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ORIGINAL RESEARCH

Relationship Between a Novel Model of Insulin Sensitivity and Arterial Stiffness in Non-Obese Patients with Type 2 Diabetes: A Cross-Sectional Study

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Aim: Insulin resistance (IR) is closely associated with arterial stiffness (AS) and cardiovascular diseases (CVDs). Recently, several non-insulin-based IR surrogate markers have been demonstrated to be related to AS. The natural log transformation of the glucose disposal rate ($\log_e$ GDR) is a novel indicator of insulin sensitivity (IS) developed in patients with type 2 diabetes (T2D). We aim to investigate the relationship between the $\log_e$ GDR and AS in non-obese patients with T2D.

Methods: A cross-sectional study of 790 non-obese patients with T2D were included. Clinical and biochemical characteristics were collected. AS was assessed by brachial-ankle pulse wave velocity (baPWV), and according to the baPWV levels, patients were divided into two groups: AS group (baPWV $\geq$ 1800 cm/s) and non-AS group (baPWV < 1800 cm/s). The correlation between AS and $\log_e$ GDR was analyzed.

Results: Compared with the non-AS group, the $\log_e$ GDR decreased in the AS group ($P < 0.001$). With the tertiles of $\log_e$ GDR increased, the bapWV and the prevalence of AS were decreased (both $P < 0.001$). Univariate analysis showed that the $\log_e$ GDR was negatively correlated with the baPWV and AS (both $P < 0.001$). Furthermore, multivariate regression analyses demonstrated that the $\log_e$ GDR was independently associated with bapWV (β: −0.162; $P < 0.001$) and AS (OR: 0.286; 95% CI: 0.110–0.743). Integrating $\log_e$ GDR modestly improved the ability of the model to identify AS (Net reclassification improvement (NRI): 0.043, 95% CI 0.009–0.079, $P = 0.011$).

Conclusion: The $\log_e$ GDR is independently correlated with AS in non-obese patients with T2D, and its utility for risk stratification requires further validation.

Keywords: type 2 diabetes, baPWV, insulin resistance, Log_e GDR

Introduction

The prevalence of diabetes, particularly type 2 diabetes (T2D), is rising globally, posing a significant public health challenge due to its various acute and chronic complications.[1] Among these complications, cardiovascular diseases (CVDs) stand out as the leading cause of death in patients with T2D.[2] Vascular dysfunctions, including arterial stiffness (AS) and impaired vasodilation, can emerge before the onset of severe CVDs symptoms.[3] Therefore, early assessment of AS is particularly important in the management of T2D. The brachial-ankle pulse wave velocity (baPWV) is a simple, effective and non-invasive method for evaluating AS,[4] and can independently predict cardiovascular risk, providing important evidence for assessing the development of CVDs in individuals.[5]

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Insulin resistance (IR) is considered a significant factor to AS and the progression of CVDs.[6] While the euglycemic hyperinsulinemic clamp (EHC) is considered the gold standard for assessing IR,[7] its invasive nature, time consuming and requirement for hospitalization limit its practical applicability. The homeostasis model assessment index (HOMA-IR) offers a simpler approach to assessing IR.[8] However, it presents specific challenges for patients undergoing insulin therapy. Recently, a growing number of non-insulin-based IR surrogate markers have been proposed, including the triglyceride-glucose (TyG) index, triglyceride-to-high-density lipoprotein cholesterol (TG/HDL-c) ratio, and metabolic score for insulin resistance (METS-IR).[9–11] These markers have been associated with various metabolic diseases. One of our previous studies examined their relationship with nonalcoholic fatty liver disease (NAFLD) in patients with T2D, highlighting their clinical relevance in this context.[12] Building on this foundation, our current study shifts the focus toward AS, a distinct yet critical cardiovascular complication in T2D. A more recent development is the natural log transformation of the glucose disposal rate ($\log_e$ GDR), a non-insulin-based model to assess insulin sensitivity (IS) in T2D patients.[13] The $\log_e$ GDR is calculated based on body mass index (BMI), triglycerides (TG), the urinary albumin to creatinine ratio (UACR) and γ-glutamyl transferase (GGT), and it has been validated and demonstrated a strong association with CVDs and mortality rates.[13] Despite these advances, no studies to date have specifically investigated the relationship between the $\log_e$ GDR and AS in T2D. Based on the groundwork laid by our earlier research, this study aims to explore the novel association between $\log_e$ GDR and AS, offering fresh insights into the complex interplay between IS and vascular health.

The prevalence of non-obese T2D is gradually increasing, particularly in Asian countries.[14,15] Although CVDs and other conditions have traditionally been associated with obesity and being overweight, recent evidence suggests that non-obese T2D patients may have higher all-cause and cardiovascular mortality rates.[16,17] This could be attributed to factors such as increased visceral fat, impaired IS, and heightened inflammatory responses despite a normal BMI.[18] Furthermore, recent studies have reported non-obese T2D patients have a comparable or even higher prevalence of AS compared to their obese counterparts[18] Due to significant differences in metabolic characteristics between obese and non-obese diabetic patients, particularly regarding IS.[19] And research exploring the relationship between IR surrogate markers and AS in non-obese patients with T2D remains limited. Therefore, we aim to analyze the relationship between the $\log_e$ GDR and AS in this population.

