Journal of Diabetes and Its Complications 31 (2017) 1127–1131

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Concordance the hemoglobin glycation index with glycation gap using glycated albumin in patients with type 2 diabetes

Mee Kyoung Kim, Jee Sun Jeong, Hyuk-Sang Kwon, Ki Hyun Baek, Ki-Ho Song *

Department of Internal Medicine, The Catholic University of Korea, Seoul, Republic of Korea

ARTICLE INFO

Article history:
Received 2 February 2017
Received in revised form 24 March 2017
Accepted 12 April 2017
Available online 18 April 2017

Keywords:
Hemoglobin glycation index
Glycation gap
Glycated albumin
Type 2 diabetes mellitus
Fructosamine

ABSTRACT

Background: The hemoglobin glycation index (HGI) is an index of differences in the glycation of hemoglobin according to blood glucose level. The glycation gap (G-gap) is an empiric measure of the extent of disagreement between hemoglobin A1C (HbA1C) and glycated albumin (GA). The aim of this study was to investigate the extent of agreement between the HGI and G-gap with respect to GA level, and to elucidate factors related to a high HGI.

Method: Data were obtained from 105 patients with type 2 diabetes, and fasting blood glucose (FBG), HbA1c, and GA values were measured simultaneously. The G-gap was calculated as the difference between the measured and GA-based predicted HbA1c levels. HGI was calculated as the difference between measured and FBG-based predicted HbA1c levels.

Results: The HGI and G-gap were highly correlated according GA ($r = 0.722$, $P < 0.001$). In general, the two indices were similar in terms of both direction and magnitude. The classification of patients as high, moderate, or low glycators based on HGI versus G-gap was consistent for the majority of the population and only 5% of patients were reclassified from high to low or low to high. Fasting C-peptide levels decreased linearly, and the percentage of patients using insulin increased linearly, between the lowest and highest HGI tertile (both $P < 0.05$).

Conclusions: There was 95% agreement between the HGI and G-gap using GA among type 2 diabetes patients. Furthermore, a high HGI was associated with a higher prevalence of insulin use among type 2 diabetes patients.

1. Introduction

Several studies have reported disagreements between hemoglobin A1C (HbA1c) and other measures of glycemic control.[1–6] In a recent study, we provided evidence that the glycation gap (G-gap) based on glycated albumin (GA) is consistent within an individual over time.[1] Although it is derived in different ways, the hemoglobin glycation index (HGI) is the difference between observed and predicted HbA1c levels; the levels are derived from an individual's blood glucose (BG).[2–4] The HGI is calculated in exactly the same way as the G-gap, except that the measured BG replaces GA or fructosamine for obtaining a predicted HbA1c level.[2] The G-gap and HGI are methods for demonstrating biological variation in the relationship between HbA1c and other measures of glycemic control.

BG and GA both reflect the extracellular glucose environment. In contrast, the glycation of hemoglobin occurs within red blood cells (RBCs). To interact with hemoglobin, glucose must first enter RBCs from the plasma space and pass through the RBC membrane into the cytoplasm.[2,3,7] Factors that increase or decrease intracellular glucose levels relative to external plasma glucose levels, or that lead to the exposure of hemoglobin to glucose, cause differences in hemoglobin glycation among individuals.[7] Differences in the hemoglobin glycation relative to BG might be due to differences in the permeability of RBCs to glucose.[2] More recent studies that have compared HbA1c levels by race have consistently demonstrated higher HbA1c levels in East Asian and African-American individuals compared with Caucasians.[8–10] Racial differences in HbA1c levels occur independently of glycemia across the spectrum of glucose tolerance. The G-gap might reflect inter-individual differences in the propensity for hemoglobin glycation independent of glycemia.[11]

A previous study of patients with type 1 DM showed that HGI calculated using the mean BG and G-gap, and measured using fructosamine, were highly correlated.[2]

We aimed to investigate whether G-gap and HGI are highly correlated in patients with type 2 DM as shown in patients with type 1 DM. Patients with type 2 diabetes have quite different clinical features characterized by older age, high BMI, presence of insulin resistance and relatively preserved beta cell function, as compared with those

Disclosure: The authors declared no conflict of interest.

