

Baseline Characteristics

The analytical cohort comprised 420 consecutively enrolled patients with T2DM, stratified by STOP-Bang questionnaire scores into low-risk (n = 126, 30.0%), intermediate-risk (n = 148, 35.2%), and high-risk groups (n = 146, 34.8%). As detailed in Table 1, we observed statistically significant intergroup differences ($p < 0.05$) in metabolic parameters: body

Table 1 Stratification Baseline Characteristics Stratified by OSA Risk

Variables	Total Patients (n = 420)	Risk Stratification for Obstructive Sleep Apnea			$F/\chi^2/H$	P
		Low (n = 126)	Intermediate (n = 148)	High (n = 146)		
Demographics, risk factors						
Age, years	63.56 ± 9.66	63.23 ± 9.81	64.02 ± 9.48	63.38 ± 9.76	0.27	0.77
Male, n (%)	264 (62.86)	72 (48.65)	94 (63.51)	98 (67.12)	2.93	0.23
BMI, kg/m^2	24.48 (22.86, 26.21)	23.89 (22.45,25.05)	24.54 (22.38,26.45)	25.05 (23.33,27.41)	23.00	<0.01
Duration of diabetes, years	6.00 (2.00, 10.00)	8.00 (3.00,13.00)	5.00 (2.00,10.00)	6.50 (3.00,10.00)	4.08	0.13
Hypertension, n (%)	282 (67.14)	59 (46.83)	103 (69.59)	120 (82.19)	38.97	<0.01
Smoking history, n (%)	95 (22.62)	34 (26.98)	26 (17.57)	35 (23.97)	3.68	0.16
Stop-Bang score	4.00 (2.00, 5.00)	1.00 (0.00,2.00)	3.00 (3.00,4.00)	6.00 (5.00,7.00)	379.12	<0.01
Antidiabetic drugs, n (%)	386 (91.90)	118 (93.65)	138 (93.24)	130 (89.04)	1.81	0.41
Statin, n (%)	351 (83.57)	105 (83.33)	128 (86.49)	118 (80.82)	1.73	0.42
Aspirin, n (%)	206 (49.05)	62 (49.21)	72 (48.65)	72 (49.32)	0.01	0.99
Clinical variables and laboratory indicators						
SBP, mmHg	142.57 ± 21.64	137.44 ± 17.83	140.50 ± 21.75	149.08 ± 23.02	11.35	<0.01
DBP, mmHg	83.64 ± 12.35	81.96 ± 11.12	83.10 ± 13.59	85.63 ± 11.83	3.24	0.04
FPG, mmol/L	7.30 (6.30, 8.81)	6.75 (5.99,7.73)	7.42 (6.47,8.81)	7.90 (6.74,10.02)	28.99	<0.01
HbA1c, %	7.30 (6.50, 8.60)	6.90 (6.40,8.10)	7.30 (6.60,8.40)	7.55 (6.70,9.00)	11.77	<0.01
TC, mmol/L	4.17 (3.37, 5.08)	3.87 (3.23,4.83)	3.89 (3.37,5.01)	4.56 (3.57,5.42)	11.33	<0.01
TG, mmol/L	1.60 (1.22, 2.36)	1.39 (1.08,1.72)	1.52 (1.20,2.06)	2.26 (1.44,3.08)	62.58	<0.001
HDL-C, mmol/L	1.01 (0.88, 1.20)	1.08 (0.92,1.25)	1.02 (0.88,1.21)	0.98 (0.86,1.11)	11.29	<0.01
LDL-C, mmol/L	1.90 (1.44, 2.67)	1.71 (1.33,2.56)	1.86 (1.46,2.55)	2.18 (1.63,2.78)	6.80	0.03
TyG index	9.17 (8.88, 9.59)	8.98 (8.72,9.11)	9.06 (8.86,9.45)	9.58 (9.27,9.99)	91.08	<0.01

Notes: Statistical symbols: F: F-statistic from one-way analysis of variance (ANOVA) for normally distributed continuous variables; H: Kruskal–Wallis H-statistic for non-normally distributed continuous variables; χ^2: Chi-square statistic for categorical variables. We report continuous variables as mean ± standard deviation (SD) when normally distributed and as median with interquartile range (IQR; 25th-75th percentiles) for non-normally distributed variables. For categorical variables, we present frequencies and percentages (n [%]).

