ORIGINAL RESEARCH

Relationship Between Estimated Glucose Disposal Rate and Type 2 Diabetic Retinopathy

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Purpose: To investigate the association between diabetic retinopathy (DR), DR intensity, and estimated glucose disposal rate (eGDR) in individuals with type 2 diabetes mellitus (T2DM).

Patients and Methods: This study comprised 1762 T2DM patients who were admitted between January and December, 2021. Overall, the DR was identified in 430 patients. Based on the eGDR, the participants were divided into four study groups. One-way analysis of variance was used to compare the groups. The correlations between eGDR and DR risk, eGDR, and DR severity were analyzed using regression analysis. Furthermore, these relationships were analyzed in different sex groups.

Results: Patients with T2DM had a 19.75% (348/1762) DR detection rate, whereas those with DR had a 22.41% (78/348) proliferative DR detection rate. The DR group had substantially reduced levels of eGDR compared with the non-DR group. Multivariate logistic regression analysis demonstrated that reduced eGDR was an independent risk factor for DR, after adjusting for confounding variables. eGDR correlated significantly with proliferative DR in women but not in men.

Conclusion: In Chinese individuals with T2DM, lower eGDR was independently associated with a higher risk of DR.

Keywords: estimated glucose disposal rate, type 2 diabetes mellitus, diabetic retinopathy

Introduction

Diabetes mellitus (DM) is a major global health concern. By 2045, there will be 693 million individuals living with DM, up from the current projection of 425 million.[1,2] Type 2 DM (T2DM) is the more prevalent type of DM. Diabetic retinopathy (DR), a highly frequent visual consequence of T2DM, affects approximately 25% of the T2DM patients.[3] DR frequency among T2DM patients ranged from 8% in the first 3 years to 25% in the 5th year, 60% in the 10th year, and 80% in the 15th year.[4,5] DR is the leading cause of blindness among adults.[6] An estimated 191 million people will be affected by DR by 2030.[7] According to a meta-analysis of 20 epidemiological studies,[8] patients with any degree of DR have a 61% increased risk of cardiovascular disease (CVD)-related and all-cause mortalities. Since diabetes impairs microcirculation, DR has historically been considered a microcirculatory illness of the retina. DR is thought to be a reliable biomarker of the deleterious effects of diabetes on individuals. Consequently, DR has established that DM is an independent risk factor for CVD and cardiovascular mortality, in addition to a significant risk of various microangiopathic consequences (diabetic nephropathy, diabetic neuropathy, and diabetic foot).[9,10] Hyperglycemia, caused by impaired insulin action resulting from insulin resistance (IR) or insulin deficiency, is the main pathogenic mechanism of DR.[11] IR always results in damage to small blood vessels, especially DR.[12] The clinical evidence for IR as a risk factor for DR came from several clinical trials, including the Diabetes Control and Complication Trial and the EURODIAB Prospective Complications studies.[13,14] Studies indicated that local IR in the retina was not only an important factor that caused DR, but also important for assessing the severity of DR.[15]

The euglycemic hyperinsulinemia clamp is the standard method used for IR measurement.[16] However, this method is expensive and intrusive, making it unsuitable for regular clinical use. To detect IR more readily, a validated method for estimating the glucose disposal rate (eGDR) was proposed based on clinical variables (waist circumference, hypertension, and glycated hemoglobin HbA1c). eGDR showed a good correlation with IR, as determined by euglycemic hyperinsulinemic clamp.[17,18] Lower eGDR scores correlate with larger IR.According to data from the Pittsburgh Epidemiology of Diabetes Complications Study, individuals with DM who have low eGDR had a higher chance of developing nephropathy,[19] peripheral vascular disease,[20,21] and coronary artery disease (CAD).[22] Kilpatrick et al discovered that patients with DM with lower levels of eGDR had a considerably higher risk of developing both microvascular and macrovascular illnesses.[23] The findings of the study by Helliwell et al[24] demonstrated that eGDR levels are related to both microvascular and macrovascular complications, independent of HbA1c. Therefore, eGDR helped stratify the risk of diabetes complications better than using each of its components separately. However, no studies have investigated the association between eGDR and DR in T2DM patients. Therefore, the present study aimed to investigate whether eGDR correlates with DR risk in Chinese T2DM patients.

Materials and Methods
Study Population
The Ethics Committee of the Hebei General Hospital in China gave its approval for conducting this study, which adhered to the Declaration of Helsinki. The patients in this study were admitted to the Hebei General Hospital in Shijiazhuang, China, between January 1 and December 31, 2020. All participants signed an informed consent form to participate in this study. Patients were screened and assessed based on the inclusion and exclusion criteria.

