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ORIGINAL RESEARCH

Elevated Fasting C-Peptide Levels Correlate with Increased 10-Year Risk of Atherosclerotic Cardiovascular Disease in Newly Diagnosed Type 2 Diabetes Patients

Xiao-Yun Zha, Chang-Shun Wei, Jia-Jia Dong, Jin-Zhi Wu, Liang-Xiao Xie, Ze-Hong Xu, Hua-Qiang Zheng, Duo-Bin Huang, Peng-Bin Lai

The First Department of Endocrinology and Metabolism, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou, Fujian, 363000, People's Republic of China

Correspondence: Peng-Bin Lai, The First Department of Endocrinology and Metabolism, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou, Fujian, 363000, People's Republic of China, Tel +8613709398727, Email 13709398727@163.com

Purpose: This study aims to analyze the impact of serum C-peptide levels in patients with newly diagnosed type 2 diabetes (T2DM) on the 10-year risk of atherosclerotic cardiovascular disease (ASCVD).

Patients and Methods: A total of 1923 patients with newly diagnosed T2DM were selected and categorized into four groups based on the interquartile range of fasting C-peptide (FCP) levels: Q1 group (FCP≤0.568 ng/mL), Q2 group (0.568 < FCP≤0.751 ng/mL), Q3 group (0.751 < FCP≤0.980 ng/mL), and Q4 group (FCP > 0.980 ng/mL). Clinical data were collected, and the China-PAR model was employed to evaluate the risk score of ASCVD within 10 years. Additionally, the correlation between FCP levels and the risk of ASCVD was analyzed.

Results: As the quartiles of FCP increased, the 10-year ASCVD risk exhibited a gradual increase. The risk score in the FCP > 0.980 ng/mL group was significantly higher than that in the other groups, with noted differences related to gender and weight. Multiple linear regression analysis indicated that, even after adjusting for confounding factors such as gender, age, body mass index (BMI), and glycosylated hemoglobin, FCP levels remained a positive predictor of the 10-year ASCVD risk.

Conclusion: High FCP levels are identified as a risk factor for ASCVD within 10 years in patients with newly diagnosed T2DM.

Keywords: type 2 diabetes, fasting C-peptide, ASCVD risk

Introduction

With the changes in global lifestyles and the intensification of population aging, the incidence of type 2 diabetes mellitus (T2DM) has increased annually, becoming a significant public health challenge worldwide.[1] It is estimated that approximately 462 million adults globally suffer from diabetes, with T2DM constituting the vast majority of these cases.[2] In China, the prevalence of diabetes is particularly severe, with the number of T2DM patients ranking first in the world.[3] This condition not only has a profound impact on patients' quality of life but also elevates the risk of cardiovascular disease. Cardiovascular disease is the leading cause of death among patients with diabetes, with atherosclerotic cardiovascular disease (ASCVD) being one of the most common complications associated with T2DM.[4]

The occurrence and progression of ASCVD significantly impact patients' quality of life and prognosis. The incidence of cardiovascular disease in diabetic patients is 2 to 4 times higher than that in non-diabetic patients.[5] Furthermore, the mortality rate from ASCVD in patients with T2DM is also markedly greater than that in non-diabetic individuals.[6] Research has demonstrated that there are variations in cardiovascular disease risk across different subtypes of type 2 diabetes mellitus (T2DM), particularly highlighting that patients with severe insulin-resistant diabetes exhibit an elevated

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risk of developing cardiovascular disease.[7] Serum C-peptide levels serve as an important indicator for disease assessment in T2DM patients, closely correlating with insulin secretion, pancreatic islet cell function, and blood glucose control.[8] Research has demonstrated that C-peptide exhibits various biological activities and may play a role in the pathogenesis of cardiovascular diseases.[9,10] While numerous studies have concentrated on the prevention and treatment of cardiovascular complications in T2DM patients, there remains a lack of research exploring the relationship between serum C-peptide levels and the risk of long-term ASCVD events in individuals newly diagnosed with T2DM. Previous investigations have indicated that C-peptide is associated with cardiovascular disease, with elevated C-peptide levels potentially increasing the risk of atherosclerosis and cardiac complications.[9] However, the role of C-peptide in diabetic vascular complications remains controversial,[11–13] highlighting the need for further research in diabetic populations with specific pathological conditions.