Abbreviations: BMI, Body mass index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; FPG, Fasting plasma glucose; HbA1c, Glycated hemoglobin A1c; TC, Total cholesterol; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; TyG, Triglyceride-glucose index.

mass index (BMI), systolic and diastolic blood pressure (SBP/DBP), STOP-Bang scores, hypertension prevalence, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglyceride-glucose (TyG) index. Conversely, we detected no statistically significant variations in demographic characteristics (age, sex distribution), clinical profiles (smoking history, disease duration), or medication regimens (hypoglycemic agents, lipid-lowering drugs, antihypertensive agents, antiplatelet therapy) between groups (all $P > 0.05$).

3.2 Distribution of research subjects based on OSA risk stratification and peri-crown fat attenuation index characteristics.

Figure 2 visually demonstrates significantly higher PCAT-FA values in all three coronary arteries (LAD, LCX, and RCA) among patients with elevated OSA risk (intermediate- and high-risk groups) compared to the low-risk group ($P < 0.05$).

Multivariable Regression Analysis for High-Risk OSA

To evaluate the independent associations between pericoronary adipose tissue inflammation and OSA risk, we developed multivariable logistic regression models employing progressive adjustment strategies (Table 2): Model 1 (Unadjusted): Base model without covariates; Model 2 (Partially Adjusted): Adjusted for demographic confounders (age, sex); Model 3 (Fully Adjusted): Adjusted for clinical covariates: hypertension status, smoking history, body mass index (BMI), glycated hemoglobin (HbA1c), and medication classes (glucose-lowering agents, lipid-modifying therapy, antiplatelet agents).

