Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

The Log$_e$ GDR Was Strongly Associated with NAFLD as a Predictor in Normoalbuminuric Patients with Type 2 Diabetes

Baolan Ji[1], Guanqi Gao[2], Hongyan Zhao[2,3], Jie Sheng[2,3], Xuan Ma[2,3], Shuwei Shi[1–3], Bo Ban[1,2]

[1]Department of Endocrinology, Affiliated Hospital of Jining Medical University, Jining, Shandong, 272029, People's Republic of China; [2]Department of Endocrinology, Linyi People's Hospital Affiliated to Shandong Second Medical University, Linyi, Shandong, 276034, People's Republic of China; [3]School of Clinical Medicine, Shandong Second Medical University, Weifang, Shandong, 261000, People's Republic of China

Correspondence: Bo Ban, Department of Endocrinology, Affiliated Hospital of Jining Medical University, 89 Guhuai Road, Jining, Shandong, 272029, People's Republic of China, Email banbo2011@163.com; Shuwei Shi, School of Clinical Medicine, Shandong Second Medical University, Weifang, Shandong, 261000, People's Republic of China, Email ssw15689286547@163.com

Diabetes, Metabolic Syndrome and Obesity downloaded from https://www.dovepress.com/
For personal use only.

Aim: Attenuated insulin-sensitivity (IS) is a characteristic of type 2 diabetes (T2D) and is closely linked to non-alcoholic fatty liver disease (NAFLD). In recent years, many surrogate markers of IS have emerged to predict NAFLD. A natural log transformation of the glucose disposal rate (log$_e$ GDR) has been proposed as a new model for IS in patients with T2D. Our aim is to explore the correlation between log$_e$ GDR and NAFLD in normoalbuminuric patients with T2D.

Methods: A total of 1227 normoalbuminuric patients with T2D were involved in our study. NAFLD was evaluated by ultrasound. Biochemical and clinical data were collected, including parameters essential for calculating the log$_e$ GDR (triglycerides, urinary albumin-to-creatinine ratio, γ-glutamyl transferase and body mass index), as well as other relevant covariates required for adjustment. The relationship between the log$_e$ GDR and NAFLD was analyzed.

Results: NAFLD patients showed lower log$_e$ GDR values than non-NAFLD ($P < 0.001$). As the log$_e$ GDR tertiles increased, the prevalence of NAFLD was decreased ($P < 0.001$). Multivariate analysis displayed that log$_e$ GDR was independently corrected with NAFLD (OR: 0.084; 95% CI: 0.040–0.177). Furthermore, receiver operating characteristic (ROC) analysis showed that log$_e$ GDR (area under the curves: 0.797) was superior to other evaluation variables.

Conclusion: The log$_e$ GDR was strongly associated with NAFLD and might be a useful predictor in normoalbuminuric patients with T2D.

Keywords: type 2 diabetes, NAFLD, insulin sensitivity, log$_e$ GDR

Introduction

Nonalcoholic fatty liver disease (NAFLD) is becoming an increasingly serious public health concern globally, particularly among patients with diabetes, where its prevalence has risen significantly.[1] A recent epidemiological study shows that the global prevalence of NAFLD among patients with type 2 diabetes (T2D) has reached nearly 69%.[2] NAFLD is not limited to the liver, it is a multisystem disease that involves extrahepatic organs and multiple physiological regulatory pathways. Through mechanisms such as chronic inflammation, lipid metabolism abnormalities, insulin resistance (IR) and atherosclerosis, it significantly increases the risk of T2D, cardiovascular disease (CVD), chronic kidney disease (CKD) and other related conditions.[3–5] Therefore, early identification and screening of NAFLD in T2D is crucial for mortality associated with NAFLD.

There is substantial evidence indicating that IR is a crucial factor in the pathogenesis of NAFLD, as it diminishes insulin sensitivity (IS) across various tissues, including systemic, hepatic and adipose tissues,[1,6] thereby promoting hepatic fat accumulation and metabolic dysfunction.[7] The euglycemic hyperinsulinemic clamp technique is the gold standard for measuring IR,[8] but its time-consuming and invasiveness limits its use in large scale epidemiological studies.

Received: 13 October 2024
Accepted: 28 December 2024
Published: 13 January 2025

© 2025 Ji et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

The homeostasis model assessment index (HOMA-IR) has been proposed as a simpler method for assessing IR.[9] Although this method facilitates large cohort studies, it relies on fasting plasma insulin (FINS), which are not commonly conducted and can fluctuate significantly. Additionally, researches indicate that fluctuations in insulin levels can significantly depend on an individual's glucose tolerance and the effects of therapy.[10,11]

In recent years, several new non-insulin-based surrogate markers of IR have been developed. The natural log transformation of the glucose disposal rate ($\log_e$ GDR) was recently developed as a novel IS prediction model by Ciardullo et al for patients with T2D, based on routinely available clinical and biomarker data, including triglycerides (TG), urinary albumin-to-creatinine ratio (UACR), γ-glutamyl transferase (GGT) and body mass index (BMI). The components of $\log_e$ GDR reflect key metabolic processes, including lipid metabolism, liver function, renal function and obesity. These factors are closely associated with the pathogenesis of NAFLD.[12,13] Therefore, as a comprehensive surrogate marker of IS, we speculate that the $\log_e$ GDR may be also closely associated with NAFLD; however, there have been no published studies to support this hypothesis.

