Observational Study

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The ratio of estimated average glucose to fasting plasma glucose level as an indicator of insulin resistance in young adult diabetes

An observational study

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Abstract

At present, glycated hemoglobin (HbA1c) and glycated albumin (GA) are used to evaluate glycemic control in diabetic patients, but they cannot reflect insulin deficiency and/or insulin resistance.

We investigated the feasibility of using estimated average glucose to fasting plasma glucose ratio (eAG/fPG ratio) to estimate insulin resistance in young adult diabetes. A total of 387 patients with type 2 diabetes were included and were stratified into 2 groups based on median values of the glycemic index ratio: the GA/A1c ratio <2.09 (n = 91) and ≥2.09 (n = 296); the eAG/fPG ratio <1.69 (n = 155) and ≥1.69 (n = 232). HbA1c, GA, fructosamine, insulin, and C-peptide levels were measured. The ratio of GA to HbA1c was calculated, and the homeostasis model assessment of β-cell function and insulin resistance were determined. The homeostasis model assessment of insulin resistance level was significantly associated with the eAG/fPG ratio, but not with the ratio of GA to HbA1c, GA, HbA1c, and fructosamine levels. The ratio of estimated average glucose to fasting plasma glucose level correlates with insulin resistance in young adult diabetes.

Abbreviations: BMI = body mass index, eAG/fPG ratio = estimated average glucose to fasting plasma glucose ratio, GA = glycated albumin, GA/A1c ratio = the ratio of GA to HbA1c, HbA1c = glycated hemoglobin, HOMA-β = homeostasis model assessment of β-cell function, HOMA-IR = homeostasis model assessment of insulin resistance, T2DM = type 2 diabetes mellitus.

Keywords: estimated average glucose to fasting plasma glucose ratio, glycated hemoglobin, homeostasis model assessment of β-cell function, type 2 diabetes mellitus, young diabetes

1. Introduction

Diabetes is a group of disorders characterized by chronic elevations in blood glucose (hyperglycemia) resulting from insulin deficiency and/or insulin resistance.[1,2] Fructosamine, glycated albumin (GA), and glycated hemoglobin (HbA1c) are glycated proteins that are used to evaluate glycemic control in diabetic patients.[3] The lifespan of HbA1c is estimated to be about 90 to 120 days. Thus, it is known as an indicator of long-term glycemic control.[4,5] However, HbA1c is not suitable for the assessment of a patient's glycemic status in certain disorders including hemoglobinopathies and disorders with abnormal red blood cell turnover. For example, in patients with anemia, HbA1c is not accurate in reflecting the real plasma glucose burden.[6]

Fructosamine is an index of glycemic control in the past 2 weeks. Fructosamine is not affected by changes in hemoglobin metabolism, but can be influenced by disorders in protein turnover (ie, dysproteinemias). In addition, substances with low molecular weight such as uric acid and urea strongly influence fructosamine levels.[7]

GA, which is not influenced by changes in the lifespan of erythrocytes, is thought to be a good alternative indicator of glycemic control in diabetic patients.[8] GA is an index of glycemic control which is not affected by disorders of hemoglobin metabolism. Additionally, it reflects the short-term status of glycemic control compared with HbA1c. Furthermore, GA is not influenced by serum albumin concentration because it calculates the ratio of total serum albumin.[9]

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GA/HbA1C ratio in patients with type 1 diabetes mellitus was shown to be significantly higher than that in patients with type 2 diabetes mellitus (T2DM).[10] There is a significant inverse correlation between GA/HbA1C ratio and homeostasis model assessment of β-cell function (HOMA-β)%, reflecting that the decreased endogenous insulin secretion is involved in an increased value of the GA/HbA1C ratio.

Few studies have closely examined the relationship between endogenous insulin production and the ratio of estimated average glucose to fasting plasma glucose levels (eAG/fPG ratio) in young adult diabetes. The present study investigated the usefulness of eAG/fPG ratio in estimating homeostasis model assessment of insulin resistance (HOMA-IR) in young adults with diabetes mellitus, and its difference with the ratio of GA to HbA1c (GA/A1c) ratio and the 3 glycated proteins.

