

Association of Glycated Albumin/Glycosylated Hemoglobin Ratio with Blood Glucose Fluctuation and Long-Term Blood Glucose Control in Patients with Type 2 Diabetes Mellitus

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Objective: This study aimed to investigate the association of the glycated albumin (GA)/glycosylated hemoglobin (HbA1c) ratio with the mean amplitude of glycemic excursion (MAGE) in type 2 diabetes mellitus (T2DM).

Methods: A total of 102 patients with T2DM who were first treated in Jinjiang Hospital of Fujian Province were enrolled in this study. The patients' general clinical data, including HbA1c, GA, fasting blood glucose, and fasting and peak C-peptide values upon diagnosis and after one year of follow-up, were collected, and their MAGE was calculated.

Results: With the increase of the GA/HbA1c ratio at baseline, the patients' fasting and peak C-peptide values decreased gradually from baseline to follow-up, while their MAGE, HbA1c, and fasting blood glucose increased gradually. A regression analysis demonstrated that the baseline MAGE was independently positively correlated with the GA/HbA1c ratio. A Cox regression analysis demonstrated that a baseline GA/HbA1c ratio of >2.78 was an independent risk factor for poor fasting blood glucose and HbA1c.

Conclusion: The GA/HbA1c ratio is closely related to the MAGE and islet function in patients with T2DM.

Keywords: type 2 diabetes mellitus, glycated albumin, glycosylated hemoglobin, blood glucose control, blood glucose fluctuation

Introduction

Diabetes mellitus is a common disease endangering human health.¹ Accumulating evidence shows that blood glucose fluctuation can induce oxidative stress, cause vascular endothelial dysfunction, promote arteriosclerosis, and is associated with the risk of vascular complications in diabetes.²⁻⁴ The mean amplitude of glycemic excursion (MAGE) helps accurately evaluate patients' blood glucose fluctuation but requires continuous glucose monitoring (CGM) and complicated calculations. In addition, numerous studies have been conducted to examine the relationship between insulin secretion and glucose fluctuation in patients with diabetes.⁵⁻⁷ Jin et al have suggested that fasting C-peptide levels are inversely associated with higher glucose fluctuation.⁶ Ohara et al have found increments of C-peptide immunoreactivity correlated with glycemic control stability.⁵ However, it remains unclear which clinical markers are independently correlated with patients' blood glucose fluctuation.

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Glycosylated hemoglobin (HbA1c) and glycated albumin (GA) can be used to evaluate the recent mean blood glucose level of diabetic patients, but they cannot reflect the patients' blood glucose fluctuation. A previous study suggests that decline of islet function is the direct cause of the increase in blood glucose fluctuation in patients with diabetes.⁸ The blood glucose fluctuation of type 1 diabetes mellitus (T1DM) can be reflected by the GA/HbA1c ratio, which is more convenient than the MAGE.⁹ The islet function of patients with type 2 diabetes mellitus (T2DM) also decreases progressively. A previous study has revealed that the GA/HbA1c ratio in patients with low C-peptide levels is significantly higher than that in patients with high C-peptide levels, even after two years of treatment and follow-up.¹⁰ This study suggests that the GA/HbA1c ratio may be a predictor of long-term glycemic control in patients with T2DM.

To determine the correlation of the GA/HbA1c ratio with blood glucose fluctuation and long-term blood glucose control in patients with T2DM, the clinical data of 102 patients newly diagnosed with T2DM are collected in this research. This study also aims to determine whether the GA/HbA1c ratio is closely related to the C-peptide level and the blood glucose fluctuation range and further analyze the correlation of the baseline GA/HbA1c ratio with fasting blood glucose (FBG) and HbA1c after one year of follow-up. Finally, it explores the predictive value of the GA/HbA1c ratio for long-term glycemic control in patients with T2DM.