Methods

Study Design and Population

We retrospectively reviewed the medical records of patients aged ≥ 18 years with T2D from the Department Endocrinology of Linyi People's Hospital, from January 2020 to March 2023. The exclusion criteria were (1) subjects missing key anthropometric measurements (height and weight); (2) subjects who had severe liver and kidney dysfunctions; (3) subjects with a history of angina, myocardial infarction and cerebrovascular accident; (4) subjects who had not undergone the baPWV tests or whose clinical data were incomplete, including GGT, TG and UACR; (5) subjects with BMI ≥ 24 kg/m^2. Ultimately, a total of 790 non-obese patients with T2D were eventually included (Figure 1).

It is important to note that a portion of the participants included in the current study were also part of our previous work, which primarily investigated the association between IR markers and NAFLD in the overall T2D population. In terms of exclusion criteria, the previous study mainly excluded confounding factors that could affect the diagnosis and analysis of fatty liver disease.[12] For the overlapping populations, we further compared differences in baseline characteristics and various IR indices between the two studies, and the results did not show significant differences, suggesting that the results of this study are relatively stable and have some replication.

Demographic Information

The sex, age, diabetes duration and self-reported current cigarette smoking and drinking status were collected.

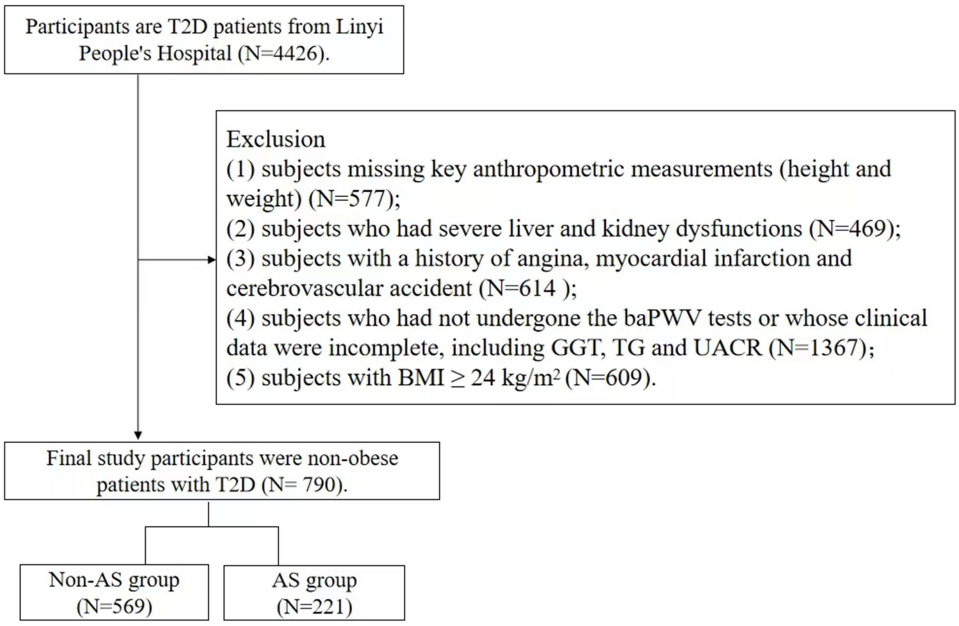

Figure 1 The flow chart of study participants selection.

Physical Examinations

According to unified standards, the height, weight, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured and collected. The bioelectrical impedance analysis (Omron DUALSCAN HDS-2000, Kyoto, Japan) was used to measure the visceral fat area (VFA) and subcutaneous fat area (SFA).

Each participant's baPWV was measured using the automated system BP-203RPE III (Omron Healthcare Co., Japan) by trained technicians. The device simultaneously recorded pulse waveforms from the brachial and tibial arteries and automatically calculated baPWV values. Before measurement, participants were required to rest in a supine position for at least 5 minutes to ensure hemodynamic stability. Subsequently, appropriately sized cuffs were placed on both upper arms and ankles, and the device was operated according to standard protocols to obtain waveform signals and compute baPWV values.[20] To enhance measurement accuracy, this study analyzed data in cases where there was a significant difference between left and right baPWV values and assessed each side's baPWV separately. AS was defined as baPWV ≥1800 cm/s.

Laboratory Measurements

Following an overnight fast, blood samples were collected and analyzed in the morning for alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, TG, HDL-c, total cholesterol (TC), low density lipoprotein-cholesterol (LDL-c), serum creatinine (Scr), uric acid (UA), Cystatin C (Cys C), hemoglobin (Hb), fasting blood glucose (FBG) and glycosylated haemoglobin (HbA1c), fasting insulin (FINS) and UACR. A comprehensive overview of the tools and methods utilized in this research is available in our earlier publication.[12] Non-obese was defined as BMI < 24 kg/m^2.

Parameter Calculation

1. BMI = weight (kg) / height^2 (m^2);
2. eGFR = 175 * Scr (mg/dL) $^{-1.234}$ * age $^{-0.179}$ * (0.79, if female);[21]
3. HOMA-IR = FBG (mmol/L) * FINS (μU/mL)/22.5;[8]
4. TyG index = ln [TG (mg/dL) × FBG (mg/dL)/2];[10]
5. TG/HDL-c ratio = TG (mmol/L)/HDL-c (mmol/L);[11]
6. METS-IR = ln [(2*FBG (mg/dL)) + TG (mg/dL)] *BMI)/(Ln [HDL-c (mg/dL)]);[9]
7. Log$_e$ GDR = 5.3505–0.3697 * log$_e$ (GGT, IU/L) - 0.2591 * log$_e$ (TG, mg/dL) - 0.1169 * log$_e$ (UACR, mg/g) - (0.0279*BMI, kg/m^2).[13]

