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Original Article

The hemoglobin glycation index correlates with efficacy of metformin therapy in individuals newly diagnosed with type 2 diabetes mellitus

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Abstract: Introduction: Metformin is a cornerstone of glucose-lowering therapy in type 2 diabetes mellitus (T2DM). Biologic variations in glucose metabolism, as reflected by the hemoglobin glycation index (HGI), may influence the therapeutic effect of this medication. This study examined the correlation between HGI and efficacy of metformin in individuals newly diagnosed with T2DM. Method: This observational study enrolled 328 individuals with new onset T2DM between December 2013 and November 2015. Participants exceeded 21 years of age and had received metformin for at least 12 months after diagnosis. Individuals who received antidiabetic medications in addition to metformin were excluded. Efficacy of metformin was compared between equally sized subgroups stratified by baseline HGI. Result: All participants attained glycemic improvement after metformin therapy, with enhanced efficacy in individuals with high HGI after adjusting for pretreatment glycemic status. Differences in therapeutic effect between HGI subgroups were maintained after one year of treatment. Even among people with comparable pretreatment hemoglobin A1c, the high HGI subgroup also demonstrated better clinical response to metformin therapy. Conclusion: HGI correlated with efficacy of metformin therapy in individuals with T2DM. Glycemic improvement was enhanced in participants with high HGI at diagnosis, for whom additional antidiabetic medications may be unnecessary. HGI is a promising guide for personalized glycemic treatment in individuals with new onset T2DM.

Keywords: Hemoglobin glycation index, diabetes mellitus, metformin, treatment outcome

Introduction

Type 2 diabetes mellitus (T2DM) is a developing epidemic in Asia that affects a sizable proportion of the adult population [1, 2]. Metformin has remained a cornerstone of glucose-lowering therapy in T2DM endorsed by both the American Diabetes Association and International Diabetes Federation, which advocate the use of this medication at diagnosis [3, 4]. Metformin effectively lowered blood glucose concentration in randomized placebo-controlled studies and demonstrated benefits beyond its glucose-lowering effect in individuals with diabetes [5, 6].

However, metformin is not uniformly effective among all patients. It enables only a subset of recipients to attain hemoglobin A1c (HbA1c) target [7, 8]. This variation in therapeutic effect may reflect individual differences in glucose metabolism. Considering the importance of early treatment to glycemic target and the cost-effectiveness of metformin [9], a predictor of its efficacy will streamline treatment decisions in individuals newly diagnosed with T2DM.

The discrepancy between observed HbA1c and HbA1c predicted from fasting plasma glucose (FPG), termed the hemoglobin glycation index (HGI), reflects biologic variations in glucose metabolism [10]. This index remains consistent over time and likely represents an individual's unique level of glucose homeostasis [11]. Since metformin alters glucose metabolism by inhibiting hepatic gluconeogenesis [12], an individu-

Table 1. Demographic characteristics of the hemoglobin glycation index subgroups

	Low HGI (*n*=109)	Moderate HGI (*n*=109)	High HGI (*n*=110)	*P* value
Age (years)	58 ± 13	61 ± 13	60 ± 12	0.29
Gender				
Female	64 (58.7)	61 (56.0)	46 (41.8)	0.027
Male	45 (41.3)	48 (44.0)	64 (58.2)*	
BMI (kg/m^2)	26.1 ± 4.1	26.0 ± 5.0	26.3 ± 4.3	0.907
SBP (mm Hg)	132 ± 15.7	131 ± 17.7	133 ± 14.5	0.734
Creatinine (mg/dL)	0.83 ± 0.21	0.84 ± 0.25	0.84 ± 0.23	0.83
HDL-C (mg/dL)	48 ± 13	47 ± 12	44 ± 10	0.145
LDL-C (mg/dL)	114 ± 39.5	111 ± 36.5	110 ± 32.0	0.661
TG (mg/dL)	136 ± 66.5	151 ± 74.0	140 ± 83.8	0.476
Metformin dose (mg)	1450 ± 435	1422 ± 420	1540 ± 429	0.1

Data are expressed as the mean with standard deviation for continuous variables or number (%) for categorical variables. *: $P < 0.05$ compared to the low HGI subgroup. Differences between subgroups are compared by ANOVA or χ^2 test. Abbreviations: HGI, hemoglobin glycation index; BMI, body mass index; SBP, systolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TG: triglyceride; HbA1c: hemoglobin A1c.

al's set-point of glucose homeostasis at diagnosis may determine the therapeutic efficacy of this medication.

This study examined the relationship between HGI and efficacy of metformin therapy in individuals with new onset T2DM.

