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Triglyceride-glucose waist-to-weight index and bone microarchitecture in type 2 diabetes: a machine-learning and regression analysis

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Triglyceride-glucose index, weight-adjusted waist index, bone microarchitecture, trabecular bone score, bone mineral density, type 2 diabetes mellitus

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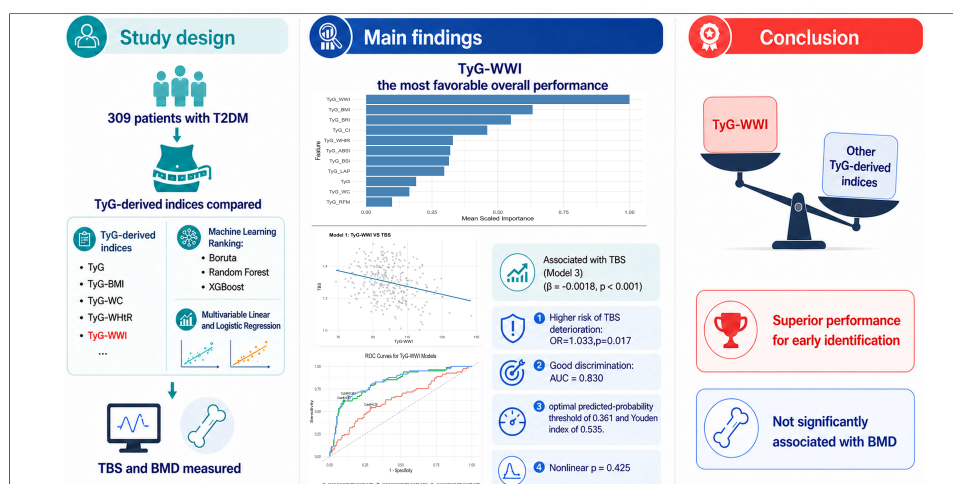
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Abstract

Aim: The triglyceride-glucose (TyG) index is a surrogate indicator of insulin resistance, which impairs bone quality and increases fracture risk. However, no study has combined TyG with the weight-adjusted waist index (WWI), an indicator of central adiposity, to evaluate associations with trabecular bone score (TBS) and bone mineral density (BMD) in individuals with type 2 diabetes mellitus (T2DM). We investigated whether TyG-WWI outperforms other TyG-derived indicators in identifying abnormal bone metabolism and microstructural deterioration in T2DM.

Methods: This cross-sectional study included 309 patients with T2DM. Boruta, random forest, and XGBoost ranked TyG-derived indices for lumbar spine TBS and BMD. Adjusted linear and logistic regression models examined TyG-WWI associations with TBS, BMD, and TBS deterioration. Restricted cubic spline analysis examined nonlinearity, and receiver operating characteristic analysis with bootstrap validation assessed discriminative performance for TBS deterioration.

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Results: TyG-WWI ranked highest for TBS. In Model 3, each 1-unit increase in TyG-WWI was associated with a 0.0018-unit decrease in TBS ($\beta = -0.0018$, $P < 0.001$) and 3.3% higher odds of TBS deterioration (OR = 1.033, 95%CI: 1.006-1.061, $P = 0.017$). Restricted cubic spline analysis showed no evidence of nonlinearity (P for nonlinearity = 0.425). Model 3 achieved an area under the curve (AUC) of 0.830 (95%CI: 0.778-0.883), an optimal model-estimated probability threshold of 0.361, and a Youden index of 0.535. TyG-WWI was not significantly associated with BMD.

Conclusion: TyG-WWI exhibited the most favorable overall performance among the evaluated TyG-derived indices for identifying bone microstructure impairment in patients with T2DM.

INTRODUCTION

Diabetes mellitus (DM) is a major global public health burden. In China, the prevalence of diabetes among the adult population is 11.2% overall and exceeds 20% among individuals aged 60 years or older^[1], and type 2 DM (T2DM) accounts for more than 90% of cases^[2]. T2DM-related complications markedly impair individual health and impose substantial social and economic burdens. Although patients with T2DM often have normal or increased bone mineral density (BMD), they may have impaired bone quality due to metabolic abnormalities, resulting in reduced bone strength and increased fracture risk^[3,4]. Diabetes-related fractures may heal slowly and are often accompanied by complications, threatening quality of life and survival. Therefore, early identification of abnormal bone metabolism in patients with diabetes and implementation of targeted interventions are clinically important.

Insulin resistance (IR) is central to the pathophysiology of T2DM and obesity. It promotes lipid deposition and alters energy metabolism by reducing the responsiveness of peripheral tissues to insulin^[5]. It may also disrupt insulin-like growth factor 1 (IGF-1) signaling, increase oxidative stress and inflammation, and disturb the balance between bone formation and resorption, thereby compromising bone integrity and increasing susceptibility to fragility fractures^[6].

Although the hyperinsulinemic-euglycemic clamp (HEC) is the reference standard for assessing IR, its complexity and cost limit its use in large-scale screening. The triglyceride-glucose (TyG) index is a simple, stable surrogate marker of IR^[7,8]. Several studies have combined the TyG index with measures of obesity to characterize metabolic risk more comprehensively^[9]. However, traditional obesity measures may not fully capture central fat distribution or body composition, which could limit their utility in studies of bone metabolism. The weight-adjusted waist index (WWI) is a newer measure of central adiposity that may reflect body composition independently of body weight and identify abnormal body composition associated with sarcopenia and obesity^[10]. WWI has been associated with metabolic syndrome, IR, atherosclerosis, and deterioration of bone microarchitecture^[11]. TyG-WWI combines the TyG index and WWI and may capture both IR-related metabolic risk and central adiposity^[12]. However, no previous study has combined WWI with the TyG index to assess associations of TyG-WWI with trabecular bone score (TBS) and BMD in patients with T2DM. Moreover, few studies have systematically compared TyG-WWI with the TyG index and other derived indices.

Accordingly, we included patients with T2DM to compare the associations of the TyG index and its derived indices with TBS and BMD, identify the metabolic indicator most strongly associated with adverse bone outcomes, and characterize its relationships with TBS and BMD. The study also aimed to clarify the relationship between IR-related metabolic abnormalities and bone microarchitectural deterioration and provide a basis for early identification and prevention of diabetes-related osteoporosis.

METHODS

Study design and population characteristics

This retrospective cross-sectional study was conducted in the Department of Endocrinology at Shenzhen Second People's Hospital from July 2022 to March 2023. Patients with T2DM who received inpatient or outpatient care were identified according to the 2023 American Diabetes Association diagnostic criteria^[13]. Individuals with a history of osteoporosis or fracture, rheumatoid arthritis, severe liver or kidney disease, active malignancy, hormone replacement therapy, glucocorticoid use, or missing key physical or laboratory data were excluded [Supplementary Figure 1]. This study was approved by the Ethics Committee of Shenzhen Second People's Hospital (Approval No. 2024-176-01PJ), ensuring compliance with the principles outlined in the Declaration of Helsinki. It was also granted permission to waive the need for patients to provide written informed consent.