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Statistical Analysis

Statistical analysis was performed using SPSS 26.0 (SPSS Inc, Chicago, USA) and R (version 4.3.2). Data were presented as means ± SD for normally distributed variables and as medians (interquartile ranges) for non-normally distributed variables. Independent-Samples *T* test and Mann–Whitney *U*-test were used for comparisons of normally and abnormally distributed continuous variables between two groups, respectively. Categorical variables were presented as percentage (%) and were compared by Chi-square test. For normally distributed data, an Analysis of Variance (ANOVA) and Student-Newman-Keuls tests were used for multiple and pairwise comparisons between the $\log_e$ GDR tertiles groups, while the Kruskal–Wallis one-way ANOVA test was used for abnormally distributed data. Pearson correlation and multiple linear stepwise regression analyses were used to evaluate the independent correlations of baPWV. Univariate logistic regression analysis and directed acyclic graphs (DAG) were used to guide the selection of covariates for AS. The DAG was constructed using the dagitty package. And the identified minimal adjustment set includes age, BMI, diabetes duration, FBG, TG, HOMA-IR, METS-IR, TG/HDL-c ratio and TyG index. Logistic regression analysis was used to analyze the independent correlates of AS. Net reclassification improvement (NRI) analysis was performed using the survIDINRI package in R to assess the incremental predictive value of $\log_e$ GDR compared with other IR markers for identifying AS. Statistical differences were defined by P-value (two-tailed) less than 0.05.

Results

Clinical and Biochemical Characteristics

The clinical and biochemical characteristics of the participants are shown in Table 1. A total of 790 non-obese patients with T2D were enrolled in our study. The subjects were divided into two groups including non-AS group (baPWV < 1800cm/s) and AS group (baPWV ≥ 1800cm/s). Compared with the non-AS group, the age, diabetes duration, VFA, SFA, SBP, DBP, AST, GGT, UA, Scr, UACR and Cys C were increased in AS group, but the HbA1c, eGFR, Hb and $\log_e$ GDR were markedly reduced (all $P < 0.05$). There were no obvious differences in BMI, TC, LDL-c, HDL-c, TG, FBG, FINS, ALT, HOMA-IR, TG/HDL-c ratio, TyG index, METS-IR and the percentages of males, smoking and drinking between the two groups (all $P > 0.05$).

Table 1 Clinical and Biochemical Characteristics by Presence of AS

Variables	All	Non-AS	AS	P
Number	790	569	221	
Age (years)	57.6 ± 12.9	53.9 ± 12.5	66.9 ± 8.7	<0.001
Diabetes duration (years)	7.0 (2.0~12.0)	5.0 (1.5~10.0)	10.0 (6.0~19.0)	<0.001
Sex (males, n, %)	339 (42.9%)	248 (43.6%)	91 (41.2%)	0.297
Smoking (n, %)	123 (15.6%)	90 (15.8%)	33 (14.9%)	0.422
Drinking (n, %)	117 (14.8%)	85 (15.0%)	32 (14.5%)	0.480
BMI (kg/m^2)	21.72 ± 1.79	21.69 ± 1.83	21.79 ± 1.71	0.504
VFA (cm^2)	59.00 (37.00~79.00)	57.00 (36.00~76.00)	64.00 (40.00~86.00)	0.006
SFA (cm^2)	123.50 (95.00~152.00)	121.00 (91.00~149.00)	129.00 (103.00~162.00)	0.002
SBP (mmHg)	125.6 ± 18.7	121.5 ± 16.7	136.0 ± 189.6	<0.001
DBP (mmHg)	77.6 ± 11.4	77.0 ± 10.9	79.0 ± 12.4	0.024
TC (mmol/L)	4.79 ± 1.17	4.80 ± 1.15	4.74 ± 1.22	0.528
LDL-c (mmol/L)	3.02 ± 0.99	3.05 ± 0.97	2.95 ± 1.02	0.217
TG (mmol/l)	1.12 (0.81~1.60)	1.10 (0.79~1.56)	1.20 (0.86~1.71)	0.079
HDL-c (mmol/L)	1.29 ± 0.38	1.29 ± 0.38	1.28 ± 0.36	0.770
FBG (mmol/L)	9.03 ± 4.22	9.18 ± 4.24	8.65 ± 4.15	0.114
FINS (μU/mL)	15.40 (7.81~21.51)	15.10 (7.48~20.71)	16.23 (8.61~25.03)	0.062
HbA1c (%)	9.78 ± 2.56	9.92 ± 2.60	9.41 ± 2.40	0.011
ALT (U/L)	16.20 (12.12~23.50)	16.10 (12.20~23.38)	16.40 (12.03~24.08)	0.616

(*Continued*)

Table 1 (Continued).

Variables	All	Non-AS	AS	P
AST (U/L)	16.90 (13.60~22.00)	16.50 (13.40~21.00)	18.40 (14.05~23.30)	0.004
GGT (U/L)	18.00 (13.00~25.00)	17.00 (13.00~25.00)	19.00 (14.00~28.00)	0.030
UA (μmolL)	266.05 ± 95.13	259.89 ± 92.05	282.01 ± 101.20	0.003
Scr (μmol/L)	64.20 ± 20.52	61.90 ± 16.69	70.14 ± 27.25	<0.001
eGFR (mL/min/1.73 m^2)	121.75 ± 35.03	126.20 ± 32.77	110.29 ± 38.02	<0.001
UACR (mg/g)	11.30 (6.00~37.60)	8.93 ± 0.70	9.42 ± 0.72	<0.001
Cys C (mg/l)	0.88 ± 0.29	0.83 ± 0.24	1.01 ± 0.36	<0.001
Hb (g/l)	136.96 ± 18.58	138.96 ± 18.58	131.76 ± 17.60	<0.001
HOMA-IR	5.38 (2.70~8.67)	5.37 (2.67~8.65)	5.39 (2.67~9.67)	0.739
TG/HDL-c ratio	0.90 (0.59~1.44)	0.89 (0.56~1.43)	0.95 (0.63~1.51)	0.165
TyG index	8.95 ± 0.77	8.95 ± 0.78	8.94 ± 0.74	0.859
METS-IR	34.10 ± 4.92	34.09 ± 4.96	34.11 ± 4.81	0.972
Log_e GDR	2.01 ± 0.37	2.15 ± 0.36	1.98 ± 0.38	<0.001