Subjects and Methods

Subjects

The clinical data of 102 patients newly diagnosed with T2DM from 2018 to 2019 at the Department of Endocrinology, Jinjiang Hospital, Fujian Province, were collected. All patients included met the diagnostic criteria formulated by the World Health Organization in 1999.¹¹ The exclusion criteria were as follows: (1) kidney insufficiency, (2) nephrotic syndrome, (3) liver insufficiency, (4) anemia, (5) hypoproteinemia, (6) pregnancy, (7) serious chronic complications of diabetes mellitus, (8) acute cardiovascular and cerebrovascular diseases, and (9) a history of taking glucocorticoids, pentamidine, nicotinic acid, thyroid hormone, diazoxide, β -adrenergic agonists, thiazide diuretics, Dilantin, interferon- γ , and other drugs that affect the blood glucose levels. This study was approved by the ethics committee of Jinjiang Hospital, and the

subjects' informed consent was obtained. This study was conducted in accordance with the Declaration of Helsinki.

Methods

(1) The patients' clinical data, including age, gender, weight, and height, were collected, and their body mass index (BMI) was calculated. Then, blood was drawn from the patients after eight hours of fasting; the maximum delivery time to the laboratory was 30 min. The blood to detect blood glucose, alanine aminotransferase (ALT), creatinine, and GA were put in coagulation tubes and measured by a Beckman automatic biochemical analyzer (Beckman Coulter Inc, CA, USA) after centrifugation at 4,000 rpm for five minutes. The blood to detect HbA1c was put in EDTA-K2 anticoagulant tubes and measured by a Tosoh G8 detector (Tosoh Bioscience, Tokyo, Japan). To detect the C-peptide levels, blood was collected in EDTA-K2 anticoagulant tubes at one, two, and three hours after oral administration of 75 g of glucose, with the highest level taken as the C-peptide peak. The C-peptide levels were measured by Roche E601 automatic immunoassay (Roche Diagnostics, Munich, Germany) after centrifugation at 4,000 rpm for five minutes.

(2) After two weeks of treatment, the patients were reminded to monitor their blood glucose levels and transmit the monitored values through the app or by phone to Jinjiang Hospital. For hospitalized patients, the blood glucose was monitored one week after subcutaneous insulin injections. The fingertip blood glucose of outpatients and inpatients was monitored seven times a day for three consecutive days (ACCU-Chek blood glucose meter, Roche Diagnosis), including before meals, two hours after meals, and before going to bed. During the monitoring period, the treatment plan and hypoglycemia dose were unchanged. On this basis, the MAGE was calculated. The calculation formula was $MAGE = \sum \lambda / \chi$, where λ is the difference between the maximum and minimum values of each effective blood glucose fluctuation and χ is the number of effective fluctuations. When the difference between the peak and trough of a blood glucose fluctuation was greater than one standard deviation of blood glucose, it was considered the effective amplitude of blood glucose fluctuation.

(3) After one year of follow-up, FBG, HbA1c, and GA were detected, the islet function was evaluated, a 75-g glucose tolerance test was conducted, and the C-peptide levels at one, two, and three hours after glucose load were detected, with the highest level taken as the peak

C-peptide value. The methods were the same as those described above.

Statistical Analysis

The patients were divided into three groups according to the baseline GA/HbA1c level: <2.62 in group T1, between 2.62 and 3.03 in group T2, and >3.03 in group T3. The normally distributed measurement data were expressed as the mean \pm standard deviation ($\bar{x} \pm SD$), compared between two groups using paired *t*-tests, and compared among all groups using general linear models. The non-normally distributed measurement data were expressed as the median (range) and compared among the groups using general linear models. These data were included in the analysis after log conversion. Percentages were compared using chi-square tests. The correlation between parameters was analyzed by multiple linear stepwise regression. A Cox regression analysis was used to analyze the prognostic factors. The data were statistically analyzed using the statistical software SPSS 13.0. The areas under the two receiver operating characteristic (ROC) curves were compared using the MedCalc 19.0.2 software.