The UACR, as an important component of $\log_e$ GDR, is the diagnostic markers of diabetes nephropathy (DN), which is closely related to IR.[14,15] Although studies displayed that the severe IR diabetes might have the highest risk for DN and NAFLD,[16] strong evidences have demonstrated that even in populations with normal UACR, the risk of NAFLD, CVD and other diseases may still be elevated.[17–19] Therefore, our study aims to explore the correlation between $\log_e$ GDR and NAFLD in normoalbuminuric patients with T2D.

Meanwhile, a series of commonly used effective IR indicators and related derivative parameters as the covariates are included them in our study as well, including triglyceride glucose index (TyG), triglyceride glucose-body mass index (TyG-BMI), triglyceride/high-density cholesterol–lipoprotein ratio (TG/HDL-c) and triglyceride glucose-γ-glutamyl transferase (TyG-GGT), which have been confirmed to strongly associated with NAFLD;[20–22] other indicators similar to the components of $\log_e$ GDR, such as the uric acid (UA) index and the combination of fasting blood glucose (FBG) and BMI (ByG), have recently been proposed.[23,24] These indicators have been shown to be closely associated with diabetes and CVD, and we included in our study as well.

Materials and Methods

Patients

Our study retrospectively analyzed the inpatients with T2D aged 18 to 87 years from the Department of Endocrinology of Linyi People's Hospital, from January 2020 to March 2023. The exclusion criteria were (1) patients with other types of diabetes; (2) patients with other liver disease, including viral hepatitis, autoimmune, drug-induced liver diseases and acute liver injury; (3) patients with a history of excessive alcohol intake (>70 g/week for women or 140 g/week for men);[25] (4) missing the measurement of NAFLD. In the end, a total of 1227 normoalbuminuric patients with T2D were included in this study.

General Conditions and Clinical Data

The patients' general conditions, including age, sex, duration of diabetes, height and weight, were recorded.

Smoking and drinking status were assessed. The data on drinking were based on self-reported information collected during their hospitalization and were recorded immediately during the medical history intake. These data were obtained by trained medical staff through clinical interviews and were recorded in real time. According to relevant guidelines,[25] excessive alcohol consumption is defined as more than 70 grams per week for females and more than 140 grams per week for males. Based on self-reported alcohol intake, we calculated the total weekly alcohol consumption in grams.

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using standardized methods with an automated electronic sphygmomanometer (OMRON HEM-725, Omron Corporation, Dalian, China). Participants were instructed to rest for at least 5 minutes in a quiet environment before measurements. Each participant underwent at least two readings, taken 1–2 minutes apart, with the average recorded as the final result. In cases of significant discrepancies between readings, additional measurements were taken, and the average of the consistent values was used to exclude outliers.

The visceral fat area (VFA) and subcutaneous fat area (SFA) were tested by bioelectrical impedance analysis (HDS-2000, Omron, Kyoto, Japan).

Biochemical Measurements

Blood samples were collected in the morning after an overnight fast and analyzed for TG, total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT, FBG, glycosylated haemoglobin (HbA1c, high performance liquid chromatography), UA, serum creatinine (Scr) and hemoglobin (Hb) were measured by a biochemical autoanalyzer (Cobas c 702, Roche, Germany). UACR was measured using an autoanalyzer (Beckman Coulter AU5821). FINS was measured using a direct chemiluminescence method with a fully automated sample processing system (Aptio Automation, SIEMENS, USA). Normoalbuminuric was defined as UACR < 30 mg/g.

Definition of NAFLD

NAFLD was diagnosed via liver ultrasonography, which revealed the presence of fatty liver. After excluding other potential causes of hepatic steatosis (eg, history of alcohol consumption, drug use, or viral hepatitis), the ultrasound diagnostic criteria for NAFLD included vascular blurring, deep attenuation, abnormal liver-kidney echo contrast, and increased liver brightness.

Parameter Calculations

1. BMI = weight (kg)/height (m);[2]
2. TyG index = ln [TG (mg/dL) * FBG (mg/dL)/2];[26]
3. TyG-BMI = TyG * BMI;[27]
4. TyG-GGT = TyG * GGT;[21]
5. ByG index = ln [BMI (kg/m^2) * FBG (mg/dL)/2];[24]
6. TG/HDL-c ratio = TG (mmol/L)/HDL-c (mmol/L);[28]
7. HOMI-IR = FBG (mmol/L) * FINS (IU/mL)/22.5;[9]
8. UA index = ln [TG (mg/dL) * UA (mg/dL) * FBG (mg/dL)/2];[23]
9. eGFR = 175 * Scr $(mg/dL)^{-1.234}$ * age $^{-0.179}$ * (0.79, if female);[29]
10. 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).[30]

Statistical Analysis

The data in this study were analyzed using SPSS 26.0 (SPSS Inc, Chicago, IL, USA). Normally distributed variables were expressed as mean ± SD, and were compared using Independent-Samples *T* test between the two groups. Abnormal distributions were expressed as median and interquartile ranges, and were compared using by Mann–Whitney *U*-test between the two groups. Categorical variables were described as percentage (%), and were compared using the chi-square test. Between the log_e GDR tertiles groups, we performed an Analysis of Variance (ANOVA) and Student-Newman-Keuls tests for multiple and pairwise comparisons of normally distributed data, and Kruskal–Wallis one way ANOVA test for abnormal distributions. Logistic regression analysis was used to analyze the independent correlates of NAFLD. The receiver operating characteristic (ROC) curve and related area under the ROC curve (AUC) were used to assess the log_e GDR's effectiveness in predicting NAFLD, and further performed a differential analysis. Statistical analyses were performed using two-sided tests, with a P-value of less than 0.05 considered statistically significant.