Notes: AS was defined as baPWV ≥ 1800cm/s. Data were presented as mean ± SD for normally distributed variables, and median (interquartile ranges) for abnormal distributions. Independent-Samples *T* test and Mann–Whitney *U*-test were used for comparisons of normally and abnormally distributed continuous variables between non-AS and AS groups, respectively. Categorical variables were presented as percentage (%), and were compared by chi-square test. Statistical differences were defined by P (two-tailed) less than 0.05.
Abbreviations: BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; FBG, fasting blood glucose; FINS, fasting serum insulin; HbA1c, glycated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; UA, uric acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio; Cys C, Cystatin C; Hb, hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; TyG index, triglyceride glucose index; METS-IR, insulin resistance metabolic score; Log_e GDR, a natural log transformation of the glucose disposal rate; baPWV, brachial-ankle pulse-wave velocity; AS, arterial stiffness.

Then, according to tertiles of log_e GDR, the participants were divided into three groups: T1 (0.25–1.98), T2 (1.98–2.28) and T3 (2.28–3.12) (Table 2). As the log_e GDR tertiles increased, the age, diabetes duration, BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, FINS, HbA1c, ALT, AST, GGT, UA, Scr, UACR, Cys C, HOMA-IR, TyG index, TG/HDL-c ratio, METS-IR, baPWV, the percentages of smoking, drinking and AS were gradually decreased, while the

Table 2 Comparison of Variables According to the Tertiles of Log_e GDR

Variables	T1 (0.25–1.98)	T2 (1.98–2.28)	T3 (2.28–3.12)	P
Number	263	264	263	
Age (years)	59.1 ± 11.9	58.0 ± 12.9	55.6 ± 13.7[ab]	0.006
Diabetes duration (years)	8.0 (3.0~15.0)	6.0 (2.0~11.5)[a]	7.0 (2.0~10.0)[a]	<0.001
Sex (male, n, %)	122 (46.4%)	103 (39.0%)	114 (43.3%)	0.481
Smoking (n, %)	51 (19.4%)	39 (14.8%)	33 (12.5%)	0.032
Drinking (n, %)	52 (19.8%)	32 (12.1%)	33 (12.6%)	0.021
BMI (kg/m^2)	22.16 ± 1.61	21.95 ± 1.62	21.04 ± 1.93[ab]	<0.001
VFA (cm^2)	69.00 (48.75~87.25)	61.00 (40.50~78.00)[a]	47.00 (28.50~66.50)[ab]	<0.001
SFA (cm^2)	132.00 (105.50~162.50)	124.50 (99.00~157.75)	111.00 (79.00~140.50)[ab]	<0.001
SBP (mmHg)	130.2 ± 20.0	124.2 ± 17.7[a]	122.3 ± 17.5[a]	<0.001
DBP (mmHg)	79.7 ± 12.0	77.3 ± 11.0[a]	76.6 ± 10.8[a]	<0.001
TC (mmol/L)	5.02 ± 1.28	4.86 ± 1.11	4.48 ± 1.04[ab]	<0.001
LDL-c (mmol/L)	3.16 ± 1.06	3.12 ± 0.96	2.78 ± 0.89[ab]	<0.001
TG (mmol/l)	1.60 (1.14~2.32)	1.22 (0.95~1.54)[a]	0.79 (0.61~0.97)[ab]	<0.001
HDL-c (mmol/L)	1.21 ± 0.42	1.27 ± 0.35	1.38 ± 0.33[ab]	<0.001
FBG (mmol/L)	9.27 ± 4.05	9.27 ± 4.37	8.56 ± 4.22	0.087

(*Continued*)

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Table 2 (Continued).