Results

A total of 102 patients with newly diagnosed T2DM were enrolled and followed up with for one year. Among these patients, 64 (62.75%) were male, and 38 (37.25%) were female. The median age was 48.50 (19.00–78.00). The average BMI was $23.61 \pm 4.01 \text{ kg/m}^2$. The average FBG after follow-up was $7.08 \pm 1.04 \text{ mmol/L}$, and the average HbA1c level was $7.09 \pm 0.89\%$. The laboratory indexes before and after follow-up were compared. After follow-up, the GA, HbA1c, and GA/HbA1c ratio levels were significantly lower than those at the baseline level. The peak C-peptide value was significantly higher than that at the baseline, and the fasting C-peptide after follow-up was higher than that at the baseline; however, the differences were not statistically significant (Table 1).

The patients were divided into groups T1, T2, and T3 according to the baseline GA/HbA1c level. The comparison of the baseline clinical characteristics between the groups is shown in Table 2. The results revealed that the differences in the age, gender, and baseline ALT and creatinine levels among the groups were not statistically significant. As the baseline GA/HbA1c ratio increased, the baseline BMI, fasting C-peptide value, peak C-peptide value, fasting C-peptide value after follow-up and peak C-peptide values after follow-up gradually decreased. The

Table 1 Comparison of Clinical Indicators Between Baseline and Follow-Up

| | Baseline | After Follow-Up | P value |
|-------------------------------------|-------------------|------------------|---------|
| HbA1c (%) | 10.31 \pm 2.85 | 7.09 \pm 0.89 | <0.001 |
| GA (%) | 29.66 \pm 11.12 | 20.33 \pm 5.25 | <0.001 |
| GA/HbA1c ratios | 2.84 \pm 0.51 | 2.59 \pm 0.61 | <0.001 |
| The fasting C-peptide (ng/mL) | 1.53 \pm 0.75 | 1.64 \pm 0.56 | 0.115 |
| The peak value of C-peptide (ng/mL) | 3.05 \pm 1.64 | 3.62 \pm 1.37 | <0.001 |

BMI was significantly higher in group T1 than in groups T2 and T3 ($P < 0.05$), but the difference between T2 and T3 was not statistically significant ($P > 0.05$). The differences in the baseline fasting and peak C-peptide values among the three groups were statistically significant ($P < 0.05$). After follow-up, the fasting C-peptide was significantly lower in group T3 than in groups T1 and T2 ($P < 0.05$). After follow-up, the peak C-peptide value was significantly lower in group T3 than in groups T1 and T2 ($P < 0.05$), but the difference between groups T1 and T2 was not statistically significant. As the baseline GA/HbA1c ratio increased, the MAGE, GA, HbA1c, FBG, and GA/HbA1c ratio at follow-up increased gradually. The MAGE was significantly higher in group T3 than in groups T1 and T2 ($P < 0.05$), but the difference between groups T1 and T2 was not statistically significant. The differences in the GA after follow-up among the three groups were statistically significant ($P < 0.001$). After follow-up, the FBG, HbA1c, and GA/HbA1c ratio were significantly higher in group T3 than in group T1, but the differences between groups T1 and T2 and between groups T2 and T3 were not statistically significant.

A multiple linear stepwise regression model was established with the baseline fasting and peak C-peptide values and MAGE as the independent variables and the baseline GA/HbA1c ratio as the dependent variable to compare age, gender, and BMI (Table 3). The results revealed that the baseline MAGE was independently positively correlated with the GA/HbA1c ratio ($P = 0.004$). The baseline fasting C-peptide ($P < 0.001$) and peak C-peptide ($P < 0.001$) levels were independently and negatively correlated with the baseline GA/HbA1c ratio. A ROC curve was made with the baseline

Table 2 Comparison of Clinical Characteristics Between Three Groups of Patients with Type 2 Diabetes