The purpose of this study was to conduct an in-depth analysis of the association between serum fasting c-peptide (FCP) levels and the 10-year risk of ASCVD events in patients with newly diagnosed T2DM, while also exploring its clinical significance. Through this research, we aimed to elucidate the potential role of FCP levels in predicting the risk of cardiovascular complications in T2DM patients, thereby providing a scientific basis for the early identification and intervention of individuals at high risk for ASCVD. Additionally, this study will examine the correlation between FCP levels and ASCVD risk across different genders and body mass index (BMI) statuses, with the objective of equipping clinicians with more precise risk assessment tools to develop personalized treatment plans aimed at reducing the incidence of cardiovascular complications in T2DM patients.

Material and Methods

Research Subjects

A cross-sectional study was conducted to select 1923 patients newly diagnosed with T2DM who were hospitalized at Zhangzhou Hospital Affiliated with Fujian Medical University from January 2021 to December 2023. This cohort comprised 1045 males and 878 females. The inclusion criteria were as follows: patients must meet the WHO diagnostic criteria for T2DM, be aged between 18 and 80 years, and gender was not restricted. The exclusion criteria included: (1) acute complications of diabetes, such as hypoglycemic coma, diabetic ketoacidosis, hyperglycemic hyperosmolar state, and lactic acidosis; (2) patients with severe liver and kidney failure, heart failure, or malignant tumors; and (3) patients with immunodeficiency. Additionally, patients with a history of antidiabetic drug use, systemic corticosteroid treatment, or the presence of type 1 diabetes autoantibodies were excluded. All patients received dietary and exercise guidance, along with individualized treatment plans.

Methods

General Survey

Demographic and medical history information was collected through questionnaires administered upon patient admission. Data included age, gender, past medical history, smoking habits, and alcohol consumption. To reflect the long-term impact of lifestyle factors on cardiovascular health, we referenced the framework of existing epidemiological studies, aiming to minimize short-term fluctuations in health data.[14–16] A 5-year threshold was established to assess smoking and drinking cessation. Participants who had smoked <100 cigarettes in the past 5 years were defined as non-smokers and others as smokers. Participants who had consumed alcoholic beverages at least once/week for at least 1 year in the past 5 years were categorized as alcohol drinkers and others as non-alcohol drinkers. Additionally, measurements were taken for systolic blood pressure (SBP), diastolic blood pressure (DBP), height, weight, waist circumference(WC), and hip circumference. BMI, and waist-to-hip ratio (WHR) were subsequently calculated.

Laboratory Examination

All research subjects fasted for 8 to 10 hours prior to the collection of fasting venous blood.

Routine laboratory tests such as biochemical analyses of fasting blood glucose (FPG), 2-hour postprandial blood glucose (2hPPBG), glycosylated hemoglobin (HbA1c), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), serum uric acid (SUA), and creatinine (Cr) were performed using the fully automatic biochemical analyser (Beckman Coulter AU5832, USA). Fasting and 2 hours postprandial C-peptide levels were estimated using an automated immunoassay analyser (ADVIA Centaur XP, Siemens, Germany) and immunochemiluminometric assays. The intra-assay coefficient of variation (CV) was 3.7%, and the inter-assay CV was 3.3%, indicating high precision of the assay. Additionally, the assay was validated for minimal cross-reactivity with proinsulin, ensuring that the C-peptide measurements are not significantly influenced by insulin precursors or proinsulin derivatives.

C-Peptide Level Stratification

Patients were subdivided into four groups based on the interquartile range of FCP levels: Q1 group (FCP ≤ 0.568 ng/mL), Q2 group (0.568 < FCP ≤ 0.751 ng/mL), Q3 group (0.751 < FCP ≤ 0.980 ng/mL), and Q4 group (FCP > 0.980 ng/mL).