2. Materials and methods

2.1. Subjects

A total of 387 patients with type 2 diabetes were studied, who came from the Tianjin Medical University Chu Hsien-I Memorial Hospital & Metabolic Diseases Hospital from October 2011 to January 2016. Their ages ranged from 10 to 25 (median age, 20 years). All patients fit the criteria for the diagnosis of diabetes by the American Diabetes Association.[11] Clinical and demographic data were collected retrospectively from a review of medical records. All patients signed at admission an informed consent, agreeing to partake in research projects as long as their confidentiality was respected. All procedures of this study respect the ethical standards of the Helsinki Declaration of 1975, as revised in 2008(5). This study was approved by the Institutional Review Board of Tianjin Medical University Chu Hsien-I Memorial Hospital & Metabolic Diseases Hospital (approval number: DXBYYhMEC2018-16).

2.2. Measurement of parameters

The following parameters were measured: glycated proteins (HbA1c, GA, and fructosamine), glucose levels (fPG and postprandial plasma glucose), glycemic index ratio (GA/A1c ratio and eAG/fPG ratio), β-cell function (C-peptide and insulin), anthropometric parameters (height, weight, and body mass index [BMI]), and glycemic index-associated parameters (serum albumin, hemoglobin, and serum creatinine). HOMA-β and HOMA-IR were determined by a HOMA calculator to assess the basal β-cell function and insulin resistance in patients with T2DM. BMI was calculated as weight in kilograms divided by the square of the height in meters. Blood specimens were collected before insulin treatment.

2.3. Calculation of eAG/fPG ratio

The eAG was calculated using the following equation: eAG (mmol/L) = 1.59 × HbA1c (%) – 2.59.[12] The eAG/fPG ratio was computed using the following formula: eAG/f PG ratio = eAG level (mmol/L)/f PG level (mmol/L). The estimated glomerular filtration rate was determined by the Schwartz formula[13]: estimated glomerular filtration rate (mL/min/1.73 m^2) = proportionality constants × height (cm)/serum creatinine level (mg/dL). Patients with T2DM were stratified into 2 groups based on median values of the glycemic index ratio listed in Table 1: the GA/A1c ratio <2.09 (n = 91) and ≥2.09 (n = 296); the eAG/fPG ratio <1.69 (n = 155) and ≥1.69 (n = 232).

Table 1

Baseline characteristics of the subject included in this study.

	Type 2 diabetes
Number of subjects	387
Age (yr)	20.72 (11–25)
Gender (male, %)	242 (62.5)
Duration of diabetes (years)	1.19 (0.1–10)
Height (cm)	170.86 ± 10.16
Weight (kg)	80.51 ± 21.70
BMI (kg/m^2)	27.73 ± 8.67
HbA1c (%)	11.22 (5.1–21.9)
Glycated albumin (%)	27.83 (21.84–39.13)
Fructosamine (μmol/L)	436 (220–820)
Fasting plasma glucose (mmol/L)	7.93 (4.07–19.77)
PP2hrs (mmol/L)	17.77 (5.47–31.17)
C-peptide (ng/mL)	2.23 (0.31–11.3)
Insulin (U/mL)	14.91 (1.09–97.84)
HOMA-β (%)	74.36 (4.39–589.39)
HOMA-IR	4.80 (0.27–16.95)
GA/A1c ratio	2.09 (1.69–4.87)
eAG/fPG ratio	1.69 (0.77–4.24)
eGFR (mL/min/1.73 m^2)	189.72 ± 4.45

Data are expressed as mean ± SD or median (range).
BMI = body mass index, eGFR = estimated glomerular filtration rate, HOMA-β = homeostasis model assessment of β-cell function, HOMA-IR = homeostasis model assessment of insulin resistance.

2.4. Statistical analysis

Data were presented as mean standard deviation if normally distributed and as median (range) if nonnormally distributed. Normality of the data distribution was tested by Kolmogorov–Smirnov 1-sample test. Categorical variables were expressed as frequencies and proportions. Mann–Whitney *U* test and Student *t*-test were used to analyze data between the 2 groups. A multivariate regression analysis of the eGA/fPG ratio, the GA/A1c ratio, GA, HbA1c, and fructosamine were conducted as a dependent variable in patients with T2DM. Adjustments for age, BMI, duration of diabetes, serum creatinine, and C-peptide levels were performed as independent variables. The *P*-value used to be considered significant as the following:

(1) $P > .05$: nonsignificant
(2) $P < .05$: significant
(3) $P < .01$: highly significant.

3. Results

3.1. eAG/fPG ratio versus GA/A1c ratio

The baseline characteristics of all subjects are summarized in Table 1.

