Scientific Research Publishing

International Journal of Clinical Medicine, 2023, 14, 357-365
https://www.scirp.org/journal/ijcm
ISSN Online: 2158-2882
ISSN Print: 2158-284X

Association of GA/HbA1c Ratio with Diabetic Retinopathy

Tianyao Zhang[1], Xu Zheng[2*]

[1]Health Management Center, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, China
[2]Intensive Care Unit, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, China
Email: *zhengxu@sysush.com

How to cite this paper: Zhang, T.Y. and Zheng, X. (2023) Association of GA/HbA1c Ratio with Diabetic Retinopathy. *International Journal of Clinical Medicine*, **14**, 357-365.
https://doi.org/10.4236/ijcm.2023.148031

Received: July 4, 2023
Accepted: August 7, 2023
Published: August 10, 2023

Abstract

Objectives: The aim of this study was to explore the potential correlation between the GA/HbA1c ratio and diabetic retinopathy (DR) in patients with type 2 diabetes (T2D), as the GA/HbA1c ratio serves as a marker for glycemic variability. **Methods:** A total of 2565 T2D patients were included in this study and grouped into five categories based on the diagnostic criteria for DR. We examined the impact of the GA/HbA1c ratio on the progression of diabetes. **Results:** The non-DR group exhibited lower GA/HbA1c levels compared to the DR group. Additionally, as the severity of DR increased among the five groups, there was a corresponding increase in the GA/HbA1c ratio. Logistic regression analysis demonstrated that the GA/HbA1c ratio independently elevated the risk of DR occurrence. **Conclusions:** The GA/HbA1c ratio can independently predict the occurrence and progression of diabetic retinopathy.

Keywords

Type 2 Diabetes, Diabetic Retinopathy, GA/HbA1c Ratio

1. Introduction

Diabetic retinopathy (DR) has been identified as a common microvascular complication of diabetes, with a global prevalence of approximately 22.27% among people with diabetes [1]. According to an 8-year prospective cohort study, fluctuating blood glucose contents will induce DR onset [2]. A recent DCCT and UKPDS study found that strictly controlling HbA1c can slow the progression of retinopathy [3]. Conversely, GA reflects a shorter glycemic control period and greater glucose fluctuations than HbA1c [4]. GA level was significantly correlated with DR incidence in type 2 diabetes (T2D) cases [5] [6] [7]. According to mounting evidence, the GA/HbA1c ratio can now be used to evaluate and diag-

nose disease in blood glucose testing [8]. The GA/HbA1c ratio has a shorter half-life and represents short-term glycemic control when compared to GA [9]. Furthermore, the GA/HbA1c ratio has been linked to fluctuating blood glucose levels and pancreatic β-cell activity [8]. According to the findings of a previous study, the GA/HbA1c ratio can be used to predict blood glucose (BG) control, which is closely related to MAGE in T2D cases [8] [10]. Therefore, GA/HbA1c is most likely a significant predictor of DR incidence. Although DR is considered potentially preventable and treatable, there is currently a lack of awareness of DR complications among domestic people. However, almost no research has been conducted on the relationship between the GA/HbA1c ratio and the severity of DR in T2DM patients. The current study examined the relationship between the GA/HbA1c ratio and DR in T2DM patients, intending to provide clinicians with correlative therapeutic strategies for DR management.

2. Methods

2.1. Subject

From January 2018 to January 2019, 1571 T2DM cases were treated at the endocrinology ward of Harbin Medical University's Second Affiliated Hospital. This study excluded patients with type 1 diabetes (T1DM), diabetes of other types, primary renal disease, advanced liver disease, thyroid disease, severe anemia, acute inflammatory diseases, pregnancy, and tumor.

T2DM was defined as diabetes mellitus (DM) symptoms, fasting BG (FBG) ≥ 7 mmol/L, random BG ≥ 11.1 mmol/L, and 2-h BG ≥ 11.1 mmol/L after the oral glucose tolerance test (in line with the 1999 criteria for T2DM released by World Health Organization).

DR was graded according to the International Classification of Diabetic Retinopathy in all cases by a medical technologist with extensive experience using the retinal camera: 1) Non-DR (Group A); 2) mild non-proliferative DR (Group B); 3) moderate non-proliferative DR (NPDR) (Group C); 4) severe NPDR (Group D); 5) proliferative DR (PDR) (Group E).