Materials and methods

Study participants

This observational study was conducted at a medical center in Taiwan. Patients who visited the endocrinology outpatient department between 1st December 2013 and 30th November 2015 were screened for eligibility. Inclusion criteria were individuals exceeding 21 years of age, with new onset T2DM, who had received at least 12 months of treatment with metformin after diagnosis. Exclusion criteria involved patients who received antidiabetic medications in addition to metformin or who discontinued metformin within 12 months of treatment. Individuals with hemoglobin disorders, pregnancy, or anemia were also ineligible. The study was approved by the ethics committee of the medical center.

Clinical and laboratory measurements

Demographic information including age, sex, weight, height, lipid profile, creatinine, and blood pressure at diagnosis of diabetes were extracted from electronic medical records. Body mass index was calculated by dividing the weight in kilograms by the square of height in meters. HbA1c and FPG were collected for each participant at diagnosis and at six month intervals for up to one year. Metformin dose for each individual was defined as the daily quantity received for the longest duration in the first year of treatment.

Calculation of HGI

HbA1c and FPG measurements from all participants were used to establish a regression equation describing the linear relationship between these variables. Predicted HbA1c was calculated by substituting baseline FPG into the linear regression equation. The difference between an individual's observed and predicted HbA1c was defined as HGI [13].

Efficacy of metformin therapy

Individuals were stratified according to baseline HGI into three subgroups of equal size. Efficacy of metformin, as indicated by the reduction in HbA1c, was compared between these subgroups after adjusting for pretreatment HbA1c. To further reduce any confounding effect of baseline glycemic status, a subgroup analysis assessed whether the HGI subgroups also correlate with clinical response when the intergroup difference in pretreatment HbA1c was negligible. This was done by selecting a subpopulation with similar baseline HbA1c between 6.5% and 7.5%.

Statistical analysis

Demographic data for the HGI subgroups were compared using analysis of variance (ANOVA) or χ^2 test. Paired t-test enabled comparison of an individual's HbA1c at diagnosis and after receiving metformin therapy. Changes in HbA1c were compared between HGI subgroups using ANOVA after adjusting for pretreatment HbA1c. Calculations were based on a two-sided hypothesis with $P < 0.05$ interpreted as significant. Statistical analysis was performed using Statistical Package for the Social Sciences (version 22.0; SPSS, Chicago, IL).

Table 2. Glycemic improvement in the hemoglobin glycation index subgroups after metformin therapy

Treatment duration (months)	Serum HbA1c (%)					
	Low HGI (*n*=109)	*P* value	Moderate HGI (*n*=109)	*P* value	High HGI (*n*=110)	*P* value
0	6.9 ± 1.4		7.1 ± 0.7		9.6 ± 1.8	
6	6.4 ± 0.7	< 0.001	6.5 ± 0.8	< 0.001	6.7 ± 1.0	< 0.001
12	6.3 ± 0.7	< 0.001	6.4 ± 0.7	< 0.001	6.7 ± 1.1	< 0.001

Data are expressed as the mean with standard deviation. Changes from baseline HbA1c are compared by paired t-test. Abbreviations: HbA1c, glycated hemoglobin A1c; HGI, hemoglobin glycation index.

Table 3. Comparison of therapeutic response between the hemoglobin glycation index subgroups after metformin therapy

Treatment duration (months)	Changes in serum HbA1c (%)			
	Low HGI (*n*=109)	Moderate HGI (*n*=109)	High HGI (*n*=110)	*P* value
6	-0.6 ± 1.5	-0.7 ± 1.0*	-2.8 ± 2.0*,#	< 0.001
12	-0.7 ± 1.7	-0.7 ± 1.0*	-2.9± 2.0*,#	< 0.001

Data are expressed as the mean with standard deviation. *: $P < 0.05$ compared to the low HGI subgroup; #: $P < 0.05$ compared to the moderate HGI subgroup. Differences between subgroups are compared by ANOVA after adjusting for pretreatment HbA1c. Changes in serum HbA1c are calculated relative to baseline data. Abbreviations: HbA1c, glycated hemoglobin A1c; HGI, hemoglobin glycation index.

Table 4. Comparison of therapeutic response between the hemoglobin glycation index subgroups for participants with similar pretreatment glycemic status

Treatment duration (months)	Changes in serum HbA1c (%)			
	Low HGI (*n*=42)	Moderate HGI (*n*=42)	High HGI (*n*=42)	*P* value
6	-0.3 ± 0.9	-0.4 ± 1.0*	-0.5 ± 0.7*,#	< 0.001
12	-0.4 ± 0.8	-0.5 ± 0.6*	-0.5 ± 0.7*,#	< 0.001

Data are expressed as the mean with standard deviation. *: $P < 0.05$ compared to the low HGI subgroup; #: $P < 0.05$ compared to the moderate HGI subgroup. Participants in the subgroup analysis had similar pretreatment HbA1c between 6.5% and 7.5%. Differences between subgroups are compared by ANOVA. Changes in serum HbA1c are calculated relative to baseline data. Abbreviations: HbA1c, glycated hemoglobin A1c; HGI, hemoglobin glycation index.