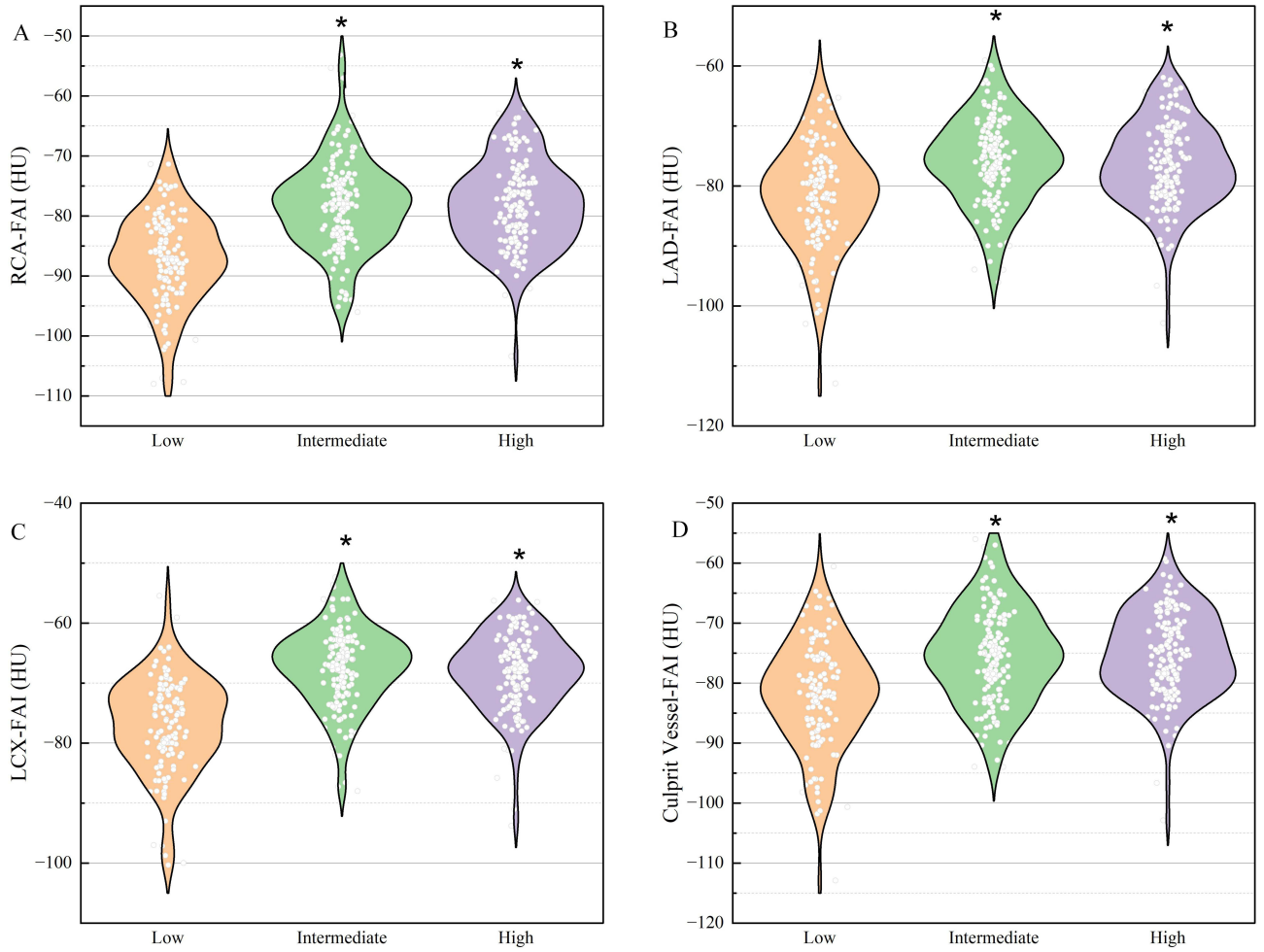

Figure 2 Pericoronary Adipose Tissue Fat Attenuation Index (PCAT-FAI) Across OSA Risk Groups (**A**) Right coronary artery (RCA); (**B**) Left anterior descending artery (LAD); (**C**) Left circumflex artery (LCX); (**D**) Culprit vessel. Color coding: Orange: Low-risk obstructive sleep apnea (OSA) (n = 126); Green: Intermediate-risk OSA (n = 148); Purple: High-risk OSA (n = 146). Statistical analysis: The Kruskal–Wallis test revealed a significant overall difference in the PCAT-FAI across the OSA risk groups. Dunn's post hoc tests showed: *$p < 0.05$ for intermediate- and high-risk groups vs low-risk group.

After full adjustment (Model 3): RCA-FAI: OR 1.06 (95% CI: 1.01–1.10; $P = 0.01$). The TyG index (OR 3.30 [95% CI: 1.92–5.67; $P < 0.01$) was significantly associated with a high risk of OSA. We identified no significant associations between perivascular fat attenuation indices—specifically LAD-FAI, LCX-FAI, or culprit vessel FAI—and high-risk OSA.(all $P > 0.05$).

Nonlinear Associations Between Coronary Inflammation and Insulin Resistance

Restricted cubic spline analyses demonstrated significant overall associations between the RCA-FAI and TyG index with OSA risk (Poverall < 0.001; Figure 3). Specifically, RCA-FAI showed a nonlinear relationship with high OSA risk ($P_{\text{nonlinearity}} = 0.007$), with a threshold effect at −80 HU. Above this threshold, each 10-HU increment conferred a 1.8- to 4.2-fold elevated risk of OSA (95% CI [1.5, 4.5]; $P_{\text{trend}} = 0.002$). TyG index exhibited no significant nonlinear association ($P_{\text{nonlinearity}} = 0.051$).

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Table 2 Associations of Pericoronary Inflammation and Insulin Resistance with High-Risk Obstructive Sleep Apnea (OSA): A Multivariable Logistic Regression Analysis