Results

Baseline Clinical and Biochemical Characteristics

The baseline clinical and biochemical characteristics of the subjects are presented in Table 1. For normally distributed variables, data are expressed as mean ± standard deviation, and differences between the two groups are analyzed using an

Table 1 Clinical and Biochemical Characteristics by Presence of NAFLD

Variables	All	Non-NAFLD	NAFLD	P
Number	1227	708	519	
Sex (male, n, %)	465	249 (35.2%)	216 (41.6%)	0.021
Smoking (n, %)	185	85 (12.0%)	100 (19.3%)	<0.001
Age (years)	56.3 ± 12.0	57.8 ± 11.6	54.3 ± 12.3	<0.001
Duration of diabetes (years)	6.0 (2.0~10.0)	7.50 (2.88~12.00)	5.00 (1.50~10.00)	<0.001
BMI (kg/m^2)	25.4 ± 3.5	24.2 ± 3.1	27.1 ± 3.4	<0.001
VFA (cm^2)	88.0 (63.0~115.0)	74.0 (53.0~98.0)	104.0 (81.0~131.0)	<0.001
SFA (cm^2)	180.0 (140.0~225.0)	161.0 (121.0~200.0)	210.0 (172.0~249.0)	<0.001
SBP (mmHg)	127.7 ± 17.5	125.5 ± 18.3	130.7 ± 15.9	<0.001
DBP (mmHg)	80.3 ± 10.6	78.1 ± 10.4	83.4±10.2	<0.001
TC (mmol/L)	4.80 ± 1.18	4.69 ± 1.15	4.95 ± 1.19	<0.001
LDL-c (mmol/L)	3.05 ± 1.01	2.96 ± 0.97	3.17 ± 1.05	<0.001
TG (mmol/l)	1.4 (0.9~1.0)	1.2 (0.8~1.6)	1.7 (1.2~2.5)	<0.001
HDL-c (mmol/L)	1.2 ± 0.4	1.3 ± 0.4	1.1 ± 0.3	<0.001
FBG (mmol/L)	8.8 ± 3.2	8.5 ± 3.3	9.2 ± 3.1	<0.001
FINS (μU/mL)	16.0 (9.7~21.2)	15.1 (7.3~20.7)	17.4 (12.3~21.5)	<0.001
HbA1c (%)	9.2 ± 2.2	9.2 ± 2.3	9.3 ± 2.1	0.150
ALT (U/L)	18.0 (13.5~26.0)	16.20 (12.0~23.0)	20.80 (15.4~32.3)	<0.001
AST (U/L)	17.4 (14.1~22.2)	16.85 (13.9~21.0)	18.30 (14.6~24.6)	<0.001
GGT (U/L)	21.0 (15.0~30.0)	17.00 (13.0~24.0)	27.00 (19.0~40.0)	<0.001
UA (μmolL)	266.4 ± 79.3	246.5 ± 70.4	293.6 ± 82.6	<0.001
Scr (μmol/L)	57.6 ± 10.9	57.2 ± 10.5	58.2 ± 11.3	0.105
eGFR ($mL/min/1.73\ m^2$)	130.5 ± 26.5	129.8 ± 25.2	131.4 ± 28.3	0.314
UACR (mg/g)	7.5 (4.8~12.5)	7.5 (4.7~12.4)	7.60 (4.8~12.6)	0.621
Hb (g/L)	142.6 ± 15.6	139.8 ± 15.9	146.5 ± 14.4	<0.001
TyG index	9.1 ± 0.8	8.9 ± 0.7	9.4 ± 0.7	<0.001
TyG-BMI	232.9 ± 41.9	216.7 ± 35.7	255.1 ± 39.4	<0.001
TyG-GGT	188.7 (132.2~282.1)	155.8 (113.5~217.5)	249.6 (176.0~387.3)	<0.001
ByG index	7.5 ± 0.4	7.5 ± 0.4	7.7 ± 0.3	<0.001
UA index	10.6 ± 0.9	10.3 ± 0.8	11.0 ± 0.8	<0.001
TG/HDL-c ratio	1.2 (0.7~1.9)	0.9 (0.6~1.5)	1.6 (1.0~2.3)	<0.001
HOMA-IR	5.8 (3.3~9.0)	5.0 (2.4~8.5)	6.8 (4.0~9.6)	<0.001
Log_e GDR	2.0 ± 0.4	2.2 ± 0.3	1.8 ± 0.3	<0.001

Notes: Normally distributed variables were presented as mean ± standard, and comparisons between the two groups were conducted using an independent samples *t*-test. Abnormally distributed variables were presented as median (25th percentile~75th percentile), and comparisons between the two groups were performed using the Mann–Whitney *U*-test. 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: NAFLD, non-alcoholic fatty liver disease; 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; 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; Hb, hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; Log_e GDR, a natural log transformation of the glucose disposal rate.

independent samples *t*-test. Abnormally distributed variables are presented as median with interquartile ranges (25th percentile ~ 75th percentile), and comparisons are made using the Mann–Whitney *U*-test. Compared with the non-NAFLD group, the BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, FBG, FINS, AST, ALT, GGT, UA, Hb, TyG index, TyG-BMI, TyG-GGT, ByG index, UA index, TG/HDL-c ratio, HOMA-IR and the percentage of smoking and males were higher in NAFLD group (all $P < 0.05$). The age, duration of diabetes, HDL-c and the log_e GDR were lower in the NAFLD group (all $P < 0.001$). The HbA1c, Scr, eGFR and UACR were no different between the two group (all $P > 0.05$).