The following were the inclusion criteria: The World Health Organization's criteria for 1999 were employed to diagnose T2DM.[10] Diabetes mellitus diagnoses based on the results of fasting glucose of ≥7 mmol/l, abnormal 2 h oral glucose tolerance test, and symptoms (polyuria, polydipsia, and unexplained weight loss) of hyperglycaemia with a random blood glucose of >11.1 mmol/l. The participants included in the study were diagnosed with T2DM.

The following were the exclusion requirements:[1] patients under the age of 18 years;[2] those with other forms of diabetes (such as type 1 DM, gestational DM, or other particular types);[3] those who had a history of myocardial infarction, cerebral hemorrhage, severe hepatic dysfunction, acute infection, or stress conditions in the previous 3 months;[4] pregnant and lactating women; and[5] participants with malignant tumors, liver surgery, severe medical disorders, or mental illnesses that made it difficult for them to comply with research requirements.

Study Methods
A thorough clinical history was obtained upon registration, including information on age, sex, waist circumference(WC), blood pressure, and body mass index (BMI). Following admission, venous blood was drawn from the patients in the early morning hours of the following day while fasting. The Clinical Detection Department performed all laboratory tests using the same equipment and reagents. Blood samples were examined for the following biomarkers: creatinine (Cr), uric acid (UA), high-density lipoprotein cholesterol (HDL), total cholesterol (TC), low-density lipoprotein cholesterol (LDL), triglyceride (TG), γ-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), HbA1c, blood urea nitrogen (BUN), fasting blood glucose (FBG), albumin (Alb), systolic blood pressure (SBP), and diastolic blood pressure (DBP). To ensure data accuracy, one assessor recorded the information into a spreadsheet, while another, a neutral assessor, double-checked it.

Definition and Severity Scale for DR
DR was graded according to the 2002 International Academy of Ophthalmology grading criteria.[25] It is a practical way to screen for DR to take at least two 45° fundus color images in each eye, one with the optic disc centered and the other with the macula centered, by trained professionals employing non-mydriatic fundus cameras.[26] For patients with moderate or more than moderate nonproliferative retinopathy found during screening, ophthalmologists made a further grading diagnosis.

Calculation of eGDR

eGDR was calculated using the following formula:[17] eGDR = 21.158 − (0.09 * WC) − (3.407 * HT) − (0.551 * HbA1c); WC = waist circumference (cm), HT = hypertension (yes = 1/no = 0), and HbA1c = HbA1c (%). Enrolled patients were classified into four groups according to eGDR quartiles, with the lowest eGDR quartile representing the highest IR. The Q4 group (the highest quartile) was used as the control group.

Statistical Analysis

Version 25.0 of the Statistical Package for the Social Sciences statistical software was employed to conduct the statistical analysis. Data were continuously gathered, and normality and homogeneity were assessed. Means ± standard deviations were used to express normally distributed data, and one-way analysis of variance was employed for the comparison of the groups. Non-parametric testing was conducted, and non-normally distributed data were presented as median (interquartile range). As a result of enumeration, the numbers (percentages) were calculated and compared using $\chi 2$ test. The Spearman correlation was used to analyze the relationships between variables. The relationship between eGDR and DR was investigated using multiple logistic regression analysis. Statistical significance was set at $P < 0.05$. The eGDR was divided into four groups according to quartiles: Q1 (lowest), Q2, Q3, and Q4 (highest). A subgroup analysis was performed to evaluate the robustness of the findings.