TyG and derived indices

The TyG index was combined with obesity-related anthropometric parameters to generate several TyG-based indices, including TyG-BMI, TyG-WC, TyG-WHtR, TyG-BRI, TyG-ABSI, TyG-WWI, TyG-LAP, TyG-CI, TyG-BSI, and TyG-RFM. The definitions and formulas are summarized in Supplementary Table 1.

Data and information collection

Demographic and clinical data were collected, including age, sex, menopausal status, smoking and alcohol use, medical history, diabetes duration, diabetic complications, and medications. Body weight, waist circumference, hip circumference, and body mass index (BMI) were measured while patients were fasting and wearing light clothing. Fasting venous blood samples were analyzed for fasting plasma glucose, glycated hemoglobin (HbA_{1c}), fasting C-peptide, lipids [total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C)], renal and liver function markers [serum creatinine (SCr), blood urea nitrogen (BUN), uric acid (UA), total bilirubin (TBIL), albumin (ALB), alanine aminotransferase (ALT), and gamma-glutamyl transferase (γ -GGT)], calcium, phosphorus, 25-(OH)VitD, parathyroid hormone (PTH), N-terminal osteocalcin, procollagen type I N-terminal propeptide (P1NP), and beta-C-terminal telopeptide (β -CTX). Urinary albumin and urine albumin-creatinine ratio (UACR) were determined from 24-h urine collections. Lumbar spine BMD (T-score), femoral neck BMD (T-score), and total hip BMD (T-score) were measured using dual-energy X-ray absorptiometry with the GE Lunar iDXA system (GE Healthcare, Madison, WI, USA). Lumbar TBS values were then derived retrospectively using TBS iNsight software (version 3.0.0; Medimaps, Switzerland). TBS deterioration was defined as TBS < 1.23^[14].

Statistical methods

The distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Normally distributed data were summarized as the mean $\pm$ SD, and nonnormally distributed data as the median and IQR. Categorical variables were summarized as frequencies and percentages. Differences between sexes were analyzed using the independent-samples t-test, Mann-Whitney U test, chi-square test, or Fisher's exact test, as appropriate.

Spearman's rank correlation was used to assess relationships among the TyG index and its derived indices. To permit comparisons across models, the TyG index and its derived indices were standardized as z-scores, so associations with TBS and lumbar spine BMD (T-score) were expressed per 1-standard deviation (SD) increase. We used three machine-learning algorithms, Boruta feature selection, random forest (RF), and XGBoost, to rank the feature importance of the TyG index and its derived indices for TBS and lumbar spine BMD (T-score) in patients with T2DM. For Boruta, the maximum number of iterations was 500, and tentative variables were resolved using the TentativeRoughFix function. For random forest, permutation-based importance was expressed as the percentage increase in mean squared error. The mtry parameter was

tuned using repeated 5-fold cross-validation with 10 repeats, and 1,000 trees were fitted. For XGBoost, feature importance was quantified using gain, and the main hyperparameters were tuned using repeated 5-fold cross-validation with 10 repeats. To assess ranking stability, the feature-importance analysis was repeated 50 times using bootstrap resampling. Because the importance metrics differed across algorithms, values were standardized before comparison, and their mean was calculated as the consensus importance score. Each standardized TyG-related index was then entered separately into adjusted linear regression models for TBS and lumbar spine BMD (T-score) and into adjusted logistic regression models for TBS deterioration. False discovery rate (FDR) correction accounted for multiple testing in the regression analyses of TyG-derived indices. FDR-adjusted P values were reported as P_{FDR} , and $P_{\text{FDR}} < 0.05$ was considered statistically significant. Standardized β coefficients were used to compare variables. Model fit was assessed using R^2 , adjusted R^2 , and RMSE, where applicable. Receiver operating characteristic analysis evaluated discrimination of TBS deterioration by the TyG-derived indices. For each standardized index, predicted probabilities were generated from the corresponding logistic regression model, and area under the curve (AUC) values were calculated. TyG-WWI and each comparator were evaluated in the same analytic sample for each paired ROC comparison. TyG-WWI was the reference, and AUC differences were tested using the paired DeLong method. DeLong P values were adjusted using the Benjamini-Hochberg FDR procedure.

TyG-WWI was selected as the primary index based on the combined comparison of multiple machine-learning algorithms and regression models. Multivariable linear and logistic regression models were used to examine the relationships of TyG-WWI with TBS and BMD in patients with T2DM. TyG-WWI was treated as the primary exposure variable. Model 1 was unadjusted, Model 2 included age and sex, and Model 3 additionally included selected clinical and biochemical covariates. As shown in [Supplementary Table 2](#), all candidate clinical and biochemical variables were entered into a random forest model, and variable importance was assessed using %IncMSE. Variables with %IncMSE > 1.0 were considered potentially informative. To reduce multicollinearity, variance inflation factors (VIFs) were assessed, and variables with VIF > 5 were excluded. ROC analysis evaluated the discrimination of TBS deterioration by logistic models incorporating TyG-WWI. AUCs and 95% CIs were calculated. The optimal cutoff was determined by maximizing the Youden index, defined as sensitivity + specificity - 1. For multivariable models, the cutoff represented a model-estimated probability threshold. Internal validation of Model 3 used 1,000 bootstrap resamples, and the optimism-corrected AUC and bootstrap-based cutoff estimates were reported. In each bootstrap resample, the model was refitted, and optimism was the difference between the AUC in the bootstrap sample and the AUC obtained when the bootstrap-fitted model was applied to the original dataset. The optimism-corrected AUC was calculated by subtracting mean optimism across all valid resamples from the apparent AUC. The optimal model-estimated probability cutoff was recalculated in each resample by maximizing the Youden index. The median represented the bootstrap cutoff, and its 95% CI was estimated using the 2.5th and 97.5th percentiles of the bootstrap distribution.

To evaluate the robustness of the main findings, a sensitivity analysis additionally adjusted Model 3 for overall antidiabetic drug use. The sensitivity model therefore included TyG-WWI, age, sex, RF-selected covariates, and antidiabetic drug use. Linear regression was used for continuous TBS, while logistic regression and ROC analysis were used for TBS deterioration.

Given the role of menopausal status in bone metabolism, we performed analyses stratified by menopausal status among women. The association between TyG-WWI and TBS deterioration in postmenopausal women was assessed using logistic regression. Three models were fitted. Interaction analyses assessed whether menopausal status, sex, or age modified the association between TyG-WWI and TBS deterioration. The nonlinear relationship between TyG-WWI and TBS was further assessed using restricted cubic spline (RCS) regression. Four knots were placed at the 5th, 35th, 65th, and 95th percentiles, and the model included the

same covariates as Model 3. Overall and nonlinear associations were tested using analysis of variance, and adjusted TBS values with 95% CIs were plotted. Participants with missing values for the corresponding TyG-related index or outcome were excluded from the relevant analysis, and exposure and outcome variables were not imputed. Missing continuous covariates were handled using multiple imputation by chained equations, whereas missing categorical covariates were retained as a separate “Unknown” category. Women with missing menopausal-status information were excluded from the menopause-stratified and menopause-interaction analyses.