Variables	High Risk of Obstructive Sleep Apnea					
	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
RCA-FAI	1.07 (1.04 ~ 1.09)	<0.01	1.05 (1.01 ~ 1.09)	0.01	1.06 (1.01 ~ 1.10)	0.01
LAD-FAI	1.04 (1.01 ~ 1.06)	0.01	0.97 (0.93 ~ 1.02)	0.22	0.97 (0.93 ~ 1.02)	0.24
LCX-FAI	1.06 (1.03 ~ 1.09)	<0.01	1.04 (1.00 ~ 1.08)	0.07	1.03 (1.00 ~ 1.07)	0.06
Culprit Vessel-FAI	1.04 (1.02 ~ 1.07)	<0.01	1.02 (0.98 ~ 1.07)	0.29	1.04 (0.99 ~ 1.09)	0.15
TyG Index	4.83 (3.22 ~ 7.26)	<0.01	4.72 (3.09 ~ 7.22)	<0.01	3.30 (1.92 ~5.67)	<0.01

Notes: Model 1: Unadjusted. Model 2: Adjusted for age and sex. Model 3: Adjusted for age, sex, body mass index(BMI), hypertension, glycated hemoglobin (HbA1c), total cholesterol(TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and medication (antidiabetic drugs, statins, aspirin) variables.

Abbreviations: BMI, Body mass index; FAI, Fat attenuation index; FPG, Fasting plasma glucose; HbA1c, Glycated hemoglobin; HDL-C, High-density lipoprotein cholesterol; LAD-FAI, Left anterior descending artery perivascular fat attenuation index; LCX-FAI, Left circumflex artery perivascular fat attenuation index; LDL-C, Low-density lipoprotein cholesterol; RCA-FAI, Right coronary artery perivascular fat attenuation index; TC, Total cholesterol; TG, Triglycerides; TyG, Triglyceride-glucose index.

Insulin Resistance-Mediated Effect of Coronary Inflammation on the High Risk of OSA

Mediation analysis demonstrated that the RCA-FAI significantly mediated the association between the TyG index and high-risk OSA (Figure 4). The mediation proportion was 11.78%, with a 95% CI of 2.3–21.1 ($P = 0.03$).