2.2. Data Collection

Medical records were used to obtain information such as age, gender, DM course, height, and weight. Diastolic blood pressure (DBP), systolic blood pressure (SBP), glucose laboratory tests, serum C-peptide, GA, HbA1c, UACR, and serum creatinine were all measured after an overnight fast. The HbA1c level was determined using high-performance liquid chromatography (HPLC), and GA was measured using an enzymatic assay. Body mass index (BMI) was calculated in this study by dividing body weight (kg) by height squared (m^2).

2.3. Statistical Analysis

For statistical analysis, SPSS25.0 software was used. The Kruskal-Wallis test was used to compute statistical differences between subgroups (the statistic H). Normally distributed variables are represented by means ± standard deviation

(the statistic F), while abnormally distributed variables are represented by the median (interquartile range). Using the non-parametric Mann-Whitney test, two data groups with non-normal distribution or uneven variance were compared (the statistic U). The chi-square test was used to compare the two groups. The effects of variables on the likelihood of DR progression were investigated using multivariate logistic regression, where $p < 0.05$ represented statistical significance.

3. Results

In total, 1571 T2DM patients were enrolled. There are 619 DR groups and 952 non-DR groups. Table 1 shows T2DM cases which developed DR had a longer disease course, older age, weight, BMI, SBP, UACR, TC, TG, apoB, GA, HbA1c, and GA: HbA1c. Patients with T2DM in the Non-DR group had higher c-peptide 0 min and c-peptide 120 min ($p < 0.05$).

Table 1. T2DM features of DR and non-DR groups.

variables	Non-DR group (n = 952)	DR group (n = 619)	p
Male (%)	599/353 (62.92%)	404/215 (65.27%)	0.344
Age (y)*	53 (45, 60)	56 (49, 63)	0.000
Duration of DM (y)*	5 (2, 10)	10 (4, 16)	0.000
Smoking (%)*	212/740 (22.27%)	216/403 (34.89%)	0.000
Drinking (%)*	298/654 (31.30%)	228/391 (36.83%)	0.023
Weight (kg) *	72.00 (64.00, 80.00)	74.00 (66.00, 81.00)	0.008
BMI (kg/m^2)*	25.39 (23.40, 27.55)	25.86 (23.81, 28.09)	0.005
Systolic BP (mmHg)*	132 (120, 144)	138 (125, 152)	0.000
Diastolic BP (mmHg)	83 (77, 91)	83 (75, 91)	0.507
GA (%)*	20.20 (16.70, 25.10)	21.20 (17.80, 25.90)	0.000
HbA1c (%)*	8.30 (7.10, 9.80)	8.50 (7.30, 9.90)	0.025
GA/HbA1C*	2.45 (2.24, 2.67)	2.51 (2.28, 2.77)	0.000
C-peptide (fasting) (pmol/L)	1.40 (0.90, 2.20)	1.50 (1.00, 2.00)	0.743
C-peptide 30 min (pmol/L)	2.20 (1.40, 3.20)	2.10 (1.50, 2.90)	0.083
C-peptide 60 min (pmol/L)*	3.30 (2.10, 4.80)	3.00 (2.10, 4.30)	0.022
C-peptide 120 min (pmol/L)	4.70 (3.20, 6.70)	4.30 (2.90, 5.90)	0.000
UACR (mg/mmol)*	1.69 (1.13, 3.41)	3.41 (1.69, 8.47)	0.000
Total cholesterol (mmol/L) *	4.84 (4.27, 5.54)	5.10 (4.39, 5.98)	0.001
Triglycerides (mmol/L) *	1.65 (1.06, 2.40)	1.76 (1.17, 2.68)	0.028
HDL-cholesterol (mmol/L)	1.23 (1.07, 1.45)	1.21 (1.03, 1.43)	0.516
LDL-cholesterol (mmol/L)	2.88 (2.35, 3.44)	2.99 (2.33, 3.71)	0.097
apoA (g/L)	1.30 (1.16, 1.45)	1.28 (1.113, 1.47)	0.818
apoB (g/L)*	0.98 (0.81, 1.13)	1.05 (0.89, 1.22)	0.000

Values are represented by means ± standard deviation or median [interquartile range] or as case numbers (percentages). *indicates $p < 0.05$. Abbreviations: BMI, body mass index; GA, glycated albumin; HbA1C, glycated hemoglobin A 1C; UACR, urine albumin-creatinine ratio; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Based on subsequent classification according to DR severity, DM duration, BMI, GA, HbA1C, GA/HbA1C, C-peptide (fasting), C-peptide 30 min, C-peptide 60 min, C-peptide 120 min, and UACR, the four groups were comparable. Table 2 shows clinical features classified according to DR severity.