Variables	T1 (0.25–1.98)	T2 (1.98–2.28)	T3 (2.28–3.12)	P
FINS (μU/mL)	18.89 (11.94~24.75)	14.54 (7.19~20.44)[a]	13.01 (5.65~19.12)[a]	<0.001
HbA1c (%)	9.90 ± 2.41	9.91 ± 2.73	9.52 ± 2.51	0.142
ALT (U/L)	17.90 (12.85~26.40)	15.90 (12.60~23.78)[a]	14.80 (11.30~20.80)[a]	<0.001
AST (U/L)	18.20 (14.40~24.10)	16.40 (13.30~20.70)[a]	16.15 (13.00~21.13)[a]	<0.001
GGT (U/L)	29.00 (20.00~42.00)	19.00 (14.78~22.15)[a]	13.00 (11.00~16.00)[ab]	<0.001
UA (μmolL)	296.55 ± 98.14	257.26 ± 85.14[a]	244.63 ± 94.29[a]	<0.001
Scr (μmol/L)	72.78 ± 27.56	60.62 ± 14.20[a]	59.22 ± 13.97[a]	<0.001
eGFR (mL/min/1.73 m^2)	109.71 ± 38.62	125.11 ± 32.26[a]	130.43 ± 30.43[a]	<0.001
UACR (mg/g)	49.40 (12.70~362.80)	11.05 (5.93~22.75)[a]	6.90 (4.60~11.10)[a]	<0.001
Cys C (mg/l)	1.01 ± 0.39	0.84 ± 0.23[a]	0.80 ± 0.17[a]	<0.001
Hb (g/L)	134.03 ± 21.58	138.57 ± 17.46[a]	138.27± 16.01[a]	0.008
HOMA-IR	6.60 (3.76~11.02)	6.74 (2.57~8.43)[a]	4.04 (2.10~7.32)[a]	<0.001
TG/HDL-c ratio	1.41 (0.87~2.23)	0.97 (0.71~1.38)[a]	0.59 (0.42~0.82)[ab]	<0.001
TyG index	9.33 ± 0.81	9.02 ± 0.62[a]	8.50 ± 0.61[ab]	<0.001
METS-IR	36.18 ± 5.07	34.65 ± 4.33[a]	31.45 ± 4.07[ab]	<0.001
baPWV (cm/s)	1768.40 ± 475.10	1606.61 ± 397.33[a]	1495.06 ± 336.31[ab]	<0.001
AS (n, %)	109 (41.4%)	64 (24.2%)	48 (18.3%)	<0.001

Notes: AS was defined as baPWV ≥ 1800cm/s. Data were presented as mean ± SD for normally distributed variables, and median (interquartile ranges) for abnormal distributions. Analysis of variance (ANOVA) and Student–Newman–Keuls tests were performed for multiple and pairwise comparisons of normally distributed data, and Kruskal–Wallis 1-way ANOVA test for abnormal distributions. Categorical variables were presented as percentage (%) and were compared by Chi-square test. Statistical differences were defined by P values (two-tailed) less than 0.05. [a] P<0.05 versus T1; [b] P<0.05 T3 versus T2.

Abbreviations: BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; FBG, fasting blood glucose; FINS, fasting serum insulin; HbA1c, glycated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; UA, uric acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio; Cys C, Cystatin C; Hb, hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; TyG index, triglyceride glucose index; METS-IR, insulin resistance metabolic score; Log_e GDR, a natural log transformation of the glucose disposal rate; baPWV, brachial-ankle pulse-wave velocity; AS, arterial stiffness.

HDL-c, Hb and eGFR were gradually elevated (all $P < 0.05$). The FBG and the percentages of males were no significant different between the three groups (both $P > 0.05$).

Correlation Between baPWV or AS and Each Variable by Univariate Analysis

As shown in Table 3, a Pearson correlation analysis was performed to analyze the association between baPWV and each variable. The results displayed that the baPWV was positively related to age, diabetes duration, VFA, SFA, SBP, DBP, TG, FINS, GGT, UA, UACR, Cys C and TG/HDL-c ratio, while negatively to the Hb, HbA1c, eGFR and log_e GDR (all $P < 0.05$). BMI, TC, LDL-c, HDL-c, FBG, ALT, AST, HOMA-IR, TyG index and METS-IR were not correlated with baPWV (all $P > 0.05$).

Moreover, univariate regression analysis was conducted to identify the factors associated with AS. The results showed that AS was positively related to the age, diabetes duration, VFA, SFA, SBP, DBP, FINS, AST, UA, UACR, Cys C, and negatively to the Hb, HbA1c, eGFR and log_e GDR (all $P < 0.05$). No significant relationships existed between AS and BMI, TC, LDL-c, TG, HDL-c, FBG, ALT, GGT, HOMA-IR, TyG index, TG/HDL-c ratio, METS-IR and the percentages of males, smoking and drinking (all $P > 0.05$).

Independent Variables of baPWV by Multiple Linear Stepwise Regression Analysis

The covariates for multivariate linear regression analysis were determined based on the results of Pearson correlation analysis and previous literature reports. A multiple linear stepwise regression analysis was conducted to analyze the independent correlations of baPWV (Table 4). The age, diabetes duration, VFA, SFA, SBP, DBP, TG, FINS, GGT, UA, UACR, Cys C,

Table 3 The Correlation Between baPWV or AS and Different Variables by Univariate Analysis

Variables	For baPWV		For AS	
	Correlation Coefficient	P	OR (95% CI)	P
Age	0.565	<0.001	1.123 (1.101–1.146)	<0.001
Diabetes duration	0.288	<0.001	1.101 (1.076–1.127)	<0.001
Smoking			0.932 (0.605–1.438)	0.751
Drinking			0.962 (0.620–1.494)	0.863
Sex			1.104 (0.805–1.512)	0.539
BMI	0.053	0.135	1.030 (0.944–1.125)	0.504
VFA	0.112	0.002	1.007 (1.002–1.013)	0.008
SFA	0.174	<0.001	1.006 (1.003–1.010)	0.001
SBP	0.394	<0.001	1.046 (1.036–1.056)	<0.001
DBP	0.127	<0.001	1.016 (1.002–1.030)	0.025
TC	−0.003	0.938	0.958 (0.837–1.096)	0.528
LDL-c	−0.016	0.659	0.904 (0.771–1.061)	0.217
TG	0.073	0.041	1.016 (0.888–1.163)	0.814
HDL-c	−0.021	0.553	0.939 (0.618–1.428)	0.770
FBG	−0.034	0.344	0.969 (0.931–1.008)	0.115
FINS	0.115	0.012	1.015 (1.000–1.029)	0.044
HbA1c	−0.118	0.001	0.923 (0.866–0.984)	0.014
ALT	−0.019	0.585	1.006 (0.996–1.016)	0.221
AST	0.056	0.113	1.016 (1.003–1.028)	0.016
GGT	0.107	0.003	1.004 (0.997–1.012)	0.256
UA	0.159	<0.001	1.002 (1.001–1.004)	0.004
eGFR	−0.233	<0.001	0.986 (0.981–0.991)	<0.001
UACR	0.292	<0.001	1.000 (1.000–1.001)	0.001
Cys C	0.300	<0.001	7.734 (3.646–16.405)	<0.001
Hb	−0.144	<0.001	0.979 (0.971–0.988)	<0.001
HOMA-IR	0.044	0.345	1.023 (0.991–1.057)	0.165
TG/HDL-c ratio	0.072	0.045	1.024 (0.915–1.145)	0.684
TyG index	0.026	0.471	0.982 (0.801–1.203)	0.859
METS-IR	0.038	0.294	1.001 (0.969–1.033)	0.972
Log_e GDR	−0.254	<0.001	0.287 (0.187–0.442)	<0.001