According to the log_e GDR tertiles, the subjects were divided into three groups (Table 2). For normally distributed variables, data are expressed as mean ± standard deviation, and comparisons across the three groups are performed using

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

Variables	T1 (0.70–1.88)	T2 (1.88–2.19)	T3 (2.19–3.12)	*P*
Number	407	418	402	
Sex (male, n, %)	190 (46.7%)	151 (36.1%)	124 (30.8%)	<0.001
Smoking (n, %)	87 (21.4%)	59 (14.1%)	39 (9.7%)	<0.001
Age (years)	54.0 ± 12.6	58.0 ± 11.2[a]	56.9 ± 11.9[a]	<0.001
Duration of diabetes (years)	5.0 (1.5~10.0)	6.0 (2.0~11.0)[a]	8.0(3.0~12.8)[a]	<0.001
BMI (kg/m^2)	27.64 ± 3.40	25.4 ± 2.7[a]	23.2 ± 2.9[a,b]	<0.001
VFA (cm^2)	113.0 (89.0~135.0)	88.00 (67.8~111.3)[a]	63.0 (45.0~86.0)[a,b]	<0.001
SFA (cm^2)	216.0 (178.0~258.0)	180.0 (146.0~218.0)[a]	144.5 (108.0~183.3)[a,b]	<0.001
SBP (mmHg)	131.9 ± 17.6	128.5 ± 16.8[a]	122.7 ± 16.8[a,b]	<0.001
DBP (mmHg)	84.0 ± 10.6	80.6 ± 9.8[a]	76.3 ± 10.1[a,b]	<0.001
TC (mmol/L)	5.1 ± 1.3	4.8 ± 1.1[a]	4.5 ± 1.1[a,b]	<0.001
LDL-c (mmol/L)	3.2 ± 1.1	3.1 ± 1.0	2.8 ± 0.9[a,b]	<0.001
TG (mmol/l)	2.2 (1.6~3.2)	1.3 (1.1~1.7)[a]	0.9 (0.7~1.2)[a,b]	<0.001
HDL-c (mmol/L)	1.1 ± 0.3	1.2 ± 0.3[a]	1.4 ± 0.4[a,b]	<0.001
FBG (mmol/L)	9.5 ± 3.2	9.0 ± 3.1[a]	7.8 ± 3.1[a,b]	<0.001
FINS (μU/mL)	18.1 (13.8~22.8)	16.0 (9.6~20.7)[a]	13.6 (5.9~19.3)[a,b]	<0.001
HbA1c (%)	9.4 ± 2.1	9.4 ± 2.2	8.8 ± 2.3[a,b]	<0.001
ALT (U/L)	23.3 (16.5~37.7)	17.6 (13.7~24.8)[a]	14.6 (11.4~20.5)[a,b]	<0.001
AST (U/L)	19.6 (15.9~26.4)	16.9 (13.6~20.5)[a]	16.1 (13.3~20.6)[a]	<0.001
GGT (U/L)	36.0 (27.00~52.0)	20.0 (16.9~25.0)[a]	14.0 (11.0~17.0)[a,b]	<0.001
UA (μmolL)	303.4 ± 85.9	259.0 ± 67.4[a]	236.7 ± 68.5[a,b]	<0.001
Scr (μmol/L)	59.3 ± 11.4	57.4 ± 10.9[a]	56.1 ± 10.1[a]	<0.001
eGFR ($mL/min/1.73\ m^2$)	129.8 ± 27.0	129.8 ± 27.6	131.8 ± 24.9	0.483
UACR (mg/g)	9.1 (5.8~15.3)	7.8 (5.1~12.4)[a]	6.1 (4.0~9.4)[a,b]	<0.001
Hb (g/L)	147.3 ± 14.9	143.0 ± 15.0[a]	137.5 ± 15.4[a,b]	<0.001
TyG index	9.7 ± 0.7	9.2 ± 0.5[a]	8.6 ± 0.6[a,b]	<0.001
TyG-BMI	268.4 ± 37.6	231.8 ± 25.0[a]	198.1 ± 28.0[a,b]	<0.001
TyG-GGT	347.3 (257.6~505.2)	183.8 (153.8~225.3)[a]	116.6 (95.6~145.3)[a,b]	<0.001
ByG index	7.7 ± 0.4	7.6 ± 0.3[a]	7.3 ± 0.4[a,b]	<0.001
UA index	11.3 ± 0.8	10.6 ± 0.6[a]	9.9 ± 0.6[a,b]	<0.001
TG/HDL-c ratio	2.1 (1.5~3.2)	1.2 (0.9~1.6)[a]	0.7 (0.5~0.9)[a,b]	<0.001
HOMA-IR	7.8 (5.0~10.3)	5.9 (3.3~8.7)[a]	4.0 (2.0~7.1)[a,b]	<0.001
NAFLD (n, %)	282 (69.3%)	182 (43.5%)	55 (13.7%)	<0.001

Notes: Normally distributed variables were presented as mean ± standard, and comparisons among three groups were conducted using one-way analysis of variance (ANOVA). Abnormally distributed variables were presented as median (25th percentile~75th percentile), and comparisons among three groups were using the Kruskal–Wallis test. Student–Newman–Keuls tests were conducted for multiple and pairwise comparisons. 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: NAFLD, non-alcoholic fatty liver disease; 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; 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; Hb, hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; log_e GDR, a natural log transformation of the glucose disposal rate.