Statistical analyses were performed using R version 4.3.0. Baseline comparisons, correlation analyses, and regression models used the stats package. Machine-learning analyses were performed with Boruta, randomForest, xgboost, and caret packages. The car, pROC, boot, rms, mice, and ggplot2 packages were used for VIF assessment, ROC analysis, bootstrap validation, restricted cubic splines, multiple imputation, and figure generation, respectively. Statistical significance was defined as a two-sided $P < 0.05$.

RESULTS

Baseline characteristics

Among the 309 patients with T2DM, 158 were women. Baseline characteristics are shown in [Table 1](#). Women were older than men (62.63 ± 9.87 vs. 58.87 ± 11.43 , $P = 0.002$). Renal function and blood biochemical indicators showed that SCr and UA were significantly lower in women than in men ($P < 0.001$), as were TBIL and γ -GGT ($P < 0.01$). Serum phosphorus was significantly higher in women than in men ($P = 0.002$), whereas serum calcium did not differ significantly between the sexes ($P = 0.354$). Regarding bone-related measures, N-terminal osteocalcin levels were slightly higher in women than in men ($P = 0.046$), whereas T-scores at the femoral neck, total hip, and lumbar spine were significantly lower in women than in men (femoral neck T-score: -1.79 vs. -1.19 ; total hip T-score: -1.11 vs. -0.51 ; lumbar spine T-score: -1.32 vs. -0.39 ; all $P < 0.001$). Lumbar spine TBS was also significantly lower in women than in men (1.26 vs. 1.34 , $P < 0.001$), consistent with poorer trabecular microarchitecture in women. TyG-WC was significantly higher in men than in women (825.32 ± 128.20 vs. 773.82 ± 123.07 , $P < 0.001$). TyG-WWI was slightly higher in women than in men, although the difference was not statistically significant (100.44 ± 12.70 vs. 97.84 ± 11.20 , $P = 0.057$). Smoking and alcohol use were less common among women (both $P < 0.001$), whereas diabetes duration, complications, antidiabetic therapy, lipid levels, and glucose-related measures did not differ significantly between the sexes.

Associations of TyG and related indices with TBS

To evaluate associations of the TyG index and its derived indices with bone microarchitecture, we combined machine-learning feature selection with multivariable linear and logistic regression. Across Boruta, RF, and XGBoost, TyG-WWI ranked first among the TyG index and its derived indices [[Figure 1](#)], indicating the highest consensus feature importance for TBS.

To permit direct comparisons across measurement scales, all TyG-derived indices were standardized as z-scores. The β coefficients and odds ratios (ORs) for these indices are therefore expressed per 1-SD increase. In the multiple linear regression model, TBS was specified as the outcome variable, and all standardized TyG-derived indices were inversely associated with TBS, with standardized TyG-WWI having the largest absolute regression coefficient. In Model 3, each 1-SD increase in TyG-WWI was associated with a 0.0217-unit decrease in TBS ($\beta = -0.0217$, standardized $\beta = -0.1983$, 95%CI: -0.0326 to -0.0108 , $P = 1.09 \times 10^{-4}$, $P_{\text{FDR}} = 0.000511$), representing the largest adjusted association with lower TBS among the evaluated indices [[Figure 2](#)].

Table 1. Baseline characteristics of patients with T2DM stratified by sex

Variable	Women	Men	P value
Age (years)	62.627 ± 9.865	58.874 ± 11.428	0.002 [*]
Duration of diabetes	11.720 ± 7.746	10.407 ± 7.627	0.134
LDL	2.816 ± 1.180	2.711 ± 0.945	0.387
TC	4.482 ± 1.402	4.258 ± 1.119	0.121
HbA1c	8.535 ± 1.963	8.842 ± 2.368	0.217
Fasting C-peptide	1.245 (0.688-1.748)	1.200 (0.730-1.740)	0.779
TBIL (μmol/L)	8.700 (7.025-10.400)	10.300 (7.700-12.300)	0.0001 [*]
Albumin (g/L)	39.900 (37.525-41.575)	40.000 (37.650-41.850)	0.562
ALT	18.000 (13.225-24.600)	18.400 (13.150-30.950)	0.152
γ-GGT	20.000 (13.000-25.000)	21.000 (16.000-31.500)	0.005
SCr (μmol/L)	55.250 (48.025-66.975)	73.500 (64.850-87.750)	0.0001 [*]
BUN (mmol/L)	5.900 (4.500-7.400)	6.200 (5.000-7.300)	0.174
UA	312.850 (257.42-380.70)	349.800 (307.10-413.45)	0.0001 [*]
Blood calcium	2.250 (2.160-2.320)	2.230 (2.155-2.310)	0.354
Serum phosphorus	1.265 (1.120-1.407)	1.180 (1.080-1.330)	0.002 [*]
Urinary albumin (mg/L)	13.195 (4.997-40.925)	13.195 (6.095-56.700)	0.448
UACR (mg/g)	21.070 (10.260-89.390)	21.070 (8.435-64.340)	0.368
25-(OH)VitD (ng/mL)	24.821 ± 8.439	25.412 ± 8.164	0.532
PTH	28.930 (20.372-39.653)	28.790 (20.095-37.960)	0.564
N-terminal osteocalcin	13.980 (12.000-16.817)	13.000 (12.000-15.945)	0.046 [*]
PINP	35.855 (26.407-43.965)	33.340 (24.165-43.090)	0.163
β-CTX	0.270 (0.170-0.417)	0.260 (0.150-0.445)	0.758
Femoral neck BMD (T-score)	-1.794 ± 0.928	-1.185 ± 0.948	0.0001 [*]
Total hip BMD (T-score)	-1.107 ± 1.113	-0.514 ± 1.049	0.0001 [*]
Lumbar spine BMD (T-score)	-1.324 ± 1.488	-0.387 ± 1.469	0.0001 [*]
TBS	1.259 ± 0.102	1.343 ± 0.100	0.0001 [*]
TyG	8.988 ± 0.748	8.995 ± 0.805	0.936
TyG-BMI	220.636 (185.876-242.285)	220.908 (197.710-247.837)	0.245
TyG-WHtR	4.946 ± 0.804	4.907 ± 0.870	0.680
TyG-WC	773.820 ± 123.068	825.320 ± 128.204	0.0001 [*]
TyG-BRI	38.716 (29.581-48.608)	37.513 (29.377-45.501)	0.326
TyG-ABSI	0.739 ± 0.088	0.744 ± 0.087	0.610
TyG-WWI	100.441 ± 12.701	97.838 ± 11.201	0.057
TyG-LAP	382.789 (195.170-617.544)	386.492 (249.954-766.778)	0.127
TyG-CI	11.524 ± 1.413	11.659 ± 1.378	0.394
TyG-BSI	1.256 ± 0.154	1.271 ± 0.150	0.394
TyG-RFM	351.885 ± 55.650	348.901 ± 53.847	0.632
Menopausal status	No: 19 (12.0%); Yes: 139 (88.0%)		
Smoking	No: 158 (100.0%); Yes: 0 (0.0%)	No: 61 (40.4%); Yes: 90 (59.6%)	0.0001 [*]
Drinking	No: 156 (98.7%); Yes: 2 (1.3%)	No: 89 (58.9%); Yes: 62 (41.1%)	0.0001 [*]
Retinal disease	No: 98 (62.0%); Yes: 34 (21.5%); Unknown: 26 (16.5%);	No: 98 (64.9%); Yes: 27 (17.9%); Unknown: 26 (17.2%);	0.724