Notes: AS was defined as baPWV ≥ 1800cm/s. Pearson correlation analysis and univariate regression analysis were respectively conducted to identify the factors between baPWV, AS and different variables.
Abbreviations: BMI, body mass index; VFA, visceral fat area; SFA, subcutaneous fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; FBG, fasting blood glucose; FINS, fasting serum insulin; HbA1c, glycated hemoglobin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; UA, uric acid; eGFR, estimated glomerular filtration rate; UACR, urinary albumin to creatinine ratio; Cys C, Cystatin C; Hb, hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; TyG index, triglyceride glucose index; METS-IR, insulin resistance metabolic score; Log_e GDR, a natural log transformation of the glucose disposal rate; baPWV, brachial-ankle pulse-wave velocity; AS, arterial stiffness; OR, odd ratio.

TG/HDL-c ratio, Hb, HbA1c, eGFR and log_e GDR were set as the dependent variables based on the results of Pearson correlation analysis, and the results displayed that the age, SBP and log_e GDR fit a regression model (all $P < 0.05$).

Independent Correlations of AS by Logistic Regression Analysis

Finally, AS was served as the dependent variable, and based on the results of univariate logistic regression analysis, the DAG diagram (Figure 2), and previous literature, the following variables were included as independent variables: age, diabetes duration, VFA, SFA, SBP, DBP, FINS, HbA1c, AST, UA, eGFR, UACR, Cys C, Hb, BMI, FBG, TG, HOMA-

Table 4 Multivariate Linear Regression Analysis with baPWV as the Dependent Variable

Variables	Unstandardized Coefficients		Standardized Coefficients	t	P	Adjusted
	β	SE	β			R^2
						0.439
Log_e GDR	−127.548	48.094	−0.162	−3.588	<0.001	
Age	17.796	1.467	0.554	12.128	<0.001	
SBP	4.849	0.971	0.229	4.993	<0.001	

Notes: The independent variables for baPWV were assessed by multiple linear stepwise regression analysis.
Abbreviations: Log_e GDR, a natural log transformation of the glucose disposal rate; SBP, systolic blood pressure; baPWV, brachial-ankle pulse-wave velocity; SE, standard error.

IR, TG/HDL-c ratio, TyG index, METS-IR, log_e GDR and the percentages of smoking and drinking. A logistic regression analysis was performed to analyze the independent correlates of AS (Table 5), and the results found that after adjusting for the other variables, the log_e GDR (OR: 0.286, 95.0% CI for OR: 0.110–0.743), age (OR: 1.196, 95.0% CI for OR: 1.138–1.258), SBP (OR: 1.053, 95.0% CI for OR: 1.031–1.075) and FBG (OR: 0.886, 95.0% CI for OR: 0.792–0.990) were independently related to AS.

Predictive Value of IR Markers for AS

To assess the incremental predictive value of various IR markers for AS, NRI analysis was performed based on logistic regression models (Table 6). All models were adjusted for potential confounders, including age, diabetes duration, VFA, SFA, SBP, DBP, FINS, HbA1c, AST, UA, eGFR, UACR, Cys C, Hb, BMI, FBG, TG, smoking and drinking. Building upon the base model without any IR marker, integrating log_e GDR yielded a modest improvement in the model's ability