According to the findings, the relationship of GA with HbA1c in four groups was investigated. As shown in Figure 1, the HbA1c in Group D increased when compared with Group B (p = 0.015). Group D had higher GA than Group B, and Group E had higher GA than Groups B and C (p = 0.000). Group D had higher GA: HbA1c than Group B (p = 0.001); Group E had higher GA: HbA1c than Groups B and C (p = 0.000); Group D had higher GA: HbA1c than Group C (p = 0.011); and Group E had higher GA: HbA1c than Group D (p = 0.001).

Table 2. Clinical features of participants based on DR progression.

variables	Group B (n = 230)	Group C (n = 183)	Group D (n = 123)	Group E (n = 83)	p
Male (%)	153/77 (66.50%)	123/60 (67.2%)	80/43 (65.00%)	48/35 (57.80%)	0.477
Age (y)	55.73 ± 10.04	56.87 ± 10.35	55.08 ± 9.91	56.43 ± 9.76	0.439
Duration of DM (y)*	8 (3, 14)	10 (5, 16)	10 (5, 16)	15 (7, 20)	0.000
Smoking (%)	152/78 (66.10%)	118/65 (64.50%)	79/44 (64.20%)	54/29 (65.10%)	0.982
Drinking (%)	137/93 (59.60%)	119/64 (36.83%)	85/38 (69.10%)	50/33 (60.20%)	0.293
BMI (kg/m^2)*	25.68 ± 3.26	26.04 ± 3.41	26.07 ± 3.06	27.03 ± 3.92	0.021
Systolic BP (mmHg)	136 (124, 148)	136.5 (123.75, 154.25)	139 (125, 155)	140 (129, 160)	0.181
Diastolic BP (mmHg)	84 (76, 90)	84 (75, 91)	83 (75, 92)	82 (73, 93)	0.995
GA (%)*	19.50 (16.60, 23.43)	21.30 (17.60, 25.60)	22.50 (19.00, 27.30)	24.00 (20.30, 27.90)	0.000
bA1C (%)*	8.20 (7.18, 9.60)	8.80 (7.50, 10.00)	8.80 (7.80, 10.30)	8.50 (7.30, 10.00)	0.012
GA/HbA1C*	2.43 (2.24, 2.63)	2.43 (2.22, 2.72)	2.59 (2.37, 2.85)	2.80 (2.59, 3.06)	0.000
C-peptide (fasting) (pmol/L)*	1.70 (1.30, 2.20)	1.50 (0.90, 2.00)	1.20 (0.90, 1.80)	1.00 (0.70, 1.50)	0.000
C-peptide 30 min (pmol/L)*	2.30 (1.80, 3.13)	2.10 (1.40, 3.20)	1.90 (1.20, 2.70)	1.50 (1.10, 2.20)	0.000
C-peptide 60 min (pmol/L)*	3.55 (2.50, 4.90)	2.90 (2.00, 4.60)	2.80 (1.70, 3.80)	2.50 (1.70, 3.40)	0.000
C-peptide 120 min (pmol/L)*	4.70 (3.48, 6.53)	4.30 (2.90, 6.10)	3.60 (2.60, 5.20)	3.60 (2.30, 4.70	0.000
UACR (mg/mmol)*	2.27 (1.69, 4.52)	3.41 (2.27, 8.47)	8.47 (3.02, 17.05)	6.82 (2.27, 17.05)	0.000
TC (mmol/l)	5.01 (4.47, 5.55)	5.05 (4.35, 5.87)	5.21 (4.36, 5.87)	5.29 (4.37, 6.46)	0.286
TG (mmol/l)	1.81 (1.16, 2.90)	1.75 (1.24, 2.92)	1.76 (1.13, 2.69)	1.68 (1.13, 2.32)	0.880
HDL (mmol/l)	1.22 (1.04, 1.41)	1.18 (1.05, 1.35)	1.22 (1.01, 1.49)	1.26 (1.01, 1.47)	0.462
LDL (mmol/l)	2.99 (2.43, 3.35)	2.95 (2.33, 3.58)	3.03 (2.19, 3.88)	3.11 (2.44, 4.06)	0.529
apoA (g/L)	1.26 (1.12, 1.49)	1.25 (1.16, 1.46)	1.30 (1.14, 1.45)	1.35 (1.09, 1.51)	0.784
apoB (g/L)*	1.01 (0.90, 1.16)	1.05 (0.90, 1.22)	1.07 (0.88, 1.23)	1.05 (0.87, 1.31)	0.877

Values are represented by means ± standard deviation or median [interquartile range] or as case numbers (percentages). * indicates $p < 0.05$.