Results

Basic Characteristics of Participants with and without DR

Overall, 1762 patients, having a mean age of 56.68±10.17 years, including 879 men and 883 women, were recruited for this research (Figure 1). Patients with T2DM had a 19.75% (348/1762) DR detection rate, whereas those with DR had
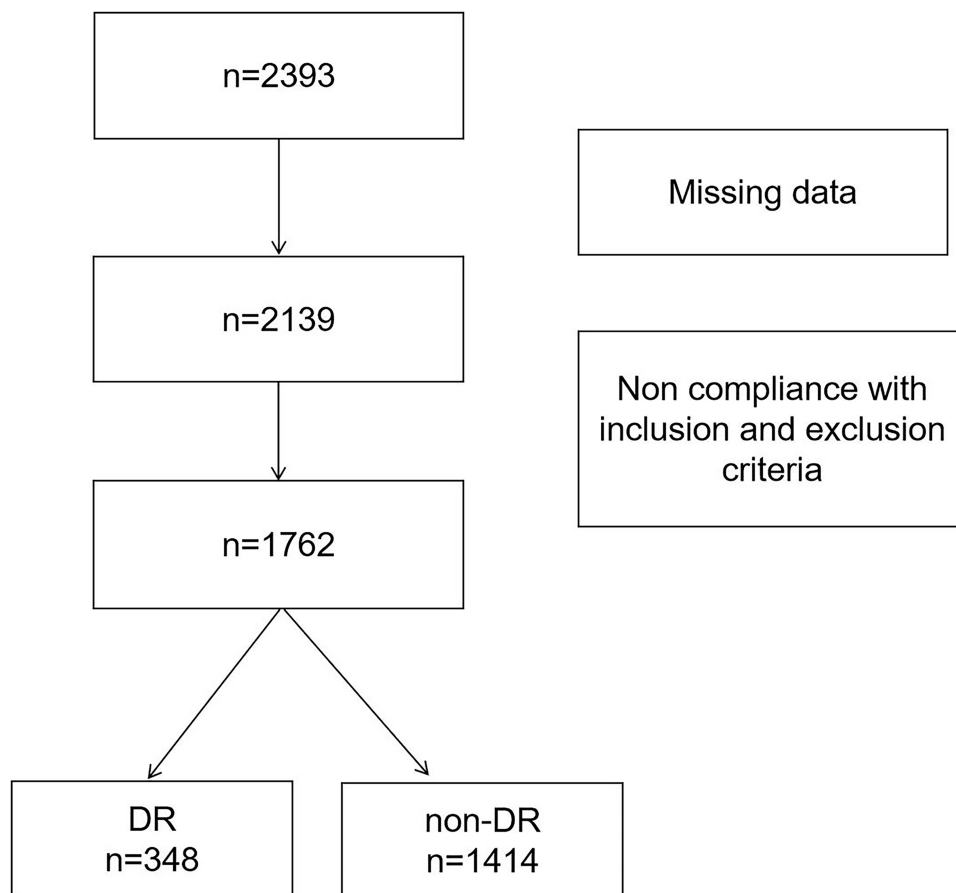

Figure 1 Flowchart of the patient selection process.

a 22.41% (78/348) proliferative DR detection rate.In comparison to the non-DR group, the age, SBP, FPG, HbA1c, and BUN were increased and BMI, DBP, Alb, ALT, AST, and eGDR significantly were decreased in the DR group (Table 1). There were no significant differences in sex, WC, GGT, TC, LDL, HDL, TG, UA, or Cr between the DR and non-DR groups.

In comparison to the non-DR group in women, the FPG, HbA1c, and HDL were increased and Alb was decreased in the DR group, with a significant difference (Table 1). In comparison to the non-DR group in men, the SBP, FPG, HbA1c, and BUN were increased and age, BMI, DBP, Alb, ALT, and AST were decreased in the DR group, with statistically significant differences (Table 1).

In women, the eGDR level was decreased significantly in the DR group, and the same result was observed in men.

Participants' Fundamental Traits in the Four eGDR Groups

The patients' baseline characteristics according to eGDR quartiles are shown in Table 2. Age, BMI, WC, SBP, DBP, FPG, HbA1c, GGT, TC, HDL, TG, ALT, BUN, and UA levels differed among the different eGDR groups. Participants with a higher eGDR had lower SBP and DBP. In the Q1 group, BMI, HbA1c, WC, GGT, FPG, and TG levels were substantially elevated compared to the other three groups. Age, TC, UA, and ALT levels were greater in the Q1 group than in the Q4 group. The Q4 group had higher HDL levels than the other three groups. The BUN levels in the Q4 group were lower than those in the other three groups. There were no differences in Alb, LDL, AST, and Cr levels between the groups. Patients with a higher eGDR showed a lower prevalence of DR. The highest DR incidence was observed in the Q1 group (Figure 2).Female-patients who had a lower eGDR showed a higher prevalence of proliferative DR (Figure 3).

Correlation of eGDR with Potential DR Risk Factors

The Spearman correlation analysis revealed that the eGDR was positively correlated with HDL (r=0.155, P<0.001) but negatively correlated with BMI (r=−0.402, P<0.001), FPG (r=−0.442, P<0.001), GGT (r=−0.244 P<0.001), Alb (r=−0.057 P=0.017), TC (r=−0.086, P<0.001), TG (r=−0.226, P<0.001), ALT (r=−0.164, P<0.001), BUN (r=−0.107 P<0.001), UA (r=−0.090 P<0.001), and age (r=−0.134, P<0.001).

Association Between eGDR and DR

Multivariate logistic regression analysis indicated that a low eGDR was an independent risk factor for DR after adjusting for age, sex, BMI, FPG, GGT, Alb, TC, LDL, HDL, TG, ALT, AST, Cr, BUN, and UA (odds ratio [OR] 0.634, 95% confidence interval [CI], 0.528–0.762, P<0.001; Table 3).To ensure the robustness of the results, the eGDR was processed as a categorical variable (quartiles) for analysis. The risk of DR gradually decreased as the eGDR level increased when unadjusted for any variable. After adjustment for confounders, it was found that low-level eGDR was an independent risk factor for DR. Additionally, the Q1 group had the highest risk of developing DR (OR 5.603, 95% CI, 2.375–13.217, P<0.001; Table 3).