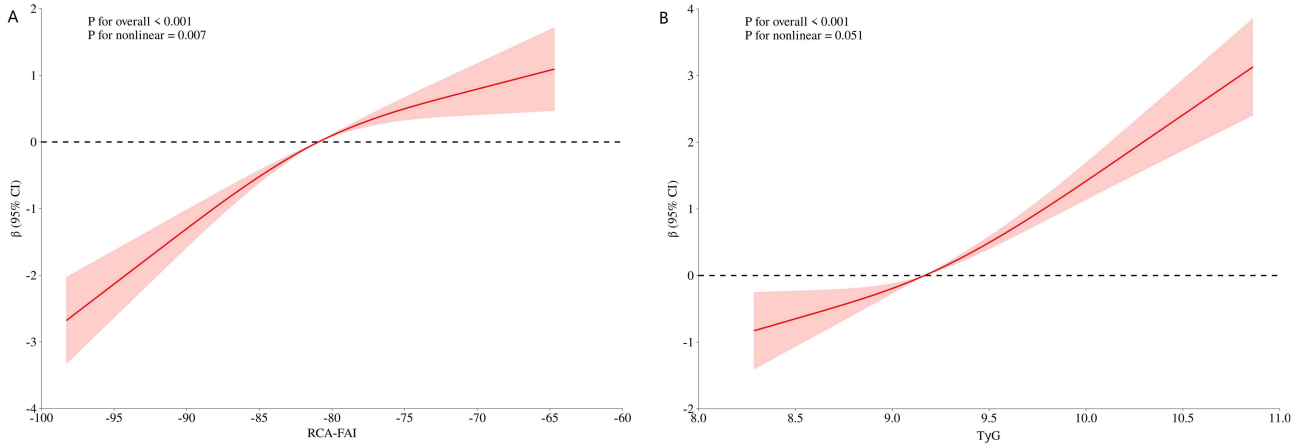

Figure 3 Restricted Cubic Spline Regression Analysis of Associations Between Vascular Inflammation (Right Coronary Artery Perivascular Fat Attenuation Index [RCA-FAI]) and Insulin Resistance (Triglyceride-Glucose [TyG] Index) Markers with High-Risk Obstructive Sleep Apnea (OSA) in Patients with Type 2 Diabetes Mellitus (T2DM) (**A**) Right Coronary Artery (RCA) Perivascular Fat Attenuation Index (FAI, Hounsfield units [HU]); (**B**)Triglyceride-Glucose (TyG) Index. Red curve: Fitted log-odds ratio for high-risk OSA (defined as STOP-Bang score ≥5); Pink band: 95% confidence interval (CI); Dashed line: Reference line (log-odds ratio = 0; corresponding to odds ratio [OR] = 1). We present continuous variables as the mean ± standard deviation (SD) for normally distributed parameters and as the median with interquartile range (IQR; 25th-75th percentiles, Q1-Q3) for non-normally distributed parameters. We report frequencies with corresponding percentages (n [%]) for categorical variables. We defined $P_{nonlinear}$ as the p-value derived from the likelihood ratio test comparing the nonlinear (spline) model against the linear model, which assesses nonlinearity. Similarly, we defined P_{linear} as the p-value testing the linear term within the spline model, which evaluates the strength of the linear association. We established statistical significance using a threshold of $p < 0.05$ based on two-tailed hypothesis testing.

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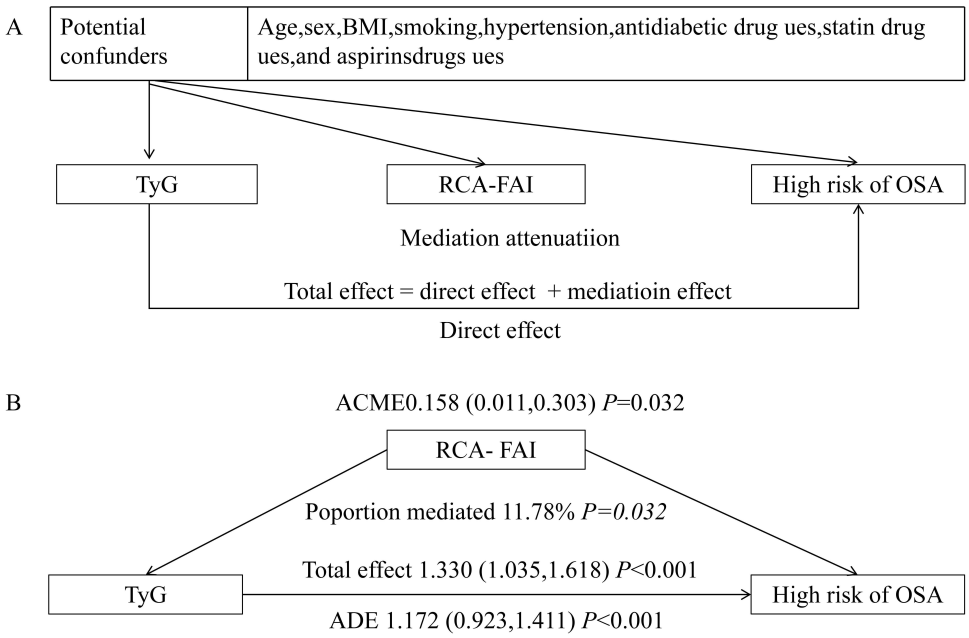

Figure 4 Mediating Role of Right Coronary Artery Perivascular Fat Attenuation Index (RCA-FAI) in the Association Between Triglyceride-Glucose (TyG) Index and High-Risk Obstructive Sleep Apnea (OSA) in Patients with Type 2 Diabetes Mellitus (T2DM) (**A**) Directed Acyclic Graph (DAG) Model of Causal Pathways. The solid arrows represent the adjusted causal pathways. The confounders included age, sex, body mass index (BMI), smoking status, hypertension, glucose-lowering medications, statins, and aspirin. (**B**) Mediation Effect Estimates.

Abbreviations: ACME, Average Causal Mediation Effect; ADE, Average Direct Effect; RCA-FAI, Right coronary artery perivascular fat attenuation index; TyG, Triglyceride-glucose index; BMI, Body mass index; OSA, Obstructive sleep apnea; T2DM, Type 2 diabetes mellitus.