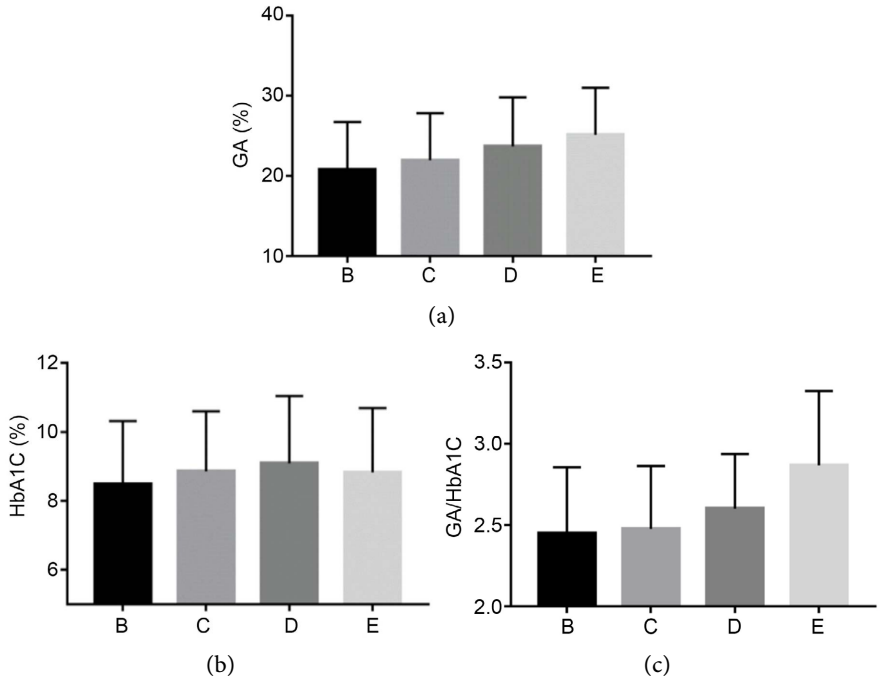

Figure 1. Correlation of diabetic retinopathy with GA, HbA1c, and GA: HbA1c. (a) Relation of GA with DR of four Groups. (b) Relation of HbA1c with DR of four groups. (c) Relation of GA: HbA1c with DR in four groups. DN, diabetic retinopathy; HbA1c, hemoglobin A1c; GA, glycated albumin.

3.1. Association between Serum GA/HbA1c Ratio and Clinical Features

Age was not found to be a significant predictor of DR. The duration of DM, BMI, c-peptide (fasting), and c-peptide 120 min all had a clear relationship with the GAHbA1c ratio (Table 3).

3.2. Multivariate Regression on Factors Affecting DR Incidence in T2DM Patients

Finally, multiple logistic regressions that included the C-peptide, UACR, and GA/HbA1c ratio as independent variables revealed that the c-peptide (fasting), UACR, and GA/HbA1c ratio independently predicted diabetic retinopathy ($p = 0.004$, $p = 0.000$, $p = 0.000$, respectively). Fasting C-peptide is a protective factor, *i.e.*, fasting C-peptide has a significant and negative impact on DR development. UACR and GA/HbA1C were risk factors; they had a significant and positive effect on DR. The rest were not DR-related influencing factors (Table 4).

4. Discussion

Umayahara Y *et al.* found that the GA/HbA1c ratio independently predicted the occurrence of DR [11]. GA changes as blood glucose levels rise or fall, reflecting BG fluctuations in a short period of time. The GA/HbA1c ratio increased due to the recent loss of glycemic control [10]. This study found that GA and HbA1c levels are related to DR in T2DM patients. A previous study found that the

Table 3. Analysis between GA/HbA1c ratio and related indexes.

variables	N	GA/HbA1C	
		Spearman's correlation coefficient	P
Age	619	0.010	0.795
Duration	619	0.158	0.000
BMI	619	0.114	0.005
C-peptide (fasting)	619	−0.302	0.000
C-peptide 120 min	619	−0.302	0.000

Table 4. Logistic regression analysis of the factors affecting the progression of fundus lesions.