Subgroup Analysis

Subgroup analyses were conducted based on sex to further evaluate how sex affected the connection between eGDR and DR. In the multivariate logistic regression analysis model, after adjustments for age, BMI, gender, hypertension, WC, FPG, GGT, ALT, AST, Alb, TC, TG, HDL-C, LDL-C, Cr, BUN, UA and course, low level of eGDR was an independent risk factor for DR in women with T2DM (OR 7.292, 95% CI 2.073–25.652 P=0.002) (Table 3).Consistently, significant association between eGDR and DR was found in men with T2DM under logistic regression analysis adjusted for age, BMI, gender, hypertension, WC, FPG, GGT, ALT, AST, Alb, TC, TG, HDL-C, LDL-C, Cr, BUN, UA and course (OR 4.682, 95% CI 1.412–15.529, P=0012) (Table 3).

Among patients with DR, a logistic regression analysis was performed with proliferative DR as the independent variable and age, BMI, gender, hypertension, WC, FPG, GGT, ALT, AST, Alb, TC, TG, HDL-C, LDL-C, Cr, BUN, UA and course as dependent variables. Multivariate logistic regression analysis demonstrated that low eGDR was

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Table 1 Characteristics of Patients Included in This Study

	All Patients			Male Patients			Female Patients		
	Non-DR	DR	P	Non-DR	DR	P	Non-DR	DR	P
n	1414	348		709	170	-	705	178	-
Sex (men)	709 (50.1%)	210 (60.34%)	0.355	-	-	-	-	-	-
Age(years)	56.79 (50.6475,64.425)	58.9 (53.4675,64.68)	0.011	56.64 (50.935,64.595)	59.045 (52.51,65.1475)	0.071	56.92 (50.235,64.33)	58.885 (53.6775,64.345)	0.011
Hypertension (%)	585 (41.40%)	166 (47.70%)	0.025	300 (42.30%)	74 (43.50%)	0.773	281 (39.90%)	92 (51.70%)	0.004
Course (years)	8.00 (5.00,13.00)	10.00 (6.00,13.00)	0.001	8.00 (5.00,13.00)	10.00 (6.00,13.00)	0.019	8.00 (5.00,13.00)	10.00 (6.00,14.00)	0.012
BMI (kg/m2)	26.5 (24.1,29.025)	25.85 (23.825,28.4)	0.023	26.5 (24.1,28.8)	25.8 (23.875,28.425)	0.114	26.5 (24.1,29.4)	25.95 (23.8,28.325)	0.023
WC(cm)	93.25 (86.3,100.1)	92.5 (85.625,99.425)	0.294	95 (88.85,102)	94.5 (87.475,100)	0.116	91 (84,98.5)	91.1(84.775,99)	0.294
SBP(mmHg)	133 (122,147)	136.75 (124,152)	0.028	133.5 (122.75,146.5)	134.25 (124,150)	0.434	132.5 (121,148.25)	140 (122,154.625)	0.028
DBP(mmHg)	80.5 (74,87)	79.5 (71.5,85.875)	0.007	82 (76,88.5)	80.5 (73.375,87)	0.054	79 (72.75,85.5)	78 (70.5,84.5)	0.007
FPG (mmol/L)	7.5 (6.1,9.535)	9.29 (7.115,12.325)	<0.001	7.7 (6.29,9.9)	9.14 (7.125,11.885)	<0.001	7.335 (6,9.2875)	9.5 (7.06,12.705)	<0.001
HbA1c (%)	6.8 (5.8,8.2)	8.2 (6.9,9.7)	<0.001	6.9 (5.8,8.2)	8.1 (6.875,9.2)	<0.001	6.8 (5.7,8.2)	8.35 (6.975,10.225)	<0.001
GGT (IU/L)	24 (17,34)	22 (16,30)	0.053	27 (20,39)	25 (18,35)	0.056	20 (15,28)	20 (15,26)	0.053
Alb (g/L)	48.8 (47,50.5)	48.2 (46.6,49.9)	<0.001	49.1 (47.4,50.8)	48.3 (46.7,50.4)	0.012	48.6 (46.7,50.2)	47.9 (46.15,49.7)	<0.001
TC (mmol/L)	4.72 (4.0725,5.41)	4.72 (4.13,5.4475)	0.5	4.5 (3.89,5.25)	4.5 (3.87,5.24)	0.888	4.89 (4.26,5.6)	4.96 (4.335,5.915)	0.5
LDL-C (mmol/L)	2.91 (2.34,3.5175)	2.955 (2.3425,3.56)	0.412	2.76 (2.24,3.41)	2.78 (2.22,3.37)	0.976	3.03 (2.42,3.655)	3.14 (2.485,3.795)	0.412
HDL -C (mmol/L)	1.22 (1.03,1.45)	1.25 (1.06,1.47)	0.094	1.14 (0.97,1.35)	1.19 (1.02,1.43)	0.027	1.29 (1.09,1.52)	1.29 (1.085,1.54)	0.094
TG (mmol/L)	1.6 (1.13,2.35)	1.55 (1.1,2.23)	0.509	1.54 (1.08,2.35)	1.4 (1,2.22)	0.172	1.64 (1.19,2.35)	1.69 (1.235,2.255)	0.509
ALT, (IU/L)	18 (14,24.75)	17 (13,22)	0.034	19 (15,27)	18 (14,25)	0.065	16 (12,22)	16 (12,20)	0.034
AST (IU/L)	18 (15,22)	17.5 (15,22)	0.016	19 (16,23)	18 (15,23)	0.393	18 (15,22)	17 (14,21)	0.016
Cr (umol/L)	68 (59,80)	67 (58,79.75)	0.984	78 (71,87)	76 (67,89)	0.736	60 (53,66)	60 (52,68)	0.984
BUN (mmol/L)	5.2 (4.3,6.2)	5.3 (4.5,6.7)	0.007	5.5 (4.6,6.6)	5.6 (4.8,7.1)	0.187	4.8 (4.1,5.8)	5.2 (4.3,6.3)	0.007
UA(umol/L)	295 (241,361)	289 (241,340.75)	0.23	325 (266,387)	309 (261,358)	0.08	270 (223,326.5)	271 (219.5,316)	0.23
eGDR	7.55 (5.47,9.3)	6.61 (4.7925,8.49)	<0.001	7.35 (5.34,9.01)	7.065 (5.0775,8.3525)	0.022	7.87 (5.585,9.62)	6.045 (4.5225,8.585)	<0.001