Discussions

In this cross-sectional study of 420 patients with T2DM, we investigated the relationship between the TyG index, FAI, and OSA risk. Consistent with prior research, the OSA group demonstrated a significantly elevated TyG index compared to non-OSA controls.[11] Our study reveals significant differences in pericoronary adipose tissue FAI across OSA risk stratifications among individuals with T2DM, establishing substantial correlations between the TyG index, FAI, and elevated OSA risk. Mechanistically, we identified FAI as an essential mediator of the TyG index-OSA risk association, accounting for 11.8% of the total effect (β = 0.32, 95% CI 0.18–0.47). This work provides the first evidence establishing the TyG-FAI pathway as a novel mechanism of OSA susceptibility, specifically in T2DM populations.

Building on the established predictive value of the TyG index for cardiovascular disease (CVD) in T2DM, recent evidence has highlighted its significant association with OSA severity and related cardiovascular risks. A systematic review and meta-analysis demonstrated that the TyG index significantly enhances the predictive power of traditional risk models for CVD in T2DM patients.[26] Furthermore, research indicates that the TyG index and its derivatives (TyG-BMI and TyG-WC) increase progressively with worsening OSA severity. This link extends to specific cardiovascular outcomes.[27] A cross-sectional study of 1059 patients with OSA revealed that each unit increase in the TyG index was associated with a 1.98-fold higher risk of coronary heart disease (OR = 1.98, 95% CI: 1.42–2.80, $p < 0.001$). The same study also found a significant nonlinear positive correlation between the TyG index and the severity of coronary atherosclerosis, as measured by the Gensini score (nonlinear test $p = 0.003$).[28] These findings collectively suggest that the TyG index serves as an effective metabolic marker for stratifying coronary heart disease risk and assessing coronary lesions in patients with OSA, confirming the association between metabolic dysregulation and OSA, and indicating a dose-response relationship between the TyG index and OSA severity. Our results are consistent with this established relationship. After multivariate adjustment, we observed an independent positive correlation between the TyG index and high OSA risk. This finding reinforces the conclusion from a recent meta-analysis, which reported a significantly higher TyG index in OSA groups compared to controls (SMD = 0.86, 95% CI: 0.58–1.13).[29]

Our analysis revealed significantly elevated FAI in the RCA, LAD, LCX, and culprit vessels among intermediate- and high-risk OSA groups compared to the low-risk group. Notably, the association between RCA-FAI and OSA risk persisted after comprehensive multivariable adjustment, indicating its predictive independence from traditional metabolic confounders such as BMI, blood pressure, and lipid profiles. This observation aligns with prior evidence that the RCA is the optimal anatomical site for assessing coronary artery inflammation,[30,31] and corroborates findings from Liu et al, who identified occult vascular inflammation in high-risk T2DM cohorts with coronary heart disease.[17] Collectively, these results suggest FAI may serve as a complementary imaging biomarker for OSA risk stratification beyond conventional metabolic metrics. Furthermore, mediation analysis demonstrated that RCA-FAI mediated 11.78% ($\beta = 0.118$) of the TyG index–OSA risk association, supporting a plausible pathological pathway wherein metabolic dysregulation promotes coronary inflammation, thereby increasing OSA susceptibility. Nevertheless, we emphasize that our cross-sectional design cannot infer causality between TyG and OSA.

Collectively, our findings advance the conceptualization of a "metabolic-inflammatory-hypoxia axis" in T2DM. We demonstrated that glycolipid metabolic dysregulation, reflected by an elevated TyG index, drives proinflammatory phenotypic transformation in PCAT, aligning with Liu et al's observations of coronary inflammation in T2DM.[17] Intermittent hypoxia (IH) secondary to OSA exacerbates insulin resistance through two key inflammatory pathways in coronary adipose tissue. First, IH activates hypoxia-inducible factor (HIF) signaling, which increases leptin secretion and macrophage infiltration.[32] Second, IH promotes macrophage ferroptosis and M1 polarization while triggering endoplasmic reticulum stress and NLRP3 inflammasome activation.[33,34] These processes collectively drive adipose tissue inflammation and impair insulin signaling via leptin overexpression and IL-6/TNF-α-mediated pathways.[32,33] The resulting vascular dysfunction manifests as impaired vasodilation and increased perivascular inflammation[34,35] (Figure S1).