* Corresponding author at: Department of Internal Medicine, Yeouido St. Mary's Hospital, The Catholic University of Korea, 10, 63-ro,Youngdeungpo-gu, Seoul, Republic of Korea 07345. Tel.: +82 2 3779 1557; fax: +82 2 780 3132.
E-mail address: kihos@catholic.ac.kr (K-H. Song).

http://dx.doi.org/10.1016/j.jdiacomp.2017.04.015
1056-8727/

Table 1
Anthropometric and biochemical characteristics of the study subjects stratified according to the hemoglobin glycation index (HGI).

	Low of HGI	Moderate of HGI	High of HGI	P-value[†]
N	35	35	35	
HGI	−1.10 ± 0.42	−0.09 ± 0.27	**1.09 ± 0.51**[*]	<0.001
G-gap	−0.45 ± 0.62	0.05 ± 0.61	**0.79 ± 0.71**[*]	<0.001
FBG (mg/dL)	144 ± 42	144 ± 38	159 ± 48	0.250
HbA1c (%)	6.7 ± 0.9	7.9 ± 0.6	**9.1 ± 0.9**[*]	<0.001
GA (%)	17.0 ± 3.5	21.2 ± 3.8	**24.8 ± 4.8**[*]	<0.001
Age (years)	57.5 ± 12.6	56.4 ± 13.2	54.5 ± 11.5	0.315
Sex (men)	13 (38%)	14 (40%)	19 (54%)	0.336
DM duration (years)	14.1 ± 10.2	15.3 ± 7.8	17.1 ± 13.1	0.511
BMI (kg/m^2)	27.1 ± 5.1	26.1 ± 4.3	25.3 ± 4.0	0.282
eGFR (mL/min/1.73m^2)	80.7 ± 36.5	79.8 ± 29.8	88.1 ± 38.7	0.563
U_{ACR} ≥ 100 mg/g creatinine (%)	7 (20%)	9 (26%)	6 (17%)	0.719
Hemoglobin (g/dL)	13.7 ± 1.6	13.5 ± 1.6	13.9 ± 1.8	0.683
Albumin (g/dL)	4.2 ± 0.4	4.3 ± 0.5	**4.4 ± 0.4**[*]	0.153
Fasting c-peptide (ng/mL)	4.06 ± 2.07	3.16 ± 1.98	**2.73 ± 2.21**[*]	0.106
Use of insulin (%)	6 (18%)	15 (43%)	**22 (63%)**[*]	0.005

HGI, hemoglobin glycation index; G-gap, glycation gap; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; GA, glycated albumin; BMI, body mass index; eGFR, estimated glomerular filtration rate.
[†] P-value is an overall P value across the three groups.
[*] P-value <0.05 compared between the T1 and T3 groups.

with type 1 diabetes. It will be important to determine whether the same correlations exist in patients with type 2 DM. There are many factors that are related to the glycability of hemoglobin and of other glycated serum proteins in diabetes.[1] Possible factors are age, body mass index (BMI), visceral obesity, absolute value of HbA1c, kidney function and treatment with insulin. We have previously demonstrated that G-gap was associated with visceral obesity and kidney function in type 2 diabetes.[1] In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[3] insulin is more likely to be prescribed for individuals with high HGI. So, we aimed to explore the factors affecting HGI.

2. Methods

2.1. Subjects

The retrospective cohort consisted of Korean patients with type 2 diabetes who attended clinics at Yeoido St. Mary's Hospital between 2010 and 2012. Patients whose fasting blood glucose (FBG), HbA1c, and GA levels had been measured on the same day were selected. The exclusion criteria included any known hemoglobinopathy, anemia (hemoglobin <10 g/dL), hypoalbuminemia (serum albumin <3.0 g/dL), renal failure (creatine clearance <3 0 mL/min/1.73 m^2), pregnancy, and liver cirrhosis. Finally, 105 patients were enrolled. The protocol was reviewed and approved by the Institutional Review Board (IRB) of The Catholic University of Korea. The requirement for informed consent was waived by the IRB because information was recorded in routine analyses in such a manner that patients could not be identified, either directly or through identifiers linked to the subjects.