Peripheral neuropathy	No: 65 (41.1%); Yes: 93 (58.9%)	No: 65 (43.0%); Yes: 85 (56.3%)	0.686
Chronic kidney disease	No: 120 (75.9%); Yes: 38 (24.1%)	No: 104 (68.9%); Yes: 47 (31.1%)	0.206
Insulin	No: 85 (53.8%); Yes: 73 (46.2%)	No: 74 (49.0%); Yes: 77 (51.0%)	0.466
Antidiabetic drugs	No: 6 (3.8%); Yes: 152 (96.2%)	No: 4 (2.6%); Yes: 146 (96.7%); Unknown: 1 (0.7%);	0.640
Hyperlipidemia	No: 67 (42.4%); Yes: 91 (57.6%)	No: 68 (45.0%); Yes: 83 (55.0%)	0.726
Hypertension	No: 63 (39.9%); Yes: 95 (60.1%)	No: 69 (45.7%); Yes: 82 (54.3%)	0.358

Data are reported as mean $\pm$ SD, median (IQR), or n (%), as appropriate. $P < 0.05$ indicates statistical significance. Continuous variables were compared using the independent-samples t -test or Mann-Whitney U test, while categorical variables were analyzed using the chi-square test or Fisher's exact test. ABSI: A Body Shape Index; ALT: alanine aminotransferase; BMI: body mass index; BRI: body roundness index; BSI: body shape index; BUN: blood urea nitrogen; CI: conicity index; HbA1c: glycated hemoglobin; LDL: low-density lipoprotein cholesterol; P1NP: procollagen type I N-terminal propeptide; PTH: parathyroid hormone; SCR: serum creatinine; T2DM: type 2 diabetes mellitus; TBS: trabecular bone score; TBIL: total bilirubin; TC: total cholesterol; TyG: triglyceride-glucose; UA: uric acid; UACR: urine albumin-creatinine ratio; WC: waist circumference; WHtR: waist-to-height ratio; WWI: weight-adjusted waist index; γ -GGT: gamma-glutamyl transferase; β -CTX: β -C-terminal telopeptide.

In logistic regression with TBS deterioration ($TBS < 1.23$) as the outcome, standardized TyG-WWI had the strongest association among the evaluated indices. In Model 3, each 1-SD increase in TyG-WWI was associated with 47.9% higher odds of TBS deterioration ($OR = 1.479$, 95%CI: 1.072 to 2.039, $P = 0.017$, $P_{FDR} = 0.0341$, $AUC = 0.83$) [Supplementary Figure 2]. Other indices showed nominal or FDR-adjusted associations, including standardized TyG-ABSI (Model 3: $OR = 1.390$, 95%CI: 1.004 to 1.924, $P = 0.0473$, $P_{FDR} = 0.0592$, $AUC = 0.826$) and standardized TyG-CI and TyG-BSI (Model 3: $OR = 1.450$, 95%CI: 1.049 to 2.005, $P = 0.0245$, $P_{FDR} = 0.0350$, $AUC = 0.828$). Standardized TyG-BRI and TyG-RFM were also positively associated with TBS deterioration across all models, whereas standardized TyG-BMI was not statistically significant in any model. Paired DeLong tests compared discrimination across TyG-derived indices using TyG-WWI as the reference. In Model 1, TyG-WWI had a significantly higher AUC than TyG-BMI, TyG-WC, TyG-LAP, TyG-CI, and TyG-BSI after FDR correction. The DeLong test results are shown in Supplementary Figure 3. Comprehensive machine-learning and regression analyses indicated that TyG-WWI had the strongest overall combination of feature importance, association magnitude, and discrimination among the TyG-derived indices in patients with T2DM. This finding was consistent for both continuous TBS and TBS deterioration outcomes.

TyG-WWI and TBS

TyG-WWI was entered into the regression models on its original scale; therefore, the β coefficients are expressed per 1-unit increase in TyG-WWI. In the linear regression analysis (Model 1), TyG-WWI was inversely associated with TBS ($\beta = -0.0025$, standardized $\beta = -0.2701$, 95%CI: -0.0034 to -0.0015, $P < 0.001$) [Supplementary Figure 4]. After adjustment for age and sex (Model 2), the inverse association between TyG-WWI and TBS remained significant ($\beta = -0.0018$, standardized $\beta = -0.2022$, 95%CI: -0.0027 to -0.0010, $P < 0.001$); age ($\beta = -0.0033$, $P < 0.001$) and female sex ($\beta = -0.0669$, $P < 0.001$) were also inversely associated with TBS. In the multivariable Model 3, which additionally included selected renal function, bone metabolism, vitamin D, and other covariates, the inverse association with TyG-WWI remained significant. Each 1-unit increase in TyG-WWI was associated with a 0.0018-unit decrease in TBS ($\beta = -0.0018$, standardized $\beta = -0.1983$, $P < 0.001$), whereas the other selected covariates were not statistically significant [Table 2].

Interaction analyses showed no significant effect modification by sex or age for the association between TyG-WWI and TBS (sex: $P = 0.485$; age: $P = 0.575$; Supplementary Table 3), indicating that there was no statistical evidence that the association varied by sex or age. Restricted cubic spline analysis then assessed potential