Table 2 Characteristics of Patients Included in This Study by eGDR Levels

	Q1	Q2	Q3	Q4	P
n	435	441	438	448	
Sex (men)	221 (50.8%)	225 (51.0%)	247 (56.4%)	186 (41.5%)	0.032
Age(years)	58.86 (53.43,65.48)	58.3 (52.025,66.21)	56.44 (50.9525,63.34)	56.45 (47.7325,62.8175)	<0.001
Hypertension(%)	430 (98.90%)	288 (65.30%)	28 (6.40%)	1(0.20%)	<0.001
Course(years)	9.00 (6.00,13.00)	8.00 (5.00,13.00)	8.00 (5.00,13.00)	8.00 (5.00,13.00)	0.122
BMI (kg/m2)	28.4 (26,31)	26.2 (24.1,28.4)	26.6 (24.3,29.2)	24.35 (22.4,26.6)	<0.001
WC(cm)	100.1 (94.7,106.3)	92.4 (87.05,98.6)	96 (88.6,101)	85.4(78.9,90.775)	<0.001
SBP(mmHg)	151 (143.5,159.5)	143.5 (130,154.75)	127.5 (119,133.5)	122.5 (114.125,130)	<0.001
DBP(mmHg)	87 (81,93)	83 (76,90)	78.5 (71.5,83)	74.5 (69.5,80.375)	<0.001
FPG (mmol/L)	9.36 (7.67,11.7)	7.95 (6.6,11.025)	8.05 (6.6,9.9)	6.27 (5.6,7.6)	<0.001
HbA1c (%)	8.2 (7.1,9.5)	7.1 (6,9.4)	7.4 (6.4,8.425)	5.75 (5.4,6.6)	<0.001
GGT (IU/L)	27 (20,40)	23 (17,32)	24 (17,36)	19 (14,27)	<0.001
Alb (g/L)	48.9 (47.2,50.5)	48.9 (47.1,50.7)	48.7 (46.8,50.4)	48.3 (46.5,50.4)	0.051
TC (mmol/L)	4.8 (4.17,5.58)	4.78 (4.12,5.48)	4.68 (4.06,5.38)	4.64 (3.975,5.275)	0.009
LDL-C (mmol/L)	2.95 (2.37,3.59)	2.99 (2.35,3.66)	2.84 (2.295,3.48)	2.89 (2.33,3.415)	0.165
HDL -C (mmol/L)	1.18 (1.02,1.37)	1.21 (1,1.43)	1.2 (1,1.445)	1.33 (1.1,1.54)	<0.001
TG (mmol/L)	1.82 (1.3,2.73)	1.68 (1.13,2.37)	1.61 (1.15,2.49)	1.36 (0.975,1.83)	<0.001
ALT, (IU/L)	19 (14,28)	17 (14,23)	18 (14,25)	16 (12,21)	<0.001
AST (IU/L)	19 (16,23)	18 (15,22)	18 (15,22)	18 (15,22)	0.239
Cr (umol/L)	69 (59,82)	70 (59,81)	67 (59.5,81)	66 (58,78)	0.306
BUN (mmol/L)	5.2 (4.4,6.5)	5.4 (4.5,6.6)	5.3 (4.5,6.3)	4.9 (4.1,5.75)	<0.001
UA (umol/L)	301 (251,362)	300 (246,360)	294 (237,358)	278 (235,347)	0.011
eGDR	4.35 (3.51,4.86)	6.16 (5.73,6.755)	8.36 (7.86,8.77)	10.01 (9.5625,10.6675)	<0.001