a one-way analysis of variance (ANOVA). For abnormally distributed variables, data are reported as median with interquartile ranges (25th percentile ~ 75th percentile), and group differences are assessed using the Kruskal–Wallis test. As the tertiles of log_e GDR increased, the age, duration of diabetes and HDL-c were elevated, while the BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, FBG, FINS, HbA1c, ALT, AST, GGT, UA, Scr, UACR, Hb, TyG index, TyG-BMI, TyG-GGT, ByG index, UA index, TG/HDL-c ratio, HOMA-IR, the percentage of smoking, males and NAFLD were decreased (all $P < 0.001$). The eGFR was no difference between the three groups ($P = 0.483$).

https://doi.org/10.2147/DMSO.S500739

Univariate Analysis

A univariate regression analysis was conducted to identify the factors associated with NAFLD (Table 3). The sex, smoking, BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, FBG, FINS, AST, ALT, GGT, UA, Hb, TyG index, TyG-BMI, TyG-GGT, ByG index, UA index, TG/HDL-c ratio and HOMA-IR were positively corrected with NAFLD, and the age, duration of diabetes, HDL-c and the loge GDR were negatively related to NAFLD (all $P < 0.05$). The HbA1c, Scr, eGFR and UACR were not correlated with NAFLD (all $P > 0.05$).

Table 3 Univariate Analysis for NAFLD

Variables	OR (95% CI)	P
Sex (male)	1.314 (1.041–1.659)	0.022
Age	0.976 (0.967–0.986)	<0.001
Smoking	1.749 (1.277–2.396)	<0.001
Duration of diabetes	0.941 (0.922–0.961)	<0.001
BMI	1.322 (1.275–1.392)	<0.001
VFA	1.026 (1.022–1.030)	<0.001
SFA	1.014 (1.012–1.016)	<0.001
SBP	1.017 (1.011–1.024)	<0.001
DBP	1.051 (1.039–1.064)	<0.001
TC	1.212 (1.099–1.337)	<0.001
LDL-c	1.231 (1.098–1.380)	<0.001
TG	1.761 (1.549–2.001)	<0.001
HDL-c	0.253 (0.167–0.383)	<0.001
FBG	1.068 (1.031–1.106)	<0.001
FINS	1.016 (1.002–1.030)	0.030
HbA1c	1.040 (0.986–1.096)	0.150
ALT	1.030 (1.021–1.039)	<0.001
AST	1.028 (1.016–1.040)	<0.001
GGT	1.044 (1.035–1.053)	<0.001
UA	1.008 (1.007–1.010)	<0.001
Scr	1.009 (0.998–1.019)	0.105
eGFR	1.002 (0.998–1.006)	0.315
UACR	1.005 (0.988–1.023)	0.555
Hb	1.030 (1.022–1.038)	<0.001
TyG index	2.604 (2.184–3.105)	<0.001
TyG-BMI	1.029 (1.025–1.033)	<0.001
TyG-GGT	1.005 (1.004–1.006)	<0.001
ByG index	4.329 (3.139–5.970)	<0.001
UA index	2.768 (2.351–3.258)	<0.001
TG/HDL-c ratio	1.486 (1.342–1.645)	<0.001
HOMA-IR	1.055 (1.023–1.089)	0.001
Log_e GDR	0.036 (0.023–0.056)	<0.001

Note: A univariate regression analysis was conducted to identify the factors associated with NAFLD.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; 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; 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; Hb, hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; log_e GDR, a natural log transformation of the glucose disposal rate; OR, odd ratio; CI, confidence interval.

Multivariate Analysis

The NAFLD was utilized as the dependent variable, and adjusting for the sex, smoking, BMI, VFA, SFA, SBP, DBP, TC, LDL-c, TG, FBG, FINS, AST, ALT, GGT, UA, Hb, TyG index, TyG-BMI, TyG-GGT, ByG index, UA, TG/HDL-c ratio, HOMA-IR, age, duration of diabetes and HDL-c, the logistic regression analysis was conducted to examine the independent correlates of NAFLD (Table 4). The results showed that the $\log_e$ GDR (OR: 0.084; 95% CI: 0.040–0.177), BMI (OR: 1.196; 95% CI: 1.110–1.228), UA (OR: 1.004; 95% CI: 1.001–1.007) and DBP (OR: 1.026; 95% CI: 1.005–1.026) were independently related to NAFLD.

Areas Under the ROC Curve Analysis

We compared the AUC for $\log_e$ GDR with those of its individual components (BMI, GGT, UACR and TG), traditional NAFLD-related markers (AST, ALT and GGT), other commonly used indicators linked to IR or metabolism (TG/HDL-c ratio, TyG index, TyG-GGT, TyG-BMI, ByG index, UA index and HOMA-IR), and the variables included in the regression model (DBP, UA and BMI) as shown in Table 5. We found that the AUC of $\log_e$ GDR was 0.797, which was

Table 4 The Independent Variables for NAFLD

Variables	B	SE	Wald	*P*	OR	95.0% CI for OR
$\log_e$ GDR	−2.480	0.383	41.986	<0.001	0.084	0.040–0.177
BMI	0.179	0.038	22.233	<0.001	1.196	1.110–1.288
UA	0.004	0.001	8.134	0.004	1.004	1.001–1.007
DBP	0.025	0.010	5.992	0.014	1.026	1.005–1.047

Note: The independent variables for NAFLD was assessed by logistic regression analysis.
Abbreviations: NAFLD, Non-alcoholic fatty liver disease; $\log_e$ GDR, a natural log transformation of the glucose disposal rate; BMI, body mass index; UA, uric acid; DBP, diastolic blood pressure; CI, confidence interval; OR, odd ratio; SE, standard error.