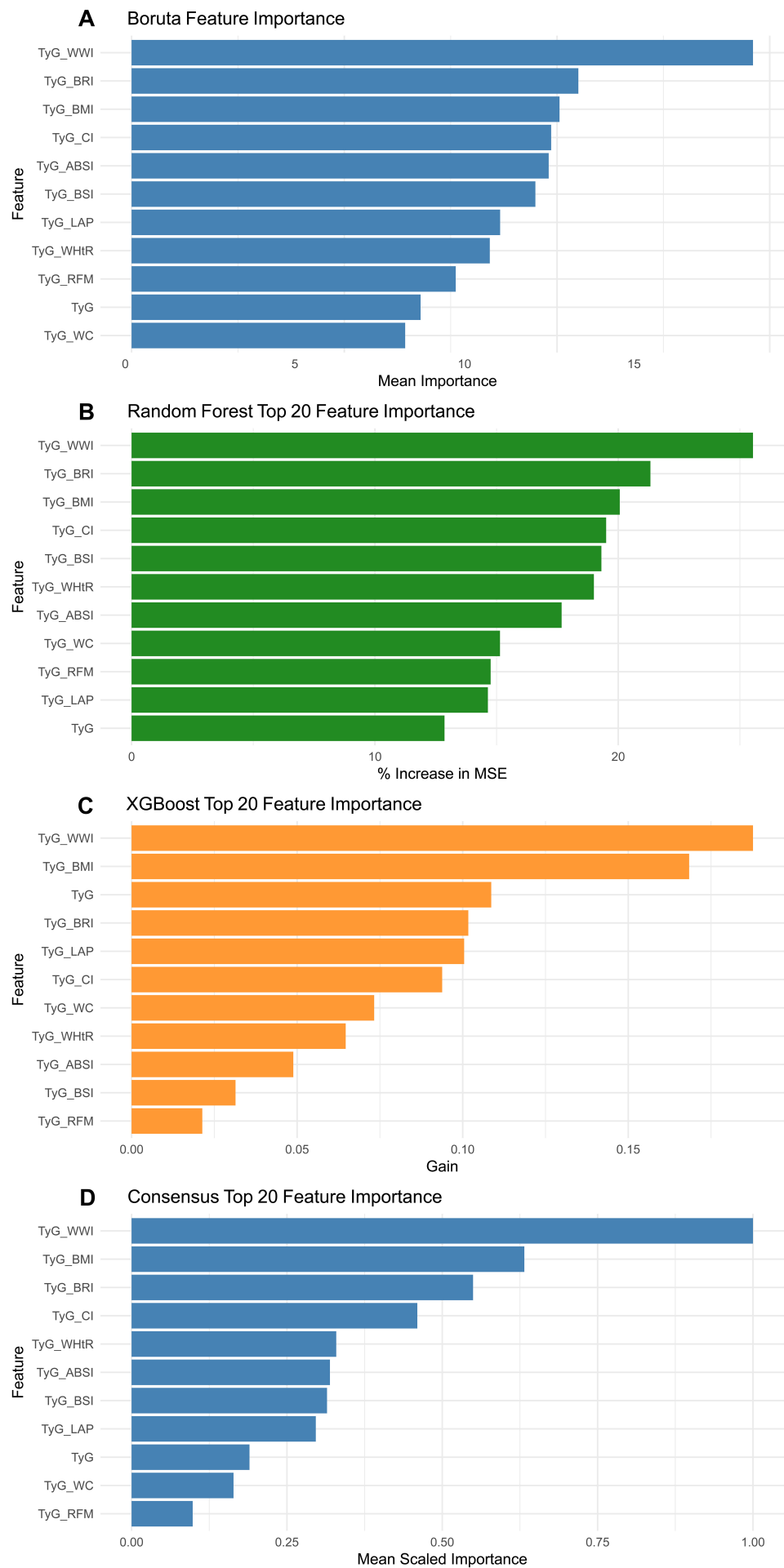


Figure 1. Feature-importance rankings of TyG-related indices for TBS in patients with T2DM using Boruta, RF, and XGBoost. (A) Boruta ranking based on mean importance scores; (B) Random forest ranking based on permutation-derived %IncMSE; (C) XGBoost ranking based on gain; (D) Overall ranking based on the mean scaled importance across the three algorithms. %IncMSE: Percentage increase in mean squared error; RF: random forest; T2DM: type 2 diabetes mellitus; TBS: trabecular bone score; TyG: triglyceride-glucose index; XGBoost: extreme gradient boosting.

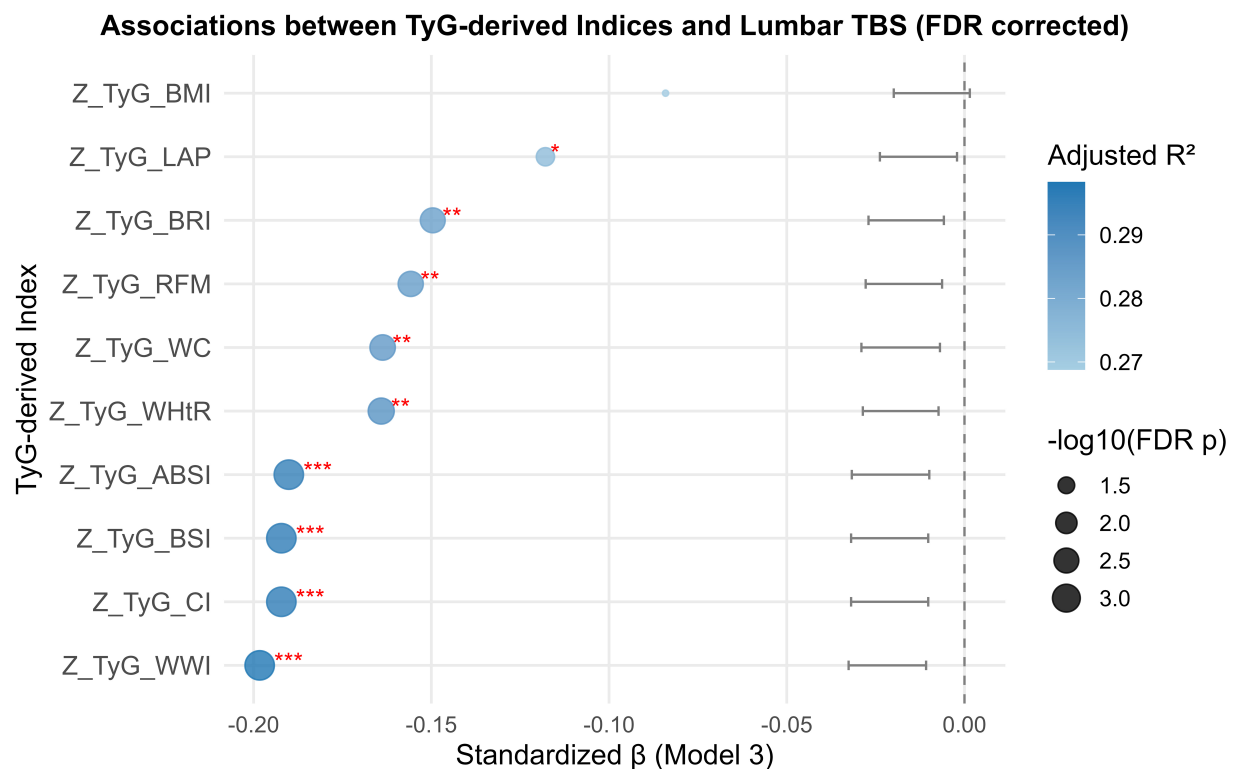


Figure 2. Standardized β coefficients of TyG-derived indices for TBS from multivariable linear regression in Model 3. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$. Bubble size = $-\log_{10}(P)$; color intensity = adjusted R^2 . A negative β indicates an inverse association between a TyG-derived index and TBS. Model 3 included each TyG-derived index, sex, age, and RF-selected covariates [SCr ($\mu\text{mol/L}$), 25-(OH)VitD (ng/mL), BUN (mmol/L), P1NP, albumin (g/L), PTH, smoking, γ -GGT, UACR (mg/g), and serum phosphorus]. BUN: Blood urea nitrogen; P1NP: procollagen type I N-terminal propeptide; PTH: parathyroid hormone; RF: random forest; SCr: serum creatinine; TBS: trabecular bone score; TyG: triglyceride-glucose index; UACR: urinary albumin-to-creatinine ratio; γ -GGT: gamma-glutamyl transferase.

nonlinearity between TyG-WWI and TBS. With knots at the 5th, 35th, 65th, and 95th percentiles, no significant nonlinear association was observed (P for nonlinearity = 0.425). The spline showed no clear threshold or U-shaped pattern, supporting an approximately linear association in the adjusted model [Supplementary Table 4 and Supplementary Figure 5].