an independent risk factor for proliferative DR in women (OR 8.537, 95% CI 1.613–45.169, P=0.03) (Table 4). In contrast, there was no statistically significant link between proliferative DR and eGDR in men with DR (OR 0.558, 95% CI 0.157–1.986, P=782) (Table 4).
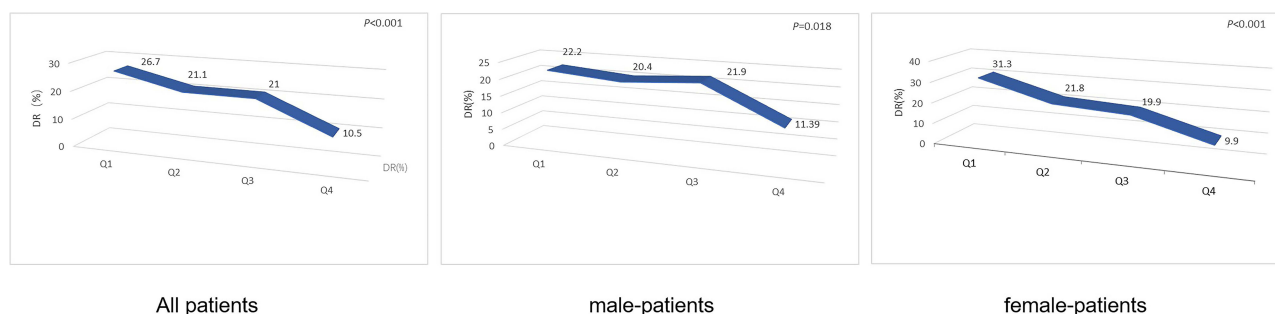

Figure 2 Comparison of the prevalence of DR in patients with T2DM who have different eGDR.
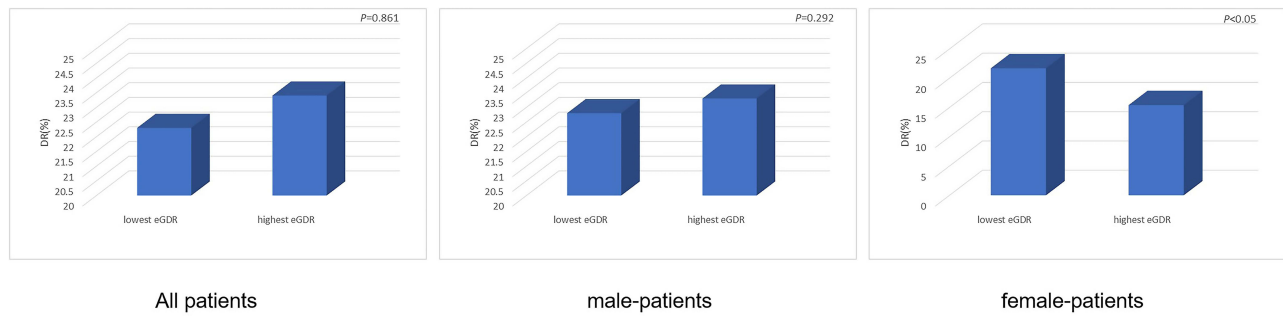
Figure 3 Comparison of the prevalence of PDR in patients with DR who have different eGDR.

Discussion

The current study examined the potential connection between eGDR and DR. To further investigate whether a difference could be detected in subgroups of different sexes, we examined the association not only with the whole sample, but also in subgroups of different sexes. Some studies have revealed that the prevalence of DR ranged from 11.9 to 43.1% in China, [27–29] which was similar to our study. In this study, the eGDR significantly decreased in the DR group. The risk of DR increased with a decrease in eGDR. A high DR risk was independently associated with low eGDR levels in the