As shown in Table 2, duration of diabetes, fasting plasma glucose, HbA1c, insulin, and HOMA-IR levels in patients with eAG/fPG ratio ≥1.69 were significantly different from those with eAG/f PG <1.69 (1.03 vs 1.42 years, 7.24 vs 8.77 mmol/L, 11.95% vs 9.59%, 13.00 vs 17.25 U/mL, 3.36 vs 6.96; All <0.05). Similarly, HbA1c and HOMA- IR level was increased in patients with GA/A1c ratio <2.09 than in those with GA/A1c ratio ≥2.09 (12.44% vs 10.72%, 6.31 vs 4.34; All <0.05).

Table 2

C-peptide, HOMA-β, and HOMA-IR levels according to the median values of the GA/A1c ratio and the eAG/fPG ratio in patients with T2DM.

	GA/A1c ratio	GA/A1c ratio	eAG/f PG ratio	eAG/f PG ratio
	<2.09	≥2.09	<1.69	≥1.69
Number of subjects	91	296	155	232
Age (yr)	20.46 (11–25)	20.82 (10–25)	20.83 (10–25)	20.65 (10–25)
BMI (kg/m^2)	26.66 (16.82–37.20)	27.96 (14.57–39.40)	27.69 (14.57–39.40)	27.76 (16.82–44.01)
Duration of diabetes (yr)	1.09 (0.1–12)	1.22 (0.1–13)	1.42 (0.1–13)	1.03 (0.1–12)[†]
Fasting plasma glucose (mmol/L)	8.08 (4.9–16.1)	7.88 (4.07–19.7)	8.77 (4.83–16.8)	7.24 (4.07–19.7)[†]
HbA1c (%)	12.44 (6.2–21.9)	10.72 (5.1–17.5)[*]	9.59 (5.1–14.6)	11.95 (6.6–21.9)[†]
Glycated albumin (%)	27.24 (22.68–39.13)	27.94 (21.84–37.99)	27.52 (22.45–37.99)	28.02 (21.84–39.13)
C-peptide (ng/mL)	1.84 (0.4–6.2)	2.36 (0.31–7.6)	2.68 (0.51–11.3)	1.86 (0.31–7.6)
insulin (U/mL)	17.71 (1.09–151.9)	13.97 (1.21–151.9)	17.25 (1.8–144.4)	13.00 (1.09–125.1)[†]
HOMA-β (%)	84.83 (4.39–589.39)	71.14 (5.99–531.23)	76.34 (4.39–589.38)	73.04 (6.53–531.23)
HOMA-IR	6.31 (0.33–58.27)	4.34 (0.27–43.35)[*]	6.96 (0.68–79.66)	3.36 (0.27–58.27)[†]

Data are expressed as median (range).

BMI = body mass index, HOMA-β = homeostasis model assessment of β-cell function, HOMA-IR = homeostasis model assessment of insulin resistance.

[*] Statistically significant ($P < .05$) versus groups with GA/A1c ratio <2.09.

[†] Statistically significant ($P < .05$) versus groups with eAG/fPG ratio <1.69.

3.2. Multivariate regression analysis

In a multivariate analysis adjusted for the independent variables, the HOMA-IR level was significantly associated with the eAG/fPG ratio, but not with the GA/A1c ratio, GA, HbA1c, or fructosamine levels ($P < .05$). There were significant correlations between the duration of diabetes and fructosamine; however, no significant correlation was observed between the eAG/fPG ratio, GA, HbA1c, GA/A1c ratio, and the duration of diabetes. The age was significantly associated with the eAG/fPG ratio, but not with the GA/A1c ratio, GA, HbA1c, or fructosamine levels. In contrast, BMI was significantly correlated to the GA, but was not correlated to the eAG/fPG ratio, GA/A1c ratio, fructosamine, or HbA1c levels (Table 3).