Relationship between TyG-WWI and TBS deterioration in patients with T2DM

In logistic regression, Model 1 showed that the odds of TBS deterioration were 4.4% higher for each 1-unit increase in TyG-WWI (OR = 1.044, 95%CI: 1.021 to 1.067; $P < 0.001$). After adjustment for age and sex in Model 2, the association remained statistically significant (OR = 1.034, 95%CI: 1.008 to 1.060, $P = 0.010$). In the fully adjusted Model 3, each 1-unit increase in TyG-WWI was associated with 3.3% higher odds of TBS deterioration (OR = 1.033, 95%CI: 1.006 to 1.061, $P = 0.017$) [Supplementary Table 5]. These findings indicated that TyG-WWI remained independently associated with deterioration of trabecular bone microarchitecture. ROC curve analysis showed that the discriminatory ability of models incorporating TyG-WWI was higher after covariate adjustment. The AUC was 0.636 (95%CI: 0.563 to 0.708) for Model 1, 0.819 (95%CI: 0.765 to 0.874) for Model 2, and 0.830 (95%CI: 0.778 to 0.883) for Model 3 [Supplementary Figure 6], with higher discrimination in the adjusted models. In Model 3, the optimal model-estimated probability threshold was 0.361 [Figure 3], with a sensitivity of 0.667, specificity of 0.868, and Youden index of 0.535. These findings suggest that Model 3 showed acceptable discrimination of TBS deterioration after internal

validation. However, the optimal model-estimated probability threshold showed noticeable variability in bootstrap analysis; therefore, this threshold should be considered exploratory and requires external validation before clinical application.

Table 2. Multivariable-adjusted association between TyG-WWI and TBS

Model	Term	β (95%CI)	P value
1	TyG-WWI	-0.0025 (-0.0034 to -0.0015)	1.45E-06***
	TyG-WWI	-0.0018 (-0.0027 to -0.0010)	3.68E-05***
2	Sex: women	-0.0669 (-0.0879 to -0.0459)	1.16E-09***
	Age	-0.0033 (-0.0043 to -0.0023)	9.82E-11***
	TyG-WWI	-0.0018 (-0.0027 to -0.0009)	1.09E-04***
	Age	-0.0034 (-0.0045 to -0.0024)	7.09E-10***
	Sex: women	-0.076 (-0.104 to -0.048)	1.97E-07***
	SCr ($\mu\text{mol/L}$)	0 (-0.0001 to 0)	0.162
	25-(OH)VitD (ng/mL)	-0.0004 (-0.0018 to 0.001)	0.574
	BUN (mmol/L)	0.0025 (-0.0024 to 0.0075)	0.317
	P1NP	-0.0002 (-0.0009 to 0.0004)	0.456
	Albumin (g/L)	-0.0006 (-0.0037 to 0.0024)	0.689
3	PTH	-0.0002 (-0.0008 to 0.0003)	0.382
	Smoking: yes	-0.0146 (-0.0452 to 0.0159)	0.346
	γ -GGT	-0.0001 (-0.0006 to 0.0003)	0.515
	UACR (mg/g)	0 (0 to 0)	0.106
	Serum phosphorus	0.0059 (-0.0095 to 0.0213)	0.452

Results were derived from multivariable linear regression models. β denotes the regression coefficient, and values in parentheses represent the 95% confidence interval. Statistical significance was defined as: * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$. Model 1: TyG-WWI only; Model 2: TyG-WWI + sex + age; Model 3: TyG-WWI + sex + age + RF-selected covariates [SCr ($\mu\text{mol/L}$), 25-(OH)VitD (ng/mL), BUN (mmol/L), P1NP, albumin (g/L), PTH, Smoking, γ -GGT, UACR (mg/g), serum phosphorus]. SCr: Serum creatinine; 25-(OH)VitD: 25-hydroxyvitamin D; BUN: blood urea nitrogen; P1NP: procollagen type I N-terminal propeptide; PTH: parathyroid hormone; γ -GGT: gamma-glutamyl transferase; UACR: urine albumin-creatinine ratio.

Given the established influence of menopausal status on bone metabolism, we performed a stratified analysis among postmenopausal women. As shown in [Supplementary Table 6](#), among 139 postmenopausal women, 63 had TBS deterioration and 76 did not. In Model 1, TyG-WWI was associated with higher odds of TBS deterioration (OR = 1.035, 95%CI: 1.007 to 1.065, $P = 0.015$; AUC = 0.619, 95%CI: 0.524 to 0.715). After adjustment for age (Model 2), the association between TyG-WWI and TBS deterioration was attenuated and no longer statistically significant (OR = 1.026, 95%CI: 0.994 to 1.058, $P = 0.110$; AUC = 0.758, 95%CI: 0.676 to 0.839). Results were similar in the fully adjusted Model 3 (OR = 1.025, 95%CI: 0.992 to 1.059, $P = 0.136$; AUC = 0.784, 95%CI: 0.707 to 0.860). The interaction between TyG-WWI and menopausal status was not statistically significant (P for interaction = 0.904; [Supplementary Figure 7](#)). Thus, there was no statistical evidence that menopausal status modified the association between TyG-WWI and TBS deterioration. However, the interaction analysis may have been underpowered and should be interpreted cautiously.

After further adjustment for antidiabetic drugs, the association between TyG-WWI and continuous TBS remained essentially unchanged. The regression coefficient was -0.0018 in both Model 3 and the sensitivity model, and the standardized β changed minimally from -0.1983 to -0.1981 [[Supplementary Table 7](#)]. For TBS deterioration, the AUC was 0.830 in Model 3 and 0.840 in the sensitivity model, with largely overlapping 95% confidence intervals [[Supplementary Figure 8](#)]. These results suggest that additional adjustment for antidiabetic drugs did not materially change the association between TyG-WWI and TBS-related outcomes.