Table 3 Logistic Regression Analysis of eGDR for DR in Patients with T2DM

	Outcomes	Model I		Model II		Model III	
All patients		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
	eGDR	0.862 (0.820,0.906)	<0.001	0.634 (0.576,0.698)	<0.001	0.634 (0.528,0.762)	<0.001
	eGDR(quartile)						
	Q1	3.103 (2.144,4.489)	<0.001	12.646 (6.875,23.26)	<0.001	5.602 (2.375,13.217)	<0.001
	Q2	2.280 (1.561,3.331)	<0.001	5.146 (3.213,8.243)	<0.001	2.976 (1.614,5.487)	<0.001
	Q3	2.269 (1.552,3.316)	<0.001	3.076 (2.071,4.569)	<0.001	2.627 (1.681,4.105)	<0.001
	Q4	Ref		Ref		Ref	
Female-patients	eGDR	0.818 (0.764,0.876)	<0.001	0.580 (0.507,0.663)	<0.001	0.563 (0.427,0.742)	<0.001
	eGDR (quartile)						
	Q1	4.137 (2.516,6.804)	<0.001	22.494 (9.547,53.000)	<0.001	7.292 (2.073,25.652)	0.002
	Q2	2.524 (1.504,4.238)	<0.001	7.004 (3.599,13.632)	<0.001	3.240 (1.333,7.873)	0.009
	Q3	2.254 (1.315,3.864)	0.003	3.225 (1.839,5.657)	<0.001	2.628 (1.338,4.975)	0.003
	Q4	Ref		Ref		Ref	
Male-patients	eGDR						
	eGDR(quartile)	0.916 (0.852,0.986)	0.020	0.708 (0.615,0.815)	<0.001	0.679 (0.526,0.876)	0.003
	Q1	2.238 (1.286,3.895)	0.004	6.640 (2.779,15.867)	<0.001	4.682 (1.412,15.529)	0.012
	Q2	2.019 (1.156,3.527)	0.014	3.668 (1.877,7.166)	<0.001	2.973 (1.252,7.058)	0.014
	Q3	2.198 (1.274,3.792)	0.005	2.721 (1.551,4.771)	<0.001	2.634 (1.393,4.981)	0.003
	Q4	Ref		Ref		Ref	

Notes: Model 1: crude model; Model 2: adjusted for age, BMI, gender, hypertension; Model 3: further adjusted for WC, FPG, GGT, ALT, AST, Alb, TC, TG, HDL-C, LDL-C, Cr, BUN, UA, course.

Table 4 Logistic Regression Analysis of eGDR for Proliferative DR in Female-Patients

	eGDR Level	OR (95%)	P
All patients	1st, 2nd and 3rd quarter	1.431 (0.566,3.617)	0.448
	4th quarter (highest eGDR)	Ref	
Female-patients	1st, 2nd and 3rd quarter	8.537 (1.613,45.169)	0.012
	4th quarter (highest eGDR)	Ref	
Male-patients	1st, 2nd and 3rd quarter	0.558 (0.157,1.986)	0.368
	4th quarter (highest eGDR)	Ref	

Notes: Adjusted for age, BMI, gender, hypertension, WC, FPG, GGT, ALT, AST, Alb, TC, TG, HDL-C, LDL-C, Cr, BUN, UA, course.

present study. This association persisted even after adjusting for various potential confounding factors. This relationship can be clearly seen independently in women, and in men. Additionally, among DR patients, women, but not men, showed a significant connection between low eGDR levels and a higher likelihood of proliferative DR. Previous studies have focused on exploring the link between eGDR and DR in type 1 DM.[30–32] These analyses indicated that elevated eGDR levels were linked to a reduced risk of DR. A study by Pop et al[31] found that eGDR was more strongly associated than some identified risk factors for DR in type 1 DM. Moreover, Rowe et al confirmed a relationship between IR and more severe DR in patients with type 1 DM.[33] It was also demonstrated by Duță et al[34] that eGDR was the most important factor of proliferative DR.

The use of eGDR has been recently advocated as a useful way to assess IR.Several studies have demonstrated that a lower eGDR is associated with higher IR.[18,30,32] It has been concluded that IR was responsible for elevation *of oxidative stress*.[35] Oxidative stress was closely related to apoptosis and endothelial cell dysfunction, which could lead to DR.[36] Insulin binding to its receptor activated the phosphatidylinositol-3-kinase (PI3-K/Akt) signaling pathway, leading to upregulation of hypoxy-inducing factor, and its direct interaction with vascular endothelial growth factor (VEGF) promoter led to increased VEGF expression.[37] Over-expression of VEGF will activate a series of signal pathways, and further disrupt the blood-retinal barrier (BRB), increase vascular permeability, induce cell proliferation and promote neovascularization.[38] Along *with* increased IR, the expression of free fatty acids in adipocytes and dimethylarginine in plasma increased, which could inhibit the activation of endogenous nitric oxide synthetase, resulting in vasomotor dysregulation and microcirculation disorders.[39] Due to the *increased retinal vascular permeability*, VEGF through *the* BRB and *into retinal tissue*, which facilitated neovascularization of the retina, resulting in DR.IR could promote the expression of retinal VEGF, so it might lead to or aggravate DR to some degree.Furthermore, the *expression* of plasminogen activator inhibitor-1 (*PAI-1*) was *also increased significantly in the* setting *of* IR.[40] PAI-1 could selectively inhibit the *vasodilatory effects*, leading *to occlusion of the* retinal *capillaries* and subsequent contributing to ischemia-induced vasculogenesis.