Results

The study enrolled 328 individuals with T2DM who were stratified according to baseline HGI into three subgroups of equal size. Demographic characteristics of the subgroups are presented in **Table 1**. Individuals in the high HGI category were more likely to be men with inadequate glycemic control relative to other subgroups. Participants in the HGI subgroups received comparable dose of metformin during the first year of therapy.

As shown in **Table 2**, participants demonstrated substantially reduced HbA1c after receiving metformin therapy. Even after adjusting for pretreatment HbA1c, individuals in the high HGI category experienced better glycemic improvement relative to other subgroups, as documented in **Table 3**. After six months of therapy, the mean HbA1c decreased by 2.8%, 0.7%, and 0.6% in the high, moderate, and low HGI subgroups, respectively. Participants in the high HGI subgroup experienced an overall 2.9% reduction in HbA1c after receiving metformin for one year.

In a subpopulation with comparable baseline HbA1c between 6.5% and 7.5%, HGI also correlated with efficacy of metformin therapy, as shown in **Table 4**. After six months of therapy, individuals with high HGI attained a mean HbA1c reduction of 0.5%, which was better than the glycemic improvement in other subgroups. After one year, participants in both moderate and high HGI subgroups demonstrated better clinical response relative to individuals with low HGI.

Discussion

Metformin is an indispensable antidiabetic medication in T2DM. Apart from its neutral effect on body weight and minimal risk of hypoglycemia, this medication also favorably affects the cardiovascular system and insulin sensitivity [14-16]. Metformin is among the most effective oral antidiabetic drugs and remains the first-line treatment for individuals with T2DM [17]. All patients should therefore receive this

medication at diagnosis in the absence of contraindications.

HGI is an established measure of glucose metabolism [18], which correlated with the glucose-lowering effect of metformin in the present study. Enhanced glycemic improvement in the high HGI subgroup may represent alterations in glucose homeostasis as mediated by metformin [19]. Importantly, HGI also correlated with clinical response even in individuals with similar pretreatment HbA1c. This observation suggests that HGI can influence clinical response independently from baseline HbA1c.

In the context of this study, people with high HGI will more frequently attain glycemic target with metformin monotherapy, whereas individuals with low HGI may require multiple antidiabetic agents due to their attenuated response to metformin alone. Decision making based on HGI can prevent overuse of second-line antidiabetic medications in the high HGI subgroup and enable early treatment to target with combination glucose-lowering agents in the low HGI category.

HGI is an expedient indicator of glucose homeostasis in clinical practice. This index can be obtained without performing additional laboratory tests other than FPG and HbA1c. A linear regression equation for predicting HbA1c from FPG will need to be established beforehand using a reference population. Unlike HbA1c measurement, which is influenced by non-glycemic factors such as oxidative stress [20], HGI demonstrates minimal variability within an individual [21]. The observation in this study that HGI correlated with therapeutic response independently from baseline HbA1c suggests that HGI can provide additional information to clinicians.

This study enrolled individuals who received metformin exclusively after diagnosis of T2DM, which precluded the confounding effects of multiple antidiabetic agents. By excluding individuals with known hemoglobin disorders, the impact of these conditions on HbA1c measurement was diminished. To demonstrate that HGI correlates with clinical response regardless of initial glycemic status, further analysis was performed in a subpopulation with minimal intergroup difference in pretreatment HbA1c between the HGI subgroups. Enrolled participants were monitored at the same medical center to minimize potential discrepancy in laboratory assays.

Several limitations may arise from the study design. Adherence to therapy certainly influenced glycemic control, and factors that precipitate hyperglycemia such as infection could not be ascertained. Since HGI is derived from HbA1c measurement, investigators have suggested that this index cannot be truly independent from HbA1c [22]. Nonetheless, since HGI is largely independent of non-glycemic factors such as oxidative stress, it may be a more reliable indicator of glucose metabolism than HbA1c.

In conclusion, HGI correlated with efficacy of metformin therapy in individuals with new onset T2DM. Individuals with high HGI at diagnosis experienced better glycemic improvement relative to participants in other subgroups. Moreover, the HGI subgroups also correlated with clinical response even with minimal intergroup difference in pretreatment HbA1c. Overall, HGI is a promising guide for tailoring glucose-lowering therapy in individuals newly diagnosed with T2DM.

Disclosure of conflict of interest

None.

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