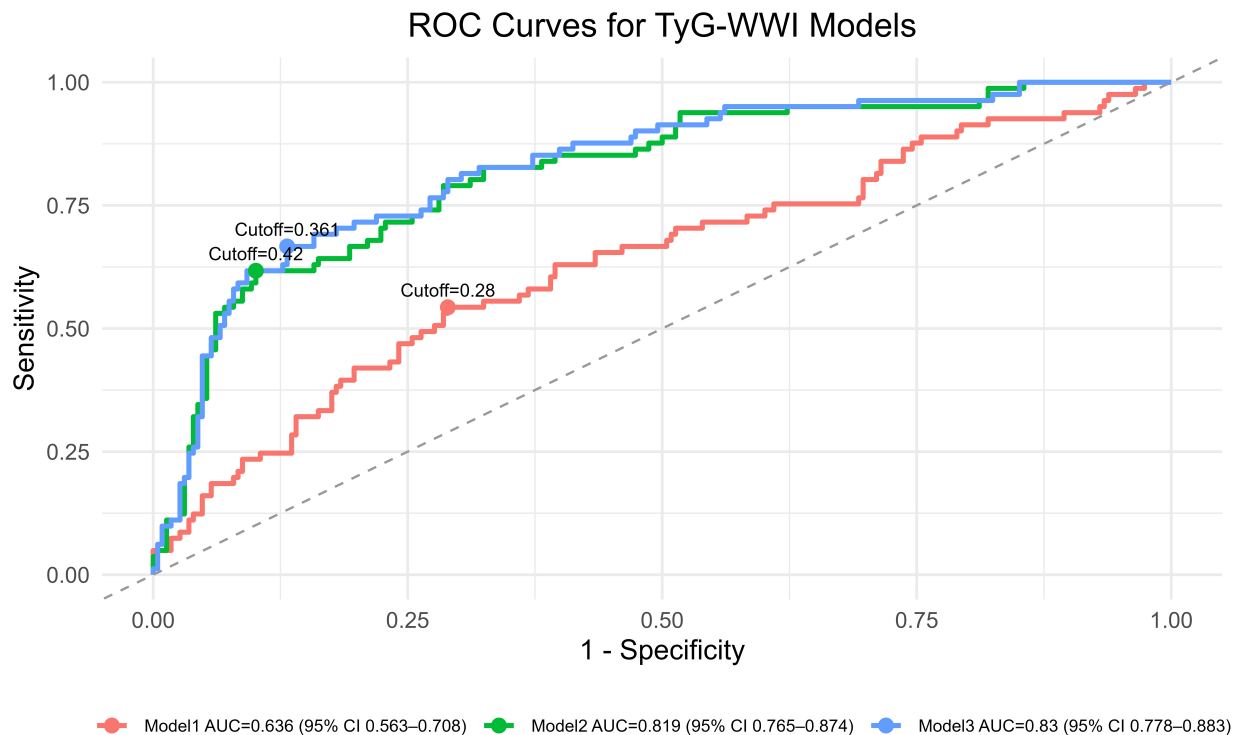


Figure 3. ROC curves of TyG-WWI-based models for discriminating TBS deterioration. Model 1 included TyG-WWI; Model 2 included TyG-WWI, age, and sex; Model 3 additionally included RF-selected covariates. RF: Random forest; ROC: receiver operating characteristic; TBS: trabecular bone score; TyG-WWI: triglyceride-glucose index combined with weight-adjusted waist index.

Association of TyG-WWI with lumbar spine BMD (T-score) in patients with T2DM

TyG-WWI was not significantly associated with lumbar spine BMD (T-score) in linear regression (Model 1) ($\beta = -0.0048$, 95%CI: -0.0193 to 0.0096 , $P = 0.509$). The association remained nonsignificant after adjustment for age and sex in Model 2 ($\beta = 0.0010$, 95%CI: -0.0128 to 0.0148 , $P = 0.883$). In multivariable Model 3, which included the RF-selected covariates, the association between TyG-WWI and lumbar spine BMD (T-score) remained nonsignificant ($\beta = 0.0007$, 95%CI: -0.0137 to 0.0150 , $P = 0.926$) [Supplementary Table 8], indicating that TyG-WWI was not independently associated with lumbar spine BMD (T-score). In multivariable Model 3, age ($\beta = -0.0251$, $P = 0.0036$), female sex ($\beta = -1.001$, $P < 0.001$), and P1NP ($\beta = -0.0105$, $P = 0.0376$) were inversely associated with lumbar spine BMD (T-score), whereas the other covariates were not statistically significant. Interaction analyses [Supplementary Table 9] showed that neither the TyG-WWI-by-age interaction ($\beta = -0.00022$, 95%CI: -0.00141 to 0.00097 , $P = 0.714$) nor the TyG-WWI-by-sex interaction ($P = 0.243$) was statistically significant. These findings indicated that the association between TyG-WWI and lumbar spine BMD (T-score) did not vary significantly by age or sex. Overall, TyG-WWI was not associated with lumbar spine BMD (T-score), and neither age nor sex significantly modified this association.

DISCUSSION

We examined the associations among TyG-WWI, TBS, and lumbar spine BMD (T-score). The combined machine-learning and regression analyses ranked TyG-WWI highest among the evaluated TyG-derived indices for both continuous TBS and TBS deterioration. These findings indicate that TyG-WWI may be more closely associated with bone microarchitecture than the other TyG-derived indices.

To place these findings in context, previous studies have linked TyG-derived indices to IR, obesity, and bone metabolism. The TyG index is widely used as a surrogate marker of IR^[15]. IR, overweight, and obesity are common in patients with T2DM and have been associated with impaired bone microarchitecture^[16]. Prior

studies have examined relationships between TyG-derived indicators and bone outcomes; however, most have focused on BMD, osteoporosis, or bone turnover markers rather than trabecular bone microarchitecture measured indirectly by TBS. Chen *et al.* showed that machine-learning analysis identified TyG-BMI as the strongest indicator of osteoporosis in middle-aged and older patients with T2DM, and that it remained an independent risk factor after multivariable adjustment^[17]. Another recent study in patients with T2DM reported that higher TyG-BMI was associated with lower levels of 25(OH)D, P1NP, osteocalcin, and β -CTX, as well as higher levels of PTH and bone-specific alkaline phosphatase, suggesting that TyG-derived adiposity indicators may be associated with biochemical markers of bone metabolism^[18]. These findings provide background evidence but do not directly support a bone turnover-mediated pathway in the present study. Population-based studies have also associated TyG-BMI, TyG-WC, and TyG-WHtR positively with BMD and inversely with osteopenia or osteoporosis^[19]. However, at higher levels, some adiposity-related TyG indicators may exhibit nonlinear or saturation effects^[9]. Together, these studies support a relationship between IR-related metabolic indices and bone health. The present study extends this evidence by focusing on TBS, an indirect measure of trabecular microarchitecture that may detect diabetes-related impairment in bone quality despite relatively preserved BMD. In addition, comparison of multiple TyG-derived indices using Boruta, random forest, and XGBoost identified TyG-WWI as having the strongest association with TBS deterioration. This pattern suggests that combined glucose and lipid dysregulation and central adiposity, as reflected by TyG-WWI, may be particularly relevant to trabecular microarchitectural impairment in patients with T2DM.

TyG-WWI combines information on fasting glucose and TG, as reflected by the TyG index, with WWI, an indicator of central adiposity^[20]. Thus, it integrates a surrogate measure of IR with a measure of central adiposity and may capture broader metabolic dysfunction. TyG-WWI was inversely associated with TBS in this study. In Model 3, each 1-unit increase in TyG-WWI was associated with a 0.0018-unit decrease in TBS; each 1-SD increase corresponded to an approximately 0.20-SD decrease in TBS (standardized $\beta = -0.1983$). Although this effect size may have clinical relevance, lower TBS has been independently associated with higher fracture risk^[21]. In the Manitoba diabetes cohort, each 1-SD decrease in lumbar spine TBS was associated with a 27% higher risk of major osteoporotic fracture among women with diabetes. Applying that external estimate to the 0.20-SD association observed here would imply an approximately 5% higher fracture risk. However, this cross-study extrapolation is indirect and should not be interpreted as an observed fracture-risk estimate for the present cohort.