ASCVD Risk Score Assessment

The 10-year ASCVD risk score was evaluated upon patient admission using the China-PAR (Prediction for ASCVD Risk in China) model, a cardiovascular risk assessment tool developed specifically for the Chinese population. This model has been validated for predicting ASCVD risk in individuals aged 18–80 years and is widely used in clinical settings across China.[17] The China-PAR model calculates the 10-year risk of ASCVD based on multiple demographic, clinical, and lifestyle factors. The risk score of ASCVD is evaluated using the cardiovascular risk assessment tool, China-PAR. The assessment factors include gender, age, treated or untreated SBP, TC, HDL-C, WC, smoking status (yes/no), place of residence (southern/northern China), urban/rural residence, and family history of ASCVD (yes/no). Each variable contributes to the overall risk score, allowing for a tailored assessment of ASCVD risk within the Chinese population. This model's reliance on population-specific data enhances its applicability in this cohort, though it is subject to potential information bias, as some data (eg, smoking status) are self-reported.

It is important to note that, as this study is cross-sectional, the China-PAR model was used to calculate risk scores rather than tracking actual ASCVD events over a 10-year follow-up period. Therefore, our analysis focuses on estimated risk rather than observed incidence of ASCVD outcomes.

Statistical Analysis

Data analyses was conducted using SPSS version 20.0. Measurement data were tested for normality using the Shapiro–Wilk method and expressed as mean±standard deviation or median and interquartile range [M (P25, P75)]. When the measurement data followed a normal distribution, single-factor ANOVA was employed. For non-normally distributed data, non-parametric tests were utilized; correlation analysis was performed using the Spearman method; count data were expressed as percentages (%), and chi-square (χ^2) tests were applied for comparisons between groups. Logistic regression analysis was conducted to examine the relationship between age, gender, BMI, smoking, alcohol consumption, FCP, HbA1c, and the 10-year ASCVD risk. A p-value < 0.05 was considered statistically significant.

Results

Comparison of Baseline Characteristics of Study Subjects Grouped by C-Peptide

As FCP levels increase, there is a corresponding rise in the levels of BMI, WHR, SUA, and 2hCP, which is associated with an increased 10-year risk of ASCVD. Conversely, the levels of HbA1c and FPG are found to be lower between the groups. These differences are statistically significant (p<0.05), as shown in Table 1.

Impact of C-Peptide on the 10-Year ASCVD Risk in Diabetic Patients Under Different Genders and BMI Levels

Table 2 presents the impact of FCP levels on the 10-year risk of ASCVD, stratified by gender and BMI. A comparative analysis by gender revealed that among male patients, those in the FCP Q4 group exhibited a significantly higher risk of developing ASCVD within 10 years compared to the Q1, Q2, and Q3 groups (p<0.05). Further stratification by BMI demonstrated that in the BMI≥24 kg/m² group, an increase in FCP levels was associated with a gradual increase in the risk of ASCVD within 10 years (p<0.05).

Table 1 Comparison of Baseline Characteristics of Subjects Grouped by FCP Quartile

Variables	Quartile1 (n = 483)	Quartile2 (n =479)	Quartile3 (n = 480)	Quartile (n =481)	P Value
Male [n (%)]	57.8%	55.1%	51.5%	53.0%	0.227
Age (years)	57 (50,65)	54 (47,62)	53 (40,63)	52 (40.63)	0.021
BMI (Kg/m^2)	22.9±2.8	24.7±3.2[a]	25.7±4.0[ab]	27.0±4.1[abc]	<0.001
WHR (m)	0.92±0.06	0.94±0.06[a]	0.94±0.07[a]	0.96±0.07[a]	0.001
Smoking [n (%)]	35.60%	26.40%	31.00%	27.60%	0.550
Drinking [n (%)]	13.80%	6.90%	9.50%	8.00%	0.432
SBP (mmHg)	132±20	132±18	132±17	134±17	0.783
DBP (mmHg)	78±11	80±11	81±12	82±11	0.139
HbA1c (%)	11 (8,12.9)	9.4 (7.1,11.1) [a]	9.85 (7.3,11.5) [a]	9.3 (7.3,10.7) [a]	0.003
FPG (mmol/L)	9.83±3.78	8.81±3.16[a]	9.10±3.47	8.31±2.94[a]	0.026
2hPPBG (mmol/L)	14.7±3.58	13.87±4.22	13.71±3.97	13.43±3.31[a]	0.149
FCP (ng/mL)	0.42±0.12	0.66±0.06[a]	0.85±0.07[ab]	1.30±0.3[abc]	<0.001
2hCP (ng/mL)	1.62±0.77	2.12±0.84[a]	2.40±0.92[ab]	3.22±1.23[abc]	<0.001
TG (mmol/L)	1.59±1.08	1.88±1.15	2.06±1.58[a]	2.92±2.56[abc]	<0.001
TC (mmol/L)	4.62±1.26	4.94±1.29	4.7±1.21	5.07±1.26[a]	0.073
LDL-C (mmol/L)	2.89±1.04	3.21±1.09[a]	2.92±1.02	3.09±0.98	0.135
HDL-C (mmol/L)	1.16±0.34	1.13±0.3	1.05±0.24[a]	1.09±0.33	0.075
SCr (umol/L)	59.39±19.67	61.23±18.62	59.16±14.91	63.71±22.04	0.319
SUA (umol/L)	285.98±95.31	311.51±80.96	315.19±101.88[a]	359.12±115.87[abc]	<0.001
10- 110-Year ASCVD risk score (%)	7.75±6.35	7.27±5.53	7.14±6.28	10.01±6.37[abc]	0.007