	β	OR	P	95% CI
C-peptide 0 min	−0.406	0.666	0.004	−0.683 - −0.130
C-peptide 30 min	0.211	1.235	0.114	−0.051 - −0.473
C-peptide 60 min	−0.142	0.868	0.203	−0.360 - 0.076
C-peptide 120 min	−0.051	0.950	0.418	−0.175 - 0.073
UACR	0.040	1.041	0.000	0.023 - 0.057
GA/HbA1C	1.323	3.755	0.000	0.931 - 1.715

OR: odds ratio; CI: confidence interval; Model: adjusted for DM duration and BMI.

changes in GA and HbA1c among T1DM patients increased when compared to T2DM patients [12]. Therefore, if a patient with type 1 diabetes only tested GA once a year, the results may not accurately reflect overall glycemic control. Although the GA and HbA1c were only used once in this study, they were chosen in accordance with previous research. It could be related to the fact that changes in GA and HbA1c among T2DM cases are lower than in non-T2DM cases. The values roughly reflect the overall glycemic control over the course of a year. In conclusion, it can be stated that GA/HbA1c is a factor that influences DR.

Dyslipidemia is common in T2DM patients. The relationship between apolipoproteins and DR was stronger than the relationship between traditional serum lipid levels and DR [13]. This study found that the TC, TG, and Apo-B levels in the DR groups increased when compared to the NPDR group ($p < 0.05$). These significant differences support the notion that dyslipidemia has a significant impact on DR. Diabetic retinopathy and nephropathy are characterized by diabetic microangiopathy caused by long-term hyperglycemia. This study's logistic regression analysis reveals that Urinary Albumin Creatinine Ratio (UACR) is a factor that influences DR, and diabetic patients with abnormal UACR should be screened as soon as possible to prevent DR. According to the findings of Selvin *et al.*, glycated albumin and fructosamine have prognostic utility in predicting DR in the community [14]. Prospective studies should be conducted to determine whether GA/HbA1c can be used to predict DR. Time in range (TIR) represented the time proportion in the 3.9 - 10.0 mmol/L glucose range. Ac-

cording to recent research, TIR is strongly linked to the occurrence of microvascular complications [15]. The hazard ratio (HR) for DR occurrence increased by 64% for every 10% decrease in TIR points, while the HR for microalbuminuria outcome increased by 40%. The HR for DR occurrence increased by 64% for every 10% decrease in TIR points, while the HR for microalbuminuria outcome increased by 40% [16]. Recent research also discovered that when TIR increased by 10%, the risk of abnormal carotid intima-media thickness (CIMT) decreased by 6.4% [17]. The inevitable trend of blood glucose monitoring is continuous blood glucose monitoring. Future research should concentrate on the relationship between GA/HbA1c and BG fluctuation and DR using glycemic variability metrics based on continuous glucose monitoring (CGM). This study classified the DR status into five groups based on the International Classification of Diabetic Retinopathy. As a result, this experiment can provide a more comprehensive understanding of the relationship between blood glucose monitoring indicators and the development of DR.

Due to the limited number of subjects with proliferative diabetic retinopathy (PDR) in this study (n = 83), it was not possible to further categorize PDR stages. Additionally, it should be noted that cross-sectional research does not establish causal relationships.

To confirm the association between glucose fluctuations, diabetic retinopathy (DR), and the GA/HbA1c ratio, it is recommended to conduct future large-scale multicenter studies utilizing continuous glucose monitoring systems. Such studies would provide more comprehensive and reliable data.

Acknowledgements

Thank the Department of Endocrinology of the Second Affiliated Hospital of Harbin Medical University and the Department of Critical Care Medicine of the Seventh Affiliated Hospital of Sun Yat-sen University for their assistance in this study. This work was supported by the Shenzhen Fundamental Research Program (JCY20190809121801664).

Data Availability

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Ethics Approval and Consent to Participate

The study was approved by the ethics review board of The Seventh Affiliated Hospital, Sun Yat-sen University (KY-2022-038-01) in accordance with the Declaration of Helsinki.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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