TyG-WWI was inversely associated with TBS but not with lumbar spine BMD (T-score). This pattern suggests that metabolic dysfunction reflected by TyG-WWI may be more closely associated with TBS than with lumbar spine BMD (T-score). TBS and BMD are complementary measures for assessing skeletal fragility and fracture risk. BMD reflects bone mineral content and provides a quantitative measure of bone mass, whereas TBS is derived from gray-level texture analysis of lumbar spine DXA images and provides an indirect assessment of trabecular microarchitecture and bone quality^[22]. However, reduced BMD only partially explains fracture risk, particularly in patients with T2DM, who often present with normal or even increased BMD despite an elevated fracture risk^[23]. In this context, TBS may help detect diabetes-related deterioration in bone microarchitecture that is not captured by BMD. Epidemiological studies have associated lower TBS with a higher risk of osteoporotic fracture in patients with diabetes, including individuals with normal BMD^[24]. This difference may reflect the distinct biological dimensions represented by TBS and BMD. BMD reflects cumulative bone mass and mineralization, whereas TBS may be more sensitive to earlier changes in trabecular connectivity, spacing, and microarchitectural integrity. Thus, metabolic abnormalities reflected by TyG-WWI may be more closely associated with impaired trabecular microarchitecture than with a measurable decline in BMD. Assessment of TBS alongside BMD may therefore provide a more complete characterization of skeletal fragility and fracture risk, particularly in the early stages of glucose and lipid metabolic disturbance.

IR may affect bone metabolism through multiple pathways. Insulin promotes osteoblast proliferation and differentiation, whereas impaired insulin signaling may reduce bone formation capacity^[25]. In addition, IR is commonly accompanied by chronic low-grade inflammation and oxidative stress, which may enhance osteoclast activity and accelerate deterioration of trabecular bone structure^[26]. Lipid peroxidation and dysregulated adipokine secretion, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and leptin, may also interfere with bone remodeling^[27]. These mechanisms, including chronic inflammation, oxidative stress, advanced glycation end-product accumulation, and adipokine dysregulation, are inferred from previous studies. Because these processes were not directly measured here, they represent biologically plausible explanations rather than mechanistic evidence from the present study. TBS may capture early trabecular microarchitectural alterations more readily than BMD; therefore, metabolic and inflammatory abnormalities may be more readily reflected by changes in TBS than by changes in BMD. The inverse association with TBS, together with the absence of an association with BMD, may be consistent with TyG-WWI reflecting both IR and central adiposity. Although patients with T2DM may have low bone turnover, the present study did not show that altered bone turnover explained the association between TyG-WWI and TBS: P1NP was not significantly associated with TBS in the fully adjusted model. The TyG-WWI finding should therefore be interpreted as an association between metabolic dysfunction and trabecular microarchitectural deterioration, not as evidence of a bone turnover-mediated mechanism. This interpretation is consistent with the stronger association of TyG-WWI with TBS than with lumbar spine BMD (T-score) in the present study. The findings support further evaluation of TBS alongside TyG-WWI in patients with T2DM. Because the model-estimated probability cutoff from Model 3 varied during bootstrap analysis and has not been externally validated, it should not yet be used as an individual-level threshold for identifying patients with TBS deterioration. Although the association with TBS deterioration was attenuated after adjustment among postmenopausal women, the overall findings still support TyG-WWI as a metabolic indicator associated with trabecular microarchitectural deterioration in patients with T2DM. The inverse association between P1NP and BMD should also be interpreted cautiously. P1NP reflects current bone formation, whereas BMD represents cumulative mineralized bone mass; their cross-sectional association therefore need not be positive. Residual confounding, menopausal status, or compensatory bone remodeling may have influenced this unexpected finding, which should not be interpreted as evidence that greater bone formation directly reduces BMD.

This study has some limitations. First, the cross-sectional design precludes causal inference regarding TyG-WWI and bone-related outcomes, including TBS and BMD. Second, despite adjustment for several covariates, unmeasured or residual confounding remains possible. Adjustment for overall antidiabetic medication use did not materially alter associations with TBS-related outcomes, but confounding by specific drug classes cannot be excluded. Third, the eligibility criteria and exclusion of participants with missing key anthropometric or biochemical data may have introduced selection bias and limited generalizability. Fourth, subgroup and interaction analyses by menopausal status were exploratory, and the small number of premenopausal women may have limited statistical power. Fifth, because bone turnover was evaluated using few markers, its role in the relationship between TyG-WWI and bone microarchitecture remains uncertain. Finally, although the AUC of Model 3 showed acceptable internal validity after bootstrap correction, the optimal model-estimated probability threshold varied across bootstrap resamples and has not been externally validated. It should therefore be regarded only as an exploratory threshold for discrimination and risk stratification. Longitudinal, multicenter studies in broader populations are needed to confirm the robustness, calibration, and clinical utility of these findings.

An important strength of this study is its extension of TyG-WWI research from diabetes and mortality outcomes to skeletal health in patients with T2DM. The study also compared multiple TyG-derived indices using three complementary machine-learning algorithms and then examined the selected index using adjusted linear and logistic regression. This combined approach provided a systematic assessment of associations with TBS and BMD. Nevertheless, these analyses establish comparative associations within this cohort rather than clinical prediction or causality.

In conclusion, TyG-WWI, a composite index reflecting IR and weight-adjusted central adiposity, was independently associated with TBS in Chinese patients with T2DM. TyG-WWI may therefore be a useful metabolic indicator of impaired trabecular bone microarchitecture. Given the cross-sectional design, prospective studies are needed to confirm its discrimination of TBS deterioration and its clinical utility.

DECLARATIONS

Authors' contributions

Conception, design, analysis, and interpretation: Chen L (Liyu Chen), Zeng H, Feng D

Data acquisition, administrative, technical, and material support: Lin J, Zheng Y

Supervision, funding, manuscript review: Chen L (Ling Chen)

Availability of data and materials

The datasets used and/or analyzed during the current study are not publicly available due to privacy and ethical restrictions involving human participants, but are available from the corresponding author upon reasonable request and subject to approval by the relevant ethics committee.

AI and AI-assisted tools statement

During the preparation of this manuscript, the AI tool ChatGPT (GPT-5.5 Thinking, released 2026-04-23) was used solely for language editing and to assist in generating some icon elements in Graphic Abstract. The tool did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This study was approved by the Ethics Committee of Shenzhen Second People's Hospital (Approval No. 2024-176-01PJ), ensuring compliance with the principles outlined in the Declaration of Helsinki. It was also granted permission to waive the need for patients to provide written informed consent.

Consent for publication

Not applicable.

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Supplementary Materials

[Supplementary Materials](#)

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