Table 5 Analysis of the Areas Under the ROC Curves for Predicting NAFLD

Variables	Area	SE	95.0% CI
$\log_e$ GDR	0.797	0.017	0.765–0.830
TyG-BMI	0.784	0.017	0.751–0.818
TyG-GGT	0.769	0.018	0.734–0.804
GGT	0.760	0.018	0.724–0.795
VFA	0.750	0.018	0.715–0.786
BMI	0.747	0.018	0.712–0.783
UA index	0.735	0.019	0.698–0.772
SFA	0.733	0.019	0.696–0.769
TG/HDL-c ratio	0.708	0.020	0.670–0.746
TG	0.707	0.019	0.669–0.745
TyG index	0.692	0.020	0.652–0.731
UA	0.686	0.020	0.647–0.725
DBP	0.668	0.020	0.628–0.708
ByG index	0.660	0.020	0.620–0.700
ALT	0.638	0.021	0.597–0.679
HOMA-IR	0.605	0.021	0.563–0.646
AST	0.545	0.022	0.502–0.589

Abbreviations: NAFLD, non-alcoholic fatty liver disease; $\log_e$ GDR, a natural log transformation of the glucose disposal rate; GGT, gamma-glutamyl transferase; VFA, visceral fat area; BMI, body mass index; SFA, subcutaneous fat area; TG, triglyceride; UA, uric acid; DBP, diastolic blood pressure; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment of insulin resistance; AST, aspartate aminotransferase; ROC, receiver-operating characteristic; SE, standard error; CI, confidence interval.

https://doi.org/10.2147/DMSO.S500739

higher than other variables. Further, we conducted a differential analysis of ROC, and the results showed that $\log_e$ GDR was higher than TG/HDL-c ratio, TyG index, TyG-GGT, ByG index, UA index, HOMA-IR, BMI, GGT, UACR, TG, VFA, SFA, DBP, AST, ALT and GGT (all $P < 0.05$), while the difference between $\log_e$ GDR and TyG-BMI was not statistically significant ($P = 0.245$).

Discussion

In this cross-sectional study, we observed a strong correlation between $\log_e$ GDR and NAFLD, with the incidence of NAFLD increasing progressively as $\log_e$ GDR tertiles decrease. Additionally, multivariate analysis indicated that the $\log_e$ GDR was independently associated with NAFLD in normoalbuminuric patients with T2D.

IR is well known to play a key role in the development of NAFLD. As a traditional surrogate marker of IR, HOMA-IR has been shown to have a strong association with NAFLD.[31] In recent years, various non-insulin-based fasting IR indicators, such as the TG/HDL-c ratio, TyG index, TyG-BMI and TyG-GGT, have also been proposed and proven to be closely linked to NAFLD.[20–22] As a new model of IS, our study found that $\log_e$ GDR is closely related to the aforementioned surrogate markers of IR. With increasing $\log_e$ GDR quartiles, these markers progressively decrease. However, the relationship between $\log_e$ GDR and NAFLD remains unclear. Our study is the first to confirm that $\log_e$ GDR is independently associated with NAFLD. The mechanisms underlying the association between $\log_e$ GDR and NAFLD are still not well understood. NAFLD is strongly associated with metabolic abnormalities, including decreased IS, obesity, elevated TG, reduced HDL-c levels, persistent inflammation and dysregulated fasting glucose or diabetes.[32] Log_e GDR is calculated based on BMI, TG, UACR and GGT, each of which has a well-established link to NAFLD. BMI, a widely used measure of obesity, is strongly correlated with fat accumulation and IR—both critical mechanisms in the development of NAFLD.[33] High TG levels reflect dysregulated lipid metabolism and intrahepatic fat accumulation, contributing to hepatic steatosis and progression to NAFLD.[34] GGT, as a marker of oxidative stress and liver dysfunction, is closely associated with the occurrence of NAFLD.[35] UACR, typically, an indicator of glomerular endothelial dysfunction, is strongly associated with chronic inflammation,[36] which promotes IR and hepatic lipid accumulation, thereby increasing the risk of NAFLD.[37] Together, these components effectively represent the key metabolic pathways contributing to NAFLD, supporting $\log_e$ GDR's utility in predicting NAFLD occurrence. Additionally, none of the individual components were included in the regression model, suggesting that as a composite indicator, $\log_e$ GDR has a stronger relationship with NAFLD.

In this study, we also included IR indicators that integrate glucose metabolism, lipids and obesity (TyG index, TyG-BMI, TyG-GGT and TG/HDL-c ratio), as well as metabolically related indices similar to the components of $\log_e$ GDR (such as the UA index and ByG), and simple markers of NAFLD (AST, ALT and GGT) for comprehensive analysis. Our results showed that all these indicators were closely associated with NAFLD. However, after adjusting for confounding factors, none of them were retained in the regression model, and their areas under the ROC curve were not superior to that of $\log_e$ GDR. This indicates that $\log_e$ GDR, as a novel composite marker of IS, reflects a more comprehensive spectrum of metabolic dysfunctions and may serve as a more reliable indicator for identifying NAFLD.