Notes: Data are expressed as means±SD for continuous variables and as percentages for categorical variables; [a]Compared with quartile 1, p<0.05; [b]Compared with quartile 2, p<0.05; [c]Compared with quartile 3, p<0.05.

Table 2 Impact of c-Peptide Quartile (Q1-Q4) on the 10-Year ASCVD Risk in Diabetic Patients Under Different Genders and BMI Levels (means±SD)

Groups	Gender		BMI	
	Male (n=1045)	Female (n=878)	<24Kg/m^2 (n=809)	≥24Kg/m^2 (n=1114)
Quartile1 (n = 483)	7.78±6.18	7.69±6.77	8.27±6.62	6.6±5.65
Quartile2 (n =479)	6.84±5.62	8.11±5.31	7.80±5.31	7.03±5.65
Quartile3 (n = 480)	6.89±5.79	7.56±7.08	6.15±5.16	7.78±6.88
Quartile4 (n =481)	10.08±6.01[abc]	9.89±6.97	8.90±6.26	9.697±6.08[abc]
P value	0.016	0.447	0.152	0.049

Notes: [a]Compared with quartile 1, p<0.05; [b]Compared with quartile 2, p<0.05; [c]Compared with quartile 3, p<0.05.

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Correlation Between Clinical Factors and ASCVD Risk Score

Spearman correlation analysis revealed that the patient's 10-year ASCVD risk was positively correlated with age, BMI, WHR, SBP, HbA1c, 2hPPBG,FCP, and 2hCP ($p<0.05$),; In contrast, LDL-C, TG, uric acid, and other indicators did not demonstrate a significant correlation with the 10-year ASCVD risk, as shown in Table 3.

Multiple Linear Regression Analysis of the Impact of FCP Levels on the 10-Year ASCVD Risk

In contrast, LDL cholesterol, TG, uric acid, and other indicators did not demonstrate a significant correlation with the 10-year ASCVD risk. Model 1 demonstrated that among 1923 newly diagnosed T2DM patients, FCP levels were positively correlated with 10-year ASCVD risk ($\beta=0.145$, $p=0.007$). Each unit change in FCP accounts for 1.8% of the 10-year ASCVD risk score. In Model 2, after further adjusting for confounding factors such as age, gender, BMI, smoking history, and drinking history, FCP remained positively associated with the 10-year ASCVD risk. Age ($\beta=0.275$, $p=0.007$) and FCP ($\beta=0.171$, $p=0.003$) together explained 7.6% of the 10-year ASCVD risk score. Model 3 further adjusted for SBP, HbA1C, 2hPPBG, and 2hCP based on Model 2. In this model, FCP continued to show a positive relationship with the 10-year ASCVD risk, with age ($\beta=0.222$, $p<0.001$), FCP ($\beta=0.152$, $p=0.008$), and SBP ($\beta=0.263$, $p<0.001$) collectively explaining 13.6% of the 10-year ASCVD risk score, as presented in Table 4.