| Project | T1 (<2.62) | T2 (2.62~3.03) | T3 (>3.03) | P value |
|--|-------------|----------------|--------------|---------|
| Age (years) | 49.94±13.35 | 47.59±12.14 | 44.53±14.57 | 0.252 |
| Gender [n(%)] | | | | 0.846 |
| Male | 20 (58.82) | 22 (64.71) | 22 (64.71) | |
| Female | 14 (41.18) | 12 (35.29) | 12 (35.29) | |
| Baseline BMI (kg/m ²) | 24.48±2.53 | 22.50±3.47* | 22.81±3.47* | 0.026 |
| ALT (IU/L) | 28.79±10.08 | 31.85±9.04 | 30.18±9.66 | 0.424 |
| Creatinine (μmol/L) | 48.15±15.92 | 54.83±15.96 | 49.48±13.95 | 0.168 |
| Fasting C-peptide (ng/mL) | 2.23±0.76 | 1.42±0.47* | 0.94±0.31** | 0.000 |
| C-peptide peak value (ng/mL) | 4.20±1.51 | 2.97±1.67* | 1.98±0.76** | 0.000 |
| MAGE after discharge from hospital (mmol/L) | 5.19±2.12 | 5.64±2.14 | 7.04±2.49** | 0.003 |
| Fasting blood glucose after follow-up (mmol/L) | 6.69±0.99 | 7.04±0.96 | 7.49±1.03* | 0.005 |
| GA after follow-up | 15.62±3.28 | 19.80±2.69* | 25.59±3.85** | 0.000 |
| HbA1c after follow-up (%) | 6.69±0.96 | 7.09±0.80 | 7.48±0.73* | 0.001 |
| Fasting C-peptide after follow-up (ng/mL) | 1.83±0.68 | 1.68±0.47 | 1.41±0.43** | 0.005 |
| C-peptide peak value after follow-up (ng/mL) | 3.96±1.49 | 3.90±1.42 | 3.01±0.94** | 0.005 |
| GA/HbA1c after follow-up | 2.36±0.56 | 2.61±0.62 | 2.80±0.61* | 0.013 |

Notes: *Compared with T1 group, P < 0.05; **compared with T2 group, P < 0.05.

GA/HbA1c ratio and MAGE as the independent variables and a fasting C-peptide value lower than 1.1 ng/mL as the dependent variable (Figure 1). The Area Under The Curve (AUC) of the baseline GA/HbA1c ratio (AUC = 0.840, P = 0.001) and baseline MAGE (AUC = 0.736, P < 0.001) revealed no statistical significance (Z = 1.926, P = 0.054).

A multiple linear stepwise regression model was established with the baseline GA, HbA1c, GA/HbA1c ratio, fasting and peak C-peptide values, and MAGE as the independent variables and the FBG at follow-up, HbA1c, GA/HbA1c ratio, and fasting and peak C-peptide values as the dependent variables to compare

age, gender, and BMI (Table 4). The results revealed that the baseline GA/HbA1c ratio was independently and positively correlated with the blood glucose at follow-up (P < 0.001), HbA1c (P < 0.001), and GA/HbA1c ratio (P = 0.006).

A Cox proportional hazard regression model was established based on whether the glycated hemoglobin one year after follow-up was lower than 7% and whether the FBG one year after follow-up was lower than 7 mmol/L as the dependent variables; the follow-up time was used as the survival time, and the baseline median GA, median HbA1c, median GA/HbA1c, age, gender, and median BMI were the independent variables. The results revealed that

Table 3 Correlation Between Baseline MAGE, Fasting C-Peptide, C-Peptide Peak and Baseline GA/HbA1c

| Independent Variables | Dependent Variables | A Multiple Linear Stepwise Regression | | R ² |
|-------------------------------|---------------------|---------------------------------------|-------|----------------|
| | | B | P | |
| Baseline MAGE | Baseline GA/HbA1c | 0.061 | 0.004 | 0.606 |
| Baseline fasting C-peptide | | -0.526 | 0.000 | |
| Baseline C-peptide peak level | | -0.006 | 0.000 | |

Note: The control variables were age, gender and BMI.

Abbreviation: R², coefficient of determination.