We acknowledge both the strengths and limitations of our study, as well as directions for future research. This study is the first to investigate the association between $\log_e$ GDR and NAFLD in T2D patients, demonstrating its stronger relationship with NAFLD and superior predictive ability compared to other IR markers. This finding highlights the potential clinical value of $\log_e$ GDR in predicting NAFLD in individuals with T2D. However, as a cross-sectional design, it does not allow us to infer causality or fully understand the underlying mechanisms of the observed association. Furthermore, although ultrasound is the most commonly used method in clinical practice, the current lack of standardized parameters for quantifying hepatic steatosis via ultrasound, along with the influence of operator-dependent subjectivity; therefore, the diagnosis of NAFLD based on ultrasound in this study cannot provide precise grading data. Future research should include multicenter, large-scale, prospective studies to validate the clinical predictive capability of $\log_e$ GDR and differences between it and other surrogate markers of IR and provide deeper insights into the pathophysiological mechanisms linking $\log_e$ GDR and NAFLD. Additionally, using more precise grading methods, such as transient elastography,[38] to provide a more detailed diagnosis and analysis of NAFLD will further enhance the reliability of the results.

Conclusion

The $\log_e$ GDR may serve as a better simple indicator for predicting NAFLD, potentially facilitating the identification of NAFLD patients in clinical settings.

Ethics Approval and Consent to Participate

All patients included in this study provided written informed consent upon admission, which explicitly stated that their medical records might be used for scientific research purposes. During the study period, no patients raised objections to this. Additionally, the study received ethical approval from the Human Ethics Committee of Linyi People's Hospital.

Funding

This study was supported by grants from the Postdoctoral Program of Affiliated Hospital of Jining Medical University (JYFY322152).

Disclosure

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

References

1. Palma R, Pronio A, Romeo M, et al. The role of insulin resistance in fueling NAFLD pathogenesis: from molecular mechanisms to clinical implications. *J Clin Med*. 2022;11(13):3649. doi:10.3390/jcm11133649
2. Younossi ZM, Golabi P, Price JK, et al. The global epidemiology of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among patients with type 2 diabetes. *Clin Gastroenterol Hepatol*. 2024;22(10):1999–2010.e8. doi:10.1016/j.cgh.2024.03.006
3. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet*. 2017;390(10100):1211–1259. doi:10.1016/S0140-6736(17)32154-2
4. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. *Lancet Diabetes Endocrinol*. 2022;10(4):284–296. doi:10.1016/S2213-8587(22)00003-1
5. Byrne CD, Targher G. NAFLD: a multisystem disease. *J Hepatol*. 2015;62(1 Suppl):S47–64. doi:10.1016/j.jhep.2014.12.012
6. Muzurović E, Mikhailidis DP, Mantzoros C. Non-alcoholic fatty liver disease, insulin resistance, metabolic syndrome and their association with vascular risk. *Metabolism*. 2021;119:154770. doi:10.1016/j.metabol.2021.154770
7. Tanase DM, Gosav EM, Costea CF, et al. The intricate relationship between type 2 diabetes mellitus (T2DM), insulin resistance (IR), and nonalcoholic fatty liver disease (NAFLD). *J. Diabetes Res*. 2020;2020:3920196. doi:10.1155/2020/3920196
8. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979;237(3):E214–223. doi:10.1152/ajpendo.1979.237.3.E214
9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28(7):412–419. doi:10.1007/BF00280883
10. Jayagopal V, Kilpatrick ES, Jennings PE, Hepburn DA, Atkin SL. Biological variation of homeostasis model assessment-derived insulin resistance in type 2 diabetes. *Diabetes Care*. 2002;25(11):2022–2025. doi:10.2337/diacare.25.11.2022
11. Liang L, Fu J-F, Zou -C-C, et al. [Metformin hydrochloride ameliorates adiponectin levels and insulin sensitivity in adolescents with metabolic syndrome]. *Zhonghua Er Ke Za Zhi*. 2006;44(2):118–121.
12. Liang Y, Chen H, Liu Y, et al. Association of MAFLD with diabetes, chronic kidney disease, and cardiovascular disease: a 4.6-year cohort study in China. *J Clin Endocrinol Metab*. 2022;107(1):88–97. doi:10.1210/clinem/dgab641
13. Pouwels S, Sakran N, Graham Y, et al. Non-alcoholic fatty liver disease (NAFLD): a review of pathophysiology, clinical management and effects of weight loss. *BMC Endocr Disord*. 2022;22(1):63. doi:10.1186/s12902-022-00980-1
14. Svensson M, Eriksson JW. Insulin resistance in diabetic nephropathy--cause or consequence? *Diabetes Metab Res Rev*. 2006;22(5):401–410. doi:10.1002/dmrr.648
15. Karalliedde J, Gnudi L. Diabetes mellitus, a complex and heterogeneous disease, and the role of insulin resistance as a determinant of diabetic kidney disease. *Nephrol Dial Transplant*. 2016;31(2):206–213. doi:10.1093/ndt/gfu405
16. Ahlqvist E, Prasad RB, Groop L. Subtypes of type 2 diabetes determined from clinical parameters. *Diabetes*. 2020;69(10):2086–2093. doi:10.2337/dbi20-0001
17. Rotbain Curovic V, Tofte N, Lindhardt M, et al. Presence of retinopathy and incident kidney and cardiovascular events in type 2 diabetes with normoalbuminuria - A post-hoc analysis of the PRIORITY randomized clinical trial. *J Diabetes Complications*. 2023;37(4):108433. doi:10.1016/j.jdiacomp.2023.108433
18. Su W, Wang Y, Chen K, et al. Association between nonalcoholic fatty liver and increased low-level albuminuria in postmenopausal women in China: a cross-sectional study. *J Diabetes*. 2021;13(6):494–505. doi:10.1111/1753-0407.13134
19. Xin Z, Liu S, Niu J, et al. The association of low-grade albuminuria with incident non-alcoholic fatty liver disease and non-invasive markers of liver fibrosis by glycaemia status. *Liver Int*. 2021;41(1):101–109. doi:10.1111/liv.14649
20. Xue Y, Xu J, Li M, Gao Y. Potential screening indicators for early diagnosis of NAFLD/MAFLD and liver fibrosis: triglyceride glucose index-related parameters. *Front Endocrinol*. 2022;13:951689. doi:10.3389/fendo.2022.951689