Discussion

This study demonstrated that fasting C-peptide (FCP) levels are significantly associated with the 10-year risk of ASCVD in patients with newly diagnosed T2DM. As FCP quartiles increased, the ASCVD risk rose correspondingly, with the highest risk observed in patients with FCP levels exceeding 0.980 ng/mL. Notably, this association was more pronounced

Table 3 Correlation Between Clinical Factors and ASCVD Risk Score

Variables	Correlation Coefficient	p Value
Age	0.281	<0.001
BMI	0.071	0.19
WHR	0.139	0.01
SBP	0.312	<0.001
DBP	0.092	0.086
HbA1c	0.115	0.033
FPG	0.082	0.13
2hPG	0.107	0.047
FCP	0.13	0.016
2hCP	0.118	0.028
TG	0.01	0.847
TC	0.04	0.457
LDL-C	0.065	0.228
HDL-C	0.035	0.513
SCr	0.077	0.156
SUA	0.05	0.354

Table 4 Multiple Linear Regression Analysis of the Impact of FCP Levels on the 10-Year ASCVD Risk Score

	Predictors	B	β	t	p	Adjust R^2
Model 1	FCP	2.460	0.145	2.711	0.007	0.018
Model 2	FCP	2.893	0.171	2.974	0.003	0.076
	Age	0.131	0.275	5.107	<0.001	
Model 3	FCP	2.585	0.152	2.672	0.008	0.136
	Age	0.106	0.222	4.084	<0.001	
	SBP	0.090	0.263	4.960	<0.001	

Abbreviations: BMI, body mass index;WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; FPG, fasting blood glucose (FPG); 2hPPBG, 2-hour postprandial blood glucose; FCP, fasting C-peptide; 2hCP, 2-hour postprandial C-peptide; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SCr, serum creatinine (Cr);SUA, serum uric acid; ASCVD, atherosclerotic cardiovascular disease.

in overweight and obese patients but not in normal-weight individuals or females. Multiple linear regression analysis indicated that, after adjusting for confounding factors such as gender, age,BMI, and HbA1c, FCP remained a significant factor influencing the 10-year risk of ASCVD. These results suggest that elevated C-peptide concentrations may serve as a reliable biomarker assessing cardiovascular risk in this patient population.

Pancreatic β-cells secrete insulin and C-peptide in equal amounts, with C-peptide recognized as a biomarker for insulin resistance and pancreatic β-cell function.[18] ASCVD is the most prevalent chronic condition and the leading cause of death globally. The relationship between C-peptide levels and the risk of chronic diseases, including cardiometabolic disorders, has yielded inconsistent findings in previous research.[12] Consistent with previous studies, this research supports the conclusion that higher FCP levels are associated with increased ASCVD risk, aligning with findings by Toprak et al, who identified elevated C-peptide as an independent risk factor for coronary atherosclerosis.[19] Conversely, a meta-analysis found that low serum C-peptide levels were significantly associated with a higher incidence of coronary heart disease and cerebral infarction.[20] Additionally, another study indicated that serum C-peptide levels in T2DM patients did not show a significant correlation with cardiovascular biomarkers or cardiovascular events.[21] These variations may stem from differences in study populations, methodologies, or definitions of cardiovascular outcomes, highlighting the need for further research.

This study also explored the role of 2-hour C-peptide (2hCP) levels in predicting ASCVD risk. Although 2hCP levels showed a positive association with 10-year ASCVD risk in univariate analyses, this association was not confirmed in multivariable models, indicating that 2hCP lacks the independent predictive value of FCP (Table 4, Model 3). This finding underscores the clinical relevance of FCP over 2hCP in cardiovascular risk assessment for newly diagnosed T2DM patients.

Current research on C-peptide and cardiovascular disease risk primarily focuses on the general population. However, given the physiological and hormonal differences between men and women,[22] these disparities may influence their responses to variations in C-peptide levels. To further elucidate whether there are gender differences in the impact of FCP on the 10-year risk of ASCVD, we conducted a gender-stratified analysis. Gender-stratified analyses revealed that the association between FCP levels and ASCVD risk was more evident in males. This discrepancy may be attributed to the protective effects of estrogen on the cardiovascular system in females.[23] Estrogen has been shown to regulate vascular function and inflammation, potentially counteracting the adverse effects of elevated C-peptide levels.[24,25] In contrast, the potential adverse effects of C-peptide on the cardiovascular system may be more pronounced in men, who typically have lower estrogen levels.These results emphasize the importance of considering gender differences in cardiovascular risk stratification and management.