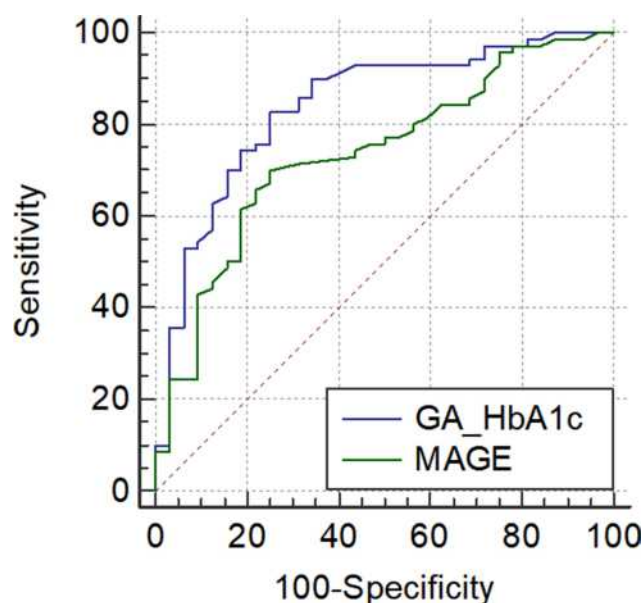


Figure 1 Comparison of area under curve ROC of MAGE and GA/HbA1c in the diagnosis of islet function.

a baseline GA/HbA1c ratio of >2.78 was an independent risk factor for poor FBG (OR 1.889, 95% CI 1.076–3.344) and HbA1c (OR 2.687, 95% CI 1.514–4.771).

Discussion

In the present study, 102 patients with newly diagnosed T2DM were followed up with. The results suggested that the baseline GA/HbA1c ratio is independently related to islet β -cell function and blood glucose fluctuation levels, indicating that this index could reflect the MAGE in patients with T2DM. As this ratio is straightforward and easy to operate, it could be used as a simple index to evaluate the MAGE in clinical practice. The results of this study also indicate that the GA/HbA1c ratio is affected by the baseline C-peptide levels. It has been suggested that the ratio is related to the function of islet cells. The present study revealed that the increase of the baseline GA/HbA1c ratio was independently related to the increase of the FBG and HbA1c one year after follow-up. This suggests that this ratio also has a predictive value for long-term blood glucose control in patients with T2DM.

In recent years, the prevalence of macrovascular diseases has significantly increased in patients with T2DM.¹² While HbA1c is a good predictor of microvascular disease in these patients, it has limitations in the prediction of macrovascular diseases.¹² A previous study revealed that the progress of cardiovascular complications in patients

with diabetes may be closely related to the fluctuation of blood glucose.¹³ However, understanding blood glucose fluctuation in patients often requires many cycles of CGM, and patient compliance is poor. Another previous study revealed that the GA/HbA1c ratio could reflect the fluctuation of blood glucose in patients with T1DM. The poorer the islet function, the higher the GA/HbA1c ratio and the greater the blood glucose fluctuation.¹⁴ However, there is still a lack of data supporting the application of the GA/HbA1c ratio in the blood glucose monitoring of patients with T2DM. The current study revealed that the GA/HbA1c ratio is positively correlated with the MAGE in patients with T2DM and negatively and significantly correlated with C-peptide levels. The increase of the GA/HbA1c ratio could be used as an alternative index to

Table 4 Correlation Between Baseline GA/HbA1c, C-Peptide Peak and Fasting Blood Glucose, HbA1c, GA/HbA1c, Fasting C-Peptide, C-Peptide Peak After Follow-Up

| Independent Variables | Dependent Variables | A Multiple Linear Stepwise Regression | |
|-------------------------------|-----------------------------------|---------------------------------------|--------|
| | | B | P |
| Baseline GA/HbA1c | Blood glucose at follow-up | 0.726 | <0.001 |
| | HbA1c at follow-up | 0.708 | <0.001 |
| | GA/HbA1c ratio at follow-up | 0.324 | <0.001 |
| | Fasting C-peptide at follow-up | - | - |
| | C-peptide peak value at follow-up | - | - |
| Baseline C-peptide peak level | Blood glucose at follow-up | - | - |
| | HbA1c at follow-up | - | - |
| | GA/HbA1c ratio at follow-up | - | - |
| | Fasting C-peptide at follow-up | 0.175 | <0.001 |
| | C-peptide peak value at follow-up | 0.460 | <0.001 |

Notes: Baseline GA, HbA1c, GA/HbA1c, fasting C-peptide, C-peptide peak, and MAGE were independent variables; fasting blood glucose, HbA1c, GA/HbA1c, fasting C-peptide, and C-peptide peak after follow-up were the dependent variables; the control variables were age, gender and BMI.

evaluate blood glucose fluctuation and islet β -cell function in patients with T2DM; its application value in this aspect is significantly higher than that of HbA1c and GA.