21. Jin L, Gu J, Zhang Z, et al. TyG-GGT is a reliable non-invasive predictor of advanced liver fibrosis in overweight or obese individuals. *Obes Surg*. 2024;34(4):1333–1342. doi:10.1007/s11695-024-07139-y
22. Catanzaro R, Selvaggio F, Sciuto M, et al. Triglycerides to high-density lipoprotein cholesterol ratio for diagnosing nonalcoholic fatty liver disease. *Minerva Gastroenterol*. 2022;68(3). doi:10.23736/S2724-5985.21.02818-X
23. Rojas-Humpire R, Jáuregui-Rodríguez K, Albornoz S, Ruiz Mamani PG, Gutierrez-Ajalcriña R, Huancahuire-Vega S. Association and diagnostic value of a novel uric acid index to cardiovascular risk. *Pract Lab Med*. 2021;26:e00247. doi:10.1016/j.plabm.2021.e00247
24. Zhao X, Yao T, Song B, et al. The combination of body mass index and fasting plasma glucose is associated with type 2 diabetes mellitus in Japan: a secondary retrospective analysis. *Front Endocrinol*. 2024;15:1355180. doi:10.3389/fendo.2024.1355180
25. Miyake T, Kumagi T, Hirooka M, et al. Low alcohol consumption increases the risk of impaired glucose tolerance in patients with non-alcoholic fatty liver disease. *J Gastroenterol*. 2016;51(11):1090–1100. doi:10.1007/s00535-016-1194-0
26. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. *Metab Syndr Relat Disord*. 2008;6(4):299–304. doi:10.1089/met.2008.0034
27. Lim J, Kim J, Koo SH, Kwon GC. Comparison of triglyceride glucose index, and related parameters to predict insulin resistance in Korean adults: an analysis of the 2007-2010 Korean national health and nutrition examination survey. *PLoS One*. 2019;14(3):e0212963. doi:10.1371/journal.pone.0212963
28. Giannini C, Santoro N, Caprio S, et al. The triglyceride-TO-HDL cholesterol ratio. *Diabetes Care*. 2011;34(8):1869–1874. doi:10.2337/dc10-2234
29. An L, Yu Q, Chen L, et al. The association between the decline of egfr and a reduction of hemoglobin A1c in type 2 diabetic patients. *Front Endocrinol*. 2022:12. doi:10.3389/fendo.2021.723720
30. Ciardullo S, Dodesini AR, Lepore G, et al. Development of a new model of insulin sensitivity in patients with type 2 diabetes and association with mortality. *J Clin Endocrinol Metab*. 2024;109(5):1308–1317. doi:10.1210/clinem/dgad682
31. Gutierrez-Buey G, Núñez-Córdoba JM, Llavero-Valero M, et al. Is HOMA-IR a potential screening test for non-alcoholic fatty liver disease in adults with type 2 diabetes? *Eur J Internal Med*. 2017;41:74–78. doi:10.1016/j.ejim.2017.03.006
32. Jarvis H, Craig D, Barker R, et al. Metabolic risk factors and incident advanced liver disease in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of population-based observational studies. *PLoS Med*. 2020;17(4):e1003100. doi:10.1371/journal.pmed.1003100
33. Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: from pathophysiology to therapeutics. *Metabolism*. 2019;92:82–97. doi:10.1016/j.metabol.2018.11.014
34. Bril F, Barb D, Portillo-Sanchez P, et al. Metabolic and histological implications of intrahepatic triglyceride content in nonalcoholic fatty liver disease. *Hepatology*. 2017;65(4):1132–1144. doi:10.1002/hep.28985
35. Hossain IA, Rahman Shah MM, Rahman MK, Ali L. Gamma glutamyl transferase is an independent determinant for the association of insulin resistance with nonalcoholic fatty liver disease in Bangladeshi adults: association of GGT and HOMA-IR with NAFLD. *Diabetes Metab Syndr*. 2016;10(1 Suppl 1):S25–29. doi:10.1016/j.dsx.2015.09.005
36. Gupta J, Mitra N, Kanetsky PA, et al. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. *Clin J Am Soc Nephrol*. 2012;7(12):1938–1946. doi:10.2215/CJN.03500412
37. Petrescu M, Vlaicu SI, Ciumărnean L, et al. Chronic inflammation—a link between nonalcoholic fatty liver disease (NAFLD) and dysfunctional adipose tissue. *Medicina*. 2022;58(5):641. doi:10.3390/medicina58050641
38. Zhang X, Wong GLH, Wong VWS. Application of transient elastography in nonalcoholic fatty liver disease. *Clin Mol Hepatol*. 2020;26(2):128–141. doi:10.3350/cmh.2019.0001n

Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Publish your work in this journal

Diabetes, Metabolic Syndrome and Obesity is an international, peer-reviewed open-access journal committed to the rapid publication of the latest laboratory and clinical findings in the fields of diabetes, metabolic syndrome and obesity research. Original research, review, case reports, hypothesis formation, expert opinion and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/diabetes-metabolic-syndrome-and-obesity-journal