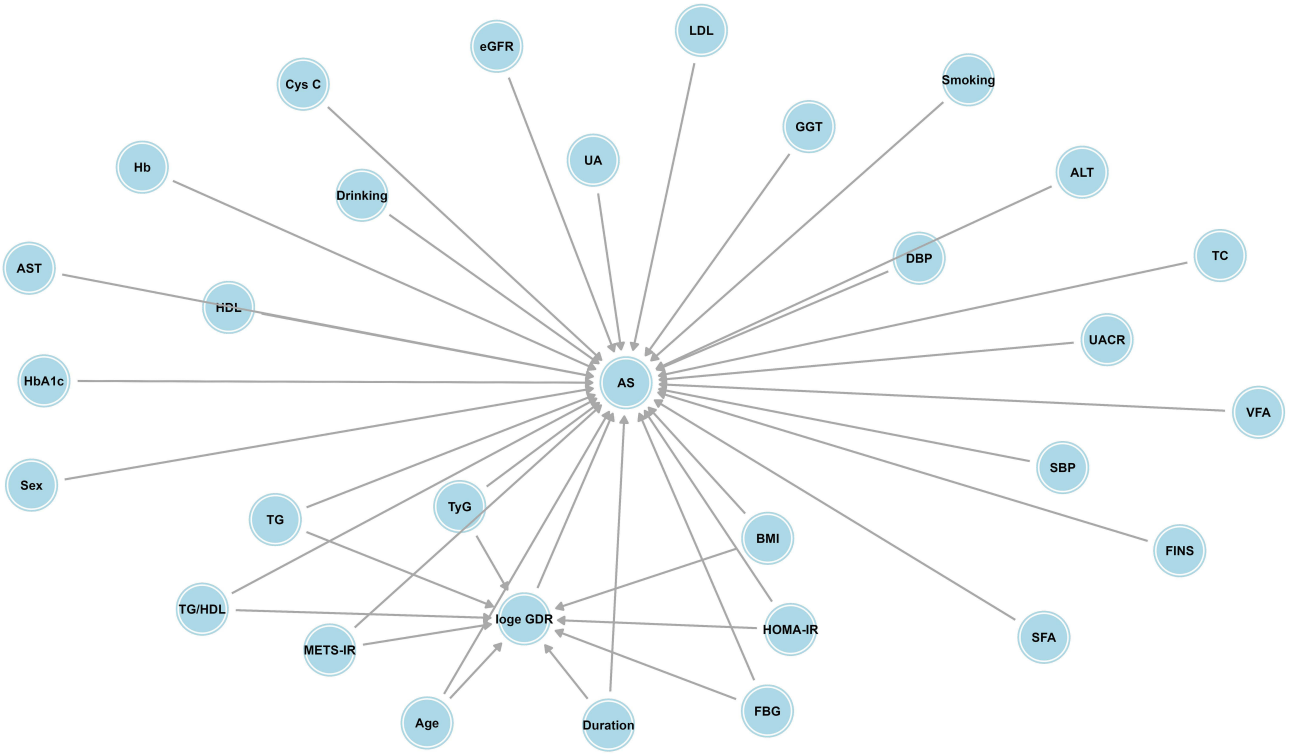

Figure 2 The DAG of identifying confounding variables.

Table 5 The Independent Variables for AS

Variables	B	SE	Wals	P	OR	95.0% CI for OR
Log_e GDR	−1.253	0.487	6.609	0.010	0.286	0.110–0.743
Age	0.179	0.026	49.084	<0.001	1.196	1.138 −1.258
SBP	0.052	0.011	24.399	<0.001	1.053	1.031 −1.075
FBG	−0.122	0.057	4.575	0.032	0.886	0.792–0.990

Notes: AS was defined as baPWV ≥ 1800cm/s. The independent variables for AS were assessed by logistic regression analysis.

Abbreviations: Log_e GDR, a natural log transformation of the glucose disposal rate; SBP, systolic blood pressure; FBG, fasting blood glucose; AS, arterial stiffness; SE, standard error; CI, confidence interval; OR, odd ratio.

Table 6 Analysis of the NRI for Predicting AS

Model	NRI	SE	95.0 % CI	P
Base Model (no IR indicator)	–	–	–	–
Model with HOMA-IR	0.007	0.018	(−0.027, 0.043)	0.697
Model with TyG index	0.011	0.012	(−0.014, 0.033)	0.356
Model with TG/HDL-c ratio	0.006	0.006	(−0.004, 0.020)	0.317
Model with METS-IR	−0.004	0.007	(−0.018, 0.011)	0.568
Model with log_e GDR	0.043	0.017	(0.009,0.079)	0.011

Notes: AS was defined as baPWV ≥ 1800cm/s.

Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance; TyG index, triglyceride glucose index; METS-IR, insulin resistance metabolic score; Log_e GDR, a natural log transformation of the glucose disposal rate; NRI, net reclassification improvement; SE, standard error; CI, confidence interval.

to reclassify patients with AS (NRI:0.043, 95% CI 0.009–0.079, P = 0.011). In contrast, building upon the base model, integrating other IR markers such as HOMA-IR (NRI:0.007, P = 0.697), TyG index (NRI:0.011, P = 0.356), TG/HDL-c ratio (NRI:0.006, P = 0.317), and METS-IR (NRI: −0.004, P = 0.568) did not significantly improve the predictive performance.

Discussion

This cross-sectional study of non-obese patients with T2D revealed a significant negative association between the log_e GDR and both baPWV and AS. Increased log_e GDR tertiles corresponded with a significant reduction in baPWV and AS incidence. Furthermore, after adjusting for confounding factors, the log_e GDR was independently associated with baPWV and AS.

IR is common among diabetic patients, leading to endothelial dysfunction and inflammatory responses that contribute to AS and atherosclerosis.[22] Although the EHC is considered the gold standard for assessing IS, its complexity, time consuming, and requirement for specialized personnel limit its use in large-scale clinical studies. HOMA-IR is a commonly used and simpler indicator of IR, but it relies on FINS. Previous studies have shown that fluctuations in insulin levels can be significantly influenced by an individual's glucose tolerance and the effects of treatment. Therefore, FINS levels may not be entirely accurate for patients with T2D undergoing treatment.[23,24] Recently, an increasing number of studies have explored the close association between non-insulin-based IR surrogate indicators and AS across various populations. For instance, a study in a healthy Japanese cohort found a significant correlation between the METS-IR and AS.[25] A study involving 1895 participants showed a close correlation between the TyG index and the TG/HDL-c ratio with AS in hypertensive patients, while no such relationship was observed in patients with prehypertension.[26] Furthermore, research on patients with T2D had indicated that the TyG index was independently and more strongly associated with the prevalence of increased AS compared to HOMA-IR.[20] The relationship between non-insulin-based IR surrogate indicators with AS had also been validated in lean postmenopausal women, Chinese non-hypertensive and older subjects.[27–29]