The mechanism of the GA/HbA1c ratio in reflecting blood glucose fluctuation is still unclear. Albumin is glycosylated 10 times faster than hemoglobin,¹⁵ making the sensitivity of GA to blood glucose change higher than that of HbA1c. Albumin has a shorter life span than hemoglobin, and GA can better reflect blood glucose changes within a short period. A great fluctuation of blood glucose can enhance the glycosylation and oxidation of albumin, increasing the GA level.^{16,17} Related studies have also confirmed that GA could better reflect patients' blood glucose fluctuation than HbA1c.^{18,19} However, blood glucose fluctuation enhances oxidative stress,²⁰ leading to a decrease in the lifespan of red cells.²¹ The greater the MAGE in patients, the higher the peak blood glucose may be, while hyperglycemia can reduce the fluidity of red cell membranes²² and reduce the lifespan of red cells, decreasing HbA1c. Therefore, when the blood glucose fluctuation increases, the GA level increases, the HbA1c decreases, and the GA/HbA1c ratio increases. However, these possible mechanisms need to be confirmed by further research.

In this study, to determine the effect of the GA/HbA1c ratio on long-term blood glucose control in patients with T2DM, the clinical data of the patients one year after follow-up were collected. The results revealed that after follow-up, the GA, HbA1c, and GA/HbA1c ratios were significantly lower than the baseline levels, while the peak C-peptide value was significantly higher than the baseline level. The results also revealed that after one year of treatment, the patients' islet function was improved, the MAGE was decreased, and the blood glucose control was improved. The baseline GA/HbA1c ratio was independently correlated with the blood glucose after follow-up, HbA1c, and GA/HbA1c ratio. This suggests that the baseline GA/HbA1c ratio could predict the level of blood glucose control after one year of treatment. The C-peptide level after follow-up was positively correlated with the peak baseline C-peptide value. The higher the GA/HbA1c ratio, the lower the peak C-peptide value was in the patients. The higher the GA/HbA1c ratio after follow-up, the poorer the islet function and the poorer the blood glucose control. Improvement of islet function depends on the baseline islet function level. A low baseline C-peptide level increases blood glucose fluctuations and may inhibit the repair of islet β -cell function due to oxidative stress and

inflammatory response.²³ A previous study revealed that the improvement of islet β -cell function is conducive to long-term blood glucose control in patients with T2DM.²⁴ Therefore, the higher the baseline GA/HbA1c ratio, the greater the blood glucose fluctuation in patients with newly diagnosed T2DM. The improvement of islet function is thereby inhibited, directly leading to poor long-term blood glucose control. The oxidative stress and inflammatory response caused by blood glucose fluctuation can also aggravate insulin resistance in patients with T2DM^{25,26} and then affect their blood glucose control. However, the present study could not further demonstrate this.

This was a retrospective study, so it had several limitations: (1) In this research, the CGM results were not used to directly reflect the blood glucose fluctuation; (2) the insulin resistance index of the patients was not evaluated, and the correlation between the baseline GA/HbA1c ratio and blood glucose control after follow-up and insulin resistance was not analyzed. The purpose of this study was to provide clinicians with an objective index to predict the long-term blood glucose control level of patients with newly diagnosed T2DM by analyzing the correlations among the GA/HbA1c ratio, blood glucose fluctuation, blood glucose, and HbA1c levels after follow-up.

Conclusion

The GA/HbA1c ratio is independently associated with C-peptide levels, and blood glucose change in patients with newly diagnosed T2DM is a sensitive index that is closely related to their islet function and can directly reflect their blood glucose changes. In addition, the baseline GA/HbA1c ratio was found to be closely related to the FBG and HbA1c levels in these patients after a one-year follow-up and may be a predictor of blood glucose control in newly diagnosed T2DM.

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Disclosure

The authors declare that they have no competing interests.

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