It is well established that obese patients tend to exhibit elevated C-peptide levels, which may be associated with insulin resistance.[10] Considering the interaction between C-peptide and body BMI, as well as their relationship with ASCVD, we conducted a further analysis of the relationship between FCP and 10-year ASCVD risk stratified by BMI.

The results indicated that obesity further amplified the relationship between FCP and ASCVD risk. In patients with a BMI ≥24 kg/m², higher FCP levels correlated with increased ASCVD risk, whereas this association was not observed in those with a BMI <24 kg/m². The distinct roles of obesity and FCP in the progression of diabetic vascular complications warrant further investigation. On one hand, the influence of obesity on diabetic complications may be dual-faceted, presenting both positive and negative effects. C-peptide levels are associated with insulin resistance and defects in insulin secretion, and the overall impact on specific organs may depend on the nature of their interactions.[26,27] This raises the question: is the association between FCP and 10-year ASCVD risk independent of BMI? Interestingly, regression analysis indicated that FCP's impact on ASCVD risk was independent of BMI, suggesting that FCP is a critical driver of cardiovascular risk, even beyond the influence of obesity.

Multiple linear regression analysis indicated that, after adjusting for age, SBP, HbA1C, and other confounding factors, FCP remains a positive predictor of 10-year ASCVD risk. This finding underscores FCP as an independent risk factor for ASCVD. Insulin resistance has been identified as a poor prognostic indicator of cardiovascular mortality.[28] Additionally, evidence suggests that C-peptide levels serve as superior predictors of cardiovascular disease and overall mortality compared to serum insulin levels.[29] C-peptide may contribute to various stages of atherogenesis, including arteriolar dilation and calcium influx into endothelial cells and macrophages through nitric oxide-dependent pathways.[30,31] Furthermore, C-peptide facilitates monocyte differentiation, migration, and the accumulation of oxidized low-density lipoproteins via peptide-induced mechanisms. These pathological roles may accelerate cardiovascular disease progression, either through insulin resistance or direct C-peptide-mediated effects.[32,33]

Although existing data link C-peptide levels to cardiovascular risk in T2DM patients, the precise mechanisms remain unclear and require further investigation. While this study primarily examined the association between FCP and ASCVD risk, the role of insulin levels in this context warrants attention. As insulin and C-peptide are co-secreted, their combined analysis may yield deeper insights into cardiovascular risk mechanisms. Future research should integrate both insulin and C-peptide measurements to clarify their interplay and collective impact on cardiovascular outcomes.Understanding how C-peptide and insulin resistance drive cardiovascular disease progression is essential for improving risk stratification and developing targeted therapies in T2DM.

This study has some limitations. First, as a cross-sectional analysis, it cannot establish causality between C-peptide levels and cardiovascular complications. Despite adjustments for known confounders, residual bias may still exist. Second, the study population was hospital-based and drawn from southern China, potentially introducing selection bias and limiting generalizability. Future studies should adopt community-based or multicenter designs to better reflect the broader population. Lastly, the ASCVD risk assessment relied on the China-PAR model, which uses self-reported data, potentially introducing information bias. Prospective studies with larger populations are warranted to validate these findings.

Conclusion

In summary, a high FCP level is a significant risk factor for ASCVD within 10 years in patients with newly diagnosed T2DM. Monitoring FCP levels may provide valuable insights for cardiovascular risk stratification and management. Clinically, reducing C-peptide levels through lifestyle interventions, such as weight management, physical activity, and balanced diets, as well as medications like metformin, may help mitigate cardiovascular risk in this population. These findings underscore the importance of incorporating FCP into routine cardiovascular risk assessments for T2DM patients.

Abbreviations

BMI, body mass index; WHR, waist-to-hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; FPG, fasting blood glucose (FPG); 2hPPBG, 2-hour postprandial blood glucose; FCP, fasting C-peptide; 2hCP, 2-hour postprandial C-peptide; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SCr, serum creatinine (Cr); SUA, serum uric acid.

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Ethics Approval and Informed Consent

This study was conducted in accordance with the World Medical Association Helsinki Declaration guidelines for studies involving human subjects. The Ethics Committee of Zhangzhou Hospital Affiliated with Fujian Medical University approved this study (Zhang Yilun No. 2024LWB292),and the patients signed an informed consent form.

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Disclosure

The author(s) report no conflicts of interest in this work.

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