Building on the FAI's role as a validated quantifier of coronary inflammation for cardiovascular risk assessment, our findings extend its clinical utility to the OSA prediction.[15] We demonstrated for the first time that the TyG index mediates the relationship between metabolic dysfunction and OSA, providing mechanistic validation for Sotak et al's adipose inflammation hypothesis.[36] Notably, the dose-response relationship between TyG and coronary risk, as well as the corresponding FAI gradient changes, reveals an inflammatory threshold phenomenon in metabolic dysregulation. The OSA risk escalated nonlinearly when the RCA-FAI was higher than −80 HU. These clinically actionable thresholds support the development of a targeted screening protocol, wherein we recommend immediate polysomnography (PSG) referral for patients with T2DM who meet the predefined high-risk criteria to facilitate timely OSA diagnosis and early intervention in the future.

Limitations and Future Direction

This study has several limitations. First, the cross-sectional design precluded definitive causal inference of the sequence of the TyG-FAI-OSA pathway. Second, although we adjusted for key confounding factors, we cannot exclude residual confounding (eg, unmeasured genetic predisposition or gut microbiome dysbiosis). Third, OSA diagnosis relied on the Stop-BANG questionnaire rather than PSG, introducing OSA severity misclassification bias. Finally, two constraints merit emphasis: the sample size (N = 420) restricts the statistical power for subgroup analyses, and ethnic homogeneity reduces the external validity for diverse populations.

Directions: To address these gaps, three research priorities merit investigation: (i) implementing longitudinal cohorts and Mendelian randomization designs to elucidate genetic associations between TyG-index traits and OSA susceptibility; (ii) integrating PSG with bioelectrical impedance analysis to delineate OSA-body composition-adipose distribution interactions; and (iii) constructing artificial intelligence frameworks integrating coronary CTA with multi-omics datasets for precision OSA risk stratification.

Conclusion

In this cohort of patients with T2DM, we demonstrate for the first time that FAI—a radiological marker of vascular inflammation—is significantly associated with high-risk OSA. The TyG index, an established indicator of insulin resistance, independently predicted high-risk OSA, with RCA-FAI mediating 11.8% of this association. Crucially, we identified a nonlinear threshold effect: OSA risk escalated when RCA-FAI exceeded −80 HU. These findings unveil

pathogenic cross-system interactions linking T2DM, coronary inflammation, and OSA, while establishing RCA-FAI as a metabolic imaging biomarker for OSA risk stratification. Therefore, integrating RCA-FAI (≥ −80 HU) and TyG index into routine T2DM risk assessment workflows may enable precision stratification of OSA-related cardiovascular risk, guiding targeted interventions. Future prospective studies are warranted to validate this multi-marker screening strategy.

Abbreviations

OSA, Obstructive Sleep Apnea; T2DM, Type 2 Diabetes Mellitus; PCAT, Pericoronary adipose tissue; TyG, Triglyceride-Glucose Index; CCTA, Coronary Computed Tomography Angiography; FAI, Fat attenuation index; RCA, Right coronary artery; LAD, Left anterior descending coronary artery; LCX, Left circumflex coronary artery; RCS, Restricted cubic splines.

Data Sharing Statement

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

This retrospective study was conducted in accordance with the Declaration of Helsinki (2013 revision) and received an exempt review approval from the Institutional Review Board of the Affiliated Hospital of Yan'an University (Ethical Approval Number: IIT-R-20230168). The institutional ethics committee waived written informed consent per the Chinese National Guidelines for Retrospective Analysis of Anonymized Data.

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Author Contributions

Mei Zhang: Conceptualization, Funding acquisition, Writing – original draft, Data curation, Validation. Hai-Mei Du: Writing – original draft, Formal analysis, Methodology, Supervision, Conceptualization, Funding acquisition, Writing – original draft. Qin Zhou: Data curation, Investigation, Writing – original draft. Ya-Xin Yao: Data curation and visualization, Writing – original draft. Lin-Juan Li: Conceptualization, Funding acquisition, Project administration, Supervision, 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.

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Disclosure

All authors declare no conflicts of interest related to this study.

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