4. Discussion

With respect to the pathophysiology of type 2 diabetes, hyperglycemia is mainly influenced by dysfunction of pancreatic β-cells and increased insulin resistance.[14] Moreover, oxidative stress and inflammation have emerged as putative mechanisms in the development of cardiovascular disease in T2DM. Reactive oxygen species, via different metabolites and biomarkers, increase the activity of thrombocytes and lead to endothelial inflammation and proliferation of cells, as well as decrease the homeostasis in the vessel wall.[15] In this study, eAG/fPG ratio was determined using HbA1c-derived average glucose and fasting plasma glucose level. We used this parameter to estimate insulin resistance in patients with T2DM, and compared it with the well-known parameters, including GA/A1c ratio, HbA1c, GA, and fructosamine. Duration of diabetes, fasting plasma glucose, HbA1c, insulin, and HOMA-IR levels were significantly lower in patients with an increased eAG/fPG ratio than in those with a decreased eAG/f PG ratio. The eAG/f PG ratio was correlated with HOMA-IR, and this correlation was stronger than the correlation between GA/A1c ratio, HbA1c, GA, or fructosamine with HOMA-IR. These results suggest that the new parameter may reflect insulin resistance in young adult patients with T2DM.

Our data support the results of Huh et al,[16] who has found that the association between HOMA-β and GA/A1c ratio was not significant in diabetic patients. In contrast, Koga et al reported that HOMA-β had a significant inverse correlation with the GA/A1c ratio. In our study, the eAG/f PG ratio showed a negative correlation with the HOMA-IR level but showed no significant correlations with HOMA-β and C-peptide levels. Ji Eun Lee found that eAG/f PG was related with HOMA-β and BMI, but not with HOMA-IR. These discrepancies may reflect the differences in patient populations, the severity of disease, the status of glucose tolerance, or the number of subjects.[17]

The eAG infers an average glucose levels derived from HbA1c concentrations. Ji Eun Lee et al found that there was a relationship between eAG/fPG ratio and HOMA-β in children diabetes. In the present study, the eAG/fPG ratio was compared with the GA/A1c ratio to assess insulin resistance in child and

Table 3

Multivariate regression analysis of the eGA/fPG ratio, the GA/A1c ratio, glycated albumin, HbA1c, and fructosamine as a respective dependent variable in patients with T2DM.

	eAG/f PG ratio		GA/A1c ratio		Glycated albumin (%)		HbA1c (%)		Fructosamine	
Variables	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**	**Model 1**	**Model 2**
HOMA-IR	0.105	0.071 (0.022)	0.035	−0.018 (0.813)	0.114	0.064 (0.309)	0.084	0.041 (0.278)	0.140	0.101 (0.407)
Duration of diabetes (yr)		0.067 (0.483)		−0.031 (0.800)		−0.049 (0.676)		−0.130 (0.232)		−0.247 (0.021)
Age (yr)		−0.288 (0.004)		−0.157 (0.197)		−0.057 (0.622)		−0.147 (0.174)		−0.132 (0.202)
BMI (kg/m^2)		0.019 (0.848)		−0.056 (0.639)		−0.292 (0.012)		−0.011 (0.302)		−0.162 (0.114)

Correlations between the glycated indices and the various independent variables are expressed as standard β (*P*-value). Model 1: unadjusted; model 2: adjusted for duration of diabetes, age, BMI.

BMI = body mass index, eAG/fPG ratio = estimated average glucose to fasting plasma glucose ratio, GA/A1c ratio = the ratio of GA to HbA1c, HbA1c = glycated hemoglobin, HOMA-IR = homeostasis model assessment of insulin resistance.

adolescent diabetes. No similar study has been reported yet in this area.

After adjusting for age, BMI, duration of disease, the regression analysis consistently demonstrated a significant relationship between the eAG/fPG ratio and HOMA-IR. However, no significant correlation was observed between the GA/A1c ratio and HOMA-IR after adjusting for the corresponding parameters. These results suggest that eAG/fPG ratio is a better indicator of insulin resistance than GA/A1c ratio.

There are some limitations of our study. First, our study is an observational study not a cohort study. Second, the study was confined to young adult diabetes. The sample size of our study was too small to analyze the data in more detail. Further prospective studies with large sample size are needed especially in adult diabetic patients for the validation of the new parameter. Despite these limitations of our study, we believe that the eAG/fPG ratio is helpful for assessing HOMA-IR at least in young adult diabetes who has only the results of fasting plasma glucose and HbA1c tests.

5. Conclusions

This study shows that the eAG/fPG ratio is more closely associated with HOMA-IR than the GA/HbA1c ratio, suggesting that the eAG/fPG ratio has a more significant implication with Insulin resistance than the GA/HbA1c ratio. Further studies are required to determine the usefulness of eAG/fPG ratio as an indicator of Insulin resistance.

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