The $\log_e$ GDR is a newly developed model for assessing IS in T2D, and it has been validated as a reliable EHC-based surrogate capable of capturing the variability of IS in patients with T2D well.[13] The inclusion of metabolic components (GGT, UACR, BMI and TG) allows $\log_e$ GDR to reflect a more comprehensive metabolic profile and potentially capturing a broader range of pathogenic mechanisms. In our study, we found that it was closely associated with IR markers as well. As the tertiles of $\log_e$ GDR increased, significant reductions were observed in other IR markers, suggesting a consistent relationship between $\log_e$ GDR and IS. Notably, we found that the $\log_e$ GDR was independently related to baPWV and AS. This relationship remains important even after adjusting for other confounding factors including IR markers (HOMA-IR, TG/HDL-c ratio, TyG index, and METS-IR).

The mechanisms potentially linking $\log_e$ GDR to AS are likely multifactorial and may involve several key pathways. The components included in the calculation of $\log_e$ GDR, including GGT, UACR, BMI and TG, may have been suggested as part of circadian syndrome.[30] Recent studies indicate that circadian syndrome may be a better predictor of CVDs risk than metabolic syndrome,[30] suggesting that $\log_e$ GDR might reflect a disruption in circadian rhythms, potentially influencing cardiovascular health. GGT is a key marker of oxidative stress, promoting endothelial dysfunction by reducing nitric oxide bioavailability and increasing vascular inflammation, both of which contribute to arterial stiffening. TG facilitates lipid accumulation in the vascular wall, leading to foam cell formation and atherosclerosis progression. Elevated TG levels are also associated with increased production of small, dense LDL particles, which enhance oxidative stress and vascular inflammation. UACR reflects endothelial dysfunction and vascular damage, as albuminuria is linked to increased vascular permeability and low-grade inflammation, both contributing to arterial remodeling. Additionally, BMI, particularly in the context of visceral adiposity, is associated with chronic low-grade inflammation and activation of the renin-angiotensin-aldosterone system, further promoting vascular stiffness. These components effectively represent the key metabolic pathways leading to AS, supporting the close relationship between $\log_e$ GDR and AS.[31–33]

Additionally, AS is a degenerative vascular process that increases with age.[34] High SBP levels may damage endothelial function, leading to progressively stiffer arteries.[35] Be consistent with the above findings, we found a strong relationship between age and SBP with AS in non-obese patients with T2D. This underscores the importance of managing SBP as a modifiable risk factor for AS, particularly in this population. Interestingly, we observed a negative correlation between AS and FBG, which was inconsistent with most studies that suggested elevated FBG was a significant risk factor for AS.[36] The multifaceted influencing factors of AS may help explain this phenomenon. As mentioned earlier, the average age in the AS group was significantly higher than that in the non-AS group, and some studies have suggested that older diabetic patients tend to have better blood glucose control.[37]

The relationship between the novel IS index $\log_e$ GDR and AS has not been extensively studied in the context of non-obese T2D. Our study is the first to observe a strong association between $\log_e$ GDR and AS in non-obese patients with T2D, highlighting its potential clinical significance. Although non-obese individuals with T2D may have normal body weight, they can still exhibit significant vascular changes. Since $\log_e$ GDR incorporates metabolic parameters including BMI, TG, UACR and GGT, it may reflect a broader metabolic disorder amenable to intervention than other IR markers. Importantly, $\log_e$ GDR demonstrated the highest NRI among the evaluated IR indicators, indicating relatively better discriminatory capacity for AS. However, the overall improvement in risk prediction was modest, suggesting that its incremental value in risk stratification may be limited. Therefore, while $\log_e$ GDR shows potential as a complementary tool for early identification of cardiovascular risk in non-obese T2D patients, its clinical utility should be interpreted with caution. Further prospective studies with larger, diverse cohorts are needed to confirm these findings and to clarify the role of $\log_e$ GDR in improving cardiovascular risk prediction models.

Several limitations of this study should be acknowledged. First, as with all cross-sectional studies, we cannot establish causality between $\log_e$ GDR and AS. Longitudinal studies are essential to determine the temporal relationship and causal pathways between these variables. Second, using BMI < 24 kg/m² to define "non-obese" may not perfectly capture individuals with increased visceral adiposity, which is a key driver of metabolic dysfunction. Future studies could consider including measures such as waist circumference or waist-to-hip ratio, which provide more direct insight into visceral fat distribution. Lastly, this study is single-center and based on a small sample size, which may limit the generalizability of the results. Future prospective multi-center studies involving larger populations are needed to confirm these findings and further investigate the underlying mechanisms.

Conclusion

In conclusion, the $\log_e$ GDR, as a new simple index of IS, is independently associated with AS in non-obese patients with T2D. Its inclusion in existing risk models modestly improved the identification of arterial stiffness. The potential utility of $\log_e$ GDR in cardiovascular risk assessment warrants further investigation and validation in future studies.

Ethics Approval and Consent to Participate

The study was approved by the Human Ethics Committee of the Linyi People's Hospital. All procedures were performed in accordance with ethical standards laid out in the Declaration of Helsinki. Informed consent was obtained from the patients.

Acknowledgments

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Disclosure

All authors declare that they have no competing interests in this study.

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