It has been shown that eGDR was linked to lipid levels and inflammation.[30] The present study also showed that as eGDR increased, the levels of TC and TG decreased. Inflammation is considered to play a substantial role in DR progression.[41] Hyperlipidemia is thought to be the main risk variable for DR development.[42] Inflammation promotes the transformation of nonproliferative DR to proliferative DR.[43,44] Cluster speckle hemorrhage and retinal vessel permeability are features of nonproliferative DR.[45] DR with proliferative features is characterized by frequent retinal exudation and retinal hemorrhage.[46] Inflammation is one of the main contributors to vascular problems in T2DM patients.[47] The pathogenesis of diabetic microangiopathy involves inflammation (such as tumor necrosis factor-alpha and C-reactive protein) and vascular endothelial growth factor (VEGF)[48] VEGF-induced retinal expression of inflammation and entrapment of leukocytes have been observed in animal models of DR.[49] Hyperglycemia is a determinant of changes in retinal structure and vision.[50,51] Inflammation and oxidative damage caused by chronic hyperglycemia increases

endothelial permeability and barrier disruption.[52,53] Subsequent microthrombi development, cell adhesion molecules, leukostasis, and cytokine activation are linked to the weakening of retinal ganglion cells and nerve fiber layers.[54–56]

In the current study, it was found that the link between eGDR and DR was stronger in women than in men, and that eGDR was associated with proliferative DR in women only among T2DM patients. The results of our study demonstrated that female sex was another independent risk factor for DR. A growing body of research has shown a link between sex and the risk of DR in T2DM. In addition, a study by Li et al[29] found that women with T2DM had an increased incidence of DR in comparison to men, and the female sex was an independent element of risk for developing DR. Although the exact mechanism is unclear, this increase in DR prevalence in women may be due to estrogen levels. Indeed, RGC-5 cells are protected from high glucose-induced damage by 17hough the exaE2) via the mitochondrial pathway.[57] Furthermore, estrogen was found to be an important regulator of retinal blood flow and reduced vascular resistance in the large vessels of the eyes by reducing the amount of cholesterol.[58] It was unknown whether sex itself, or some other related risk factor(s), such as cultural socioeconomic factors or etiology, contributed to the male-female differences in DR.

As a systemic disease, oxidative stress, inflammation, vascular alterations, angiogenesis, and apoptosis can play a role in the development of DR.[59–61] Evidence from emerging studies has also suggested that complex gene-environment interactions facilitate the pathogenesis of diabetes-related microvascular complications.[62]

Our study found no statistically significant difference in WC among T2DM patients with or without DR, which was consistent with previously published findings.[63,64] Results by Iwasaki et al showed that WC was not associated with the presence of DR in Japanese patients with T2DM.[65] A study published in 2022[66] announced that abdominal obesity was not associated with DR in patients with diabetes.WC of participants in this study was similar to that in previous studies.[66–68]

In our study, we found that ALT and GGT levels decreased with the increase of eGDR.Fabrice Bonnet et.al[69] found increased GGT and ALT were biomarkers of both systemic and hepatic IR with concomitant increased insulin secretion and decreased hepatic IR. ALT level may be a marker of visceral fat deposits in the liver and thus refilflect the status of IR.[70] ALT level is correlated with subclinical systemic inflflammation, increased oxidative stress and higher hepatic cytokine production. These factors may cause impaired insulin signaling.[71]

The current study had several limitations. First, because this study was cross-sectional, no conclusions about causal correlations could be drawn. Second, information on current/previous smoking was lacking; thus, we were unable to adjust for this important confounder. The single ethnicity of the study population calls into question the generalizability of the findings. Large studies in multiple centers and different countries are required to understand the prospective significance of eGDR in routine clinical practice. Another limitation of our study is that we lacked detailed laboratory markers of inflammation, such as C-reactive protein which was associated DR.Finally, eGDR has previously been shown to be a reliable approximation of IR; however, its equations only contain clinical variables, which might be another limitation. This advantage could also be attributed to the fact that the eGDR equation provides reliable information for clinical decision making and is easy to calculate. Therefore, eGDR could serve as a risk marker for DR, and future longitudinal studies are needed to investigate this possibility.

Conclusion

In summary, our study showed that the occurrence of DR was independently correlated with a lower eGDR level. Among women with DR, low-level eGDR was associated with proliferative DR. There was no relationship between eGDR and proliferative DR in men. In addition, larger prospective cohort studies can further assess the utility of eGDR in risk stratification for diabetes complications and how eGDR compares to currently used measures such as HbA1c.

Disclosure

The authors declared no conflicts of interest.

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