2.2. Laboratory measurements

All blood samples were taken in the morning following a minimum 8-h fast. The hexokinase method with the Beckman Glucose Analyzer (Beckman Coulter Inc., Fullerton, CA, USA) was used to measure blood glucose. HbA1C levels were measured using automated high performance liquid chromatography (HPLC) (HLC-723 G7; Tosoh Corp., Tokyo, Japan); the reference range was 4.0–6.0%. The intra- and inter-assay coefficients of variation were 0.89% and 1.56%, respectively, at an HbA1C level of 5.6%. GA levels were measured using a Toshiba 200FR analyzer (Toshiba Medical Systems Co., Tokyo, Japan) and an enzymatic method involving an albumin-specific proteinase, ketoamine oxidase, and an albumin detection reagent (Lucica GA-L; Asahi Kasei Pharma Co., Tokyo, Japan).

2.3. HGI calculation

HGI was defined as the difference between the measured HbA1c level and that predicted from FBG levels, calculated using the HbA1c-FBG regression equation. The regression equation is based on data obtained from all of the study subjects (N = 105). The correlation between HbA1c and FBG was examined using linear regression analysis. The following equation was established (Supplemental Fig. 1): Predicted HbA1c level = 0.0143 × FBG [mg/dL] + 5.828 (r = 0.67; P < 0.001).

G-gaps were calculated using the method of Cohen et al.[5,6] Briefly, each G-gap was defined as the difference between the measured HbA1c level and that predicted from the GA level, as calculated using the HbA1c-GA regression equation. The regression equation was derived from our previous study[1]: Predicted HbA1c level = 0.146 × GA level + 4.722 (r = 0.749; P < 0.001).

2.4. Statistical analysis

The clinical characteristics of the type 2 diabetic patients were compared by HGI tertile. Chi-squared tests (χ^2) and analysis of variance (ANOVA) were used to compare proportions and means, respectively, between groups. Pearson's correlation coefficients were calculated between the HGI and experimental variables. Multiple linear regression models were used to identify factors affecting the HGI. Age, sex, BMI, and albumin and hemoglobin levels were the adjusted-for confounding variables. All data were analyzed using the SPSS statistical package (SPSS Inc., Chicago, IL, USA), and a P value <0.05 was considered to indicate statistical significance.

3. Results

3.1. Clinical characteristics of the study subjects according to the HGI

Despite FBG being equal across the HGI tertiles, G-gap, HbA1c, and GA increased proportionally from the lowest to the highest HGI tertile (Table 1). The numbers of patients that used insulin increased linearly from the lowest to the highest HGI tertile. Patients with a high HGI (T3) were more likely to have a long duration of diabetes and low fasting C-peptide levels compared with those with a low HGI (T1). The high HGI group was more likely to receive insulin (P for trend = 0.005; Table 1).

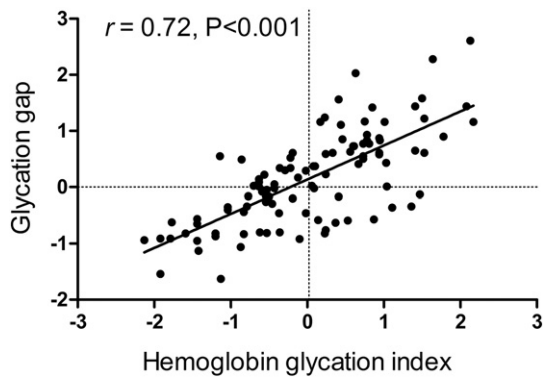

Fig. 1. Correlation between hemoglobin glycation index (HGI) and glycation gap using glycated albumin.