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Hemoglobin A1C but not Glycated Albumin Overestimates Glycemic Control due to Iron Deficiency in Pregnant Women with Diabetes

Tatsumi Moriya[1], Madoka Matsubara[1] and Masafumi Koga[2]*

[1]Health Care Center, Kitasato University, Kanagawa, Japan
[2]Department of Internal Medicine, Kawanishi City Hospital, Hyogo, Japan

Abstract

Background: Pregnant women are frequently complicated with iron deficiency. Because Hemoglobin A1c (HbA1c) shows an apparently high value in patients with iron-deficiency, HbA1c was reported to be elevated due to iron deficiency in pregnant women with or without diabetes. In the present study, we investigated whether HbA1c or Glycated Albumin (GA) accurately reflects glycemic control state estimated from the Mean Blood Glucose (MBG) obtained by Continuous Glucose Monitoring (CGM) in pregnant women with diabetes.

Methods: We studied 20 pregnant women with diabetes whose glycemic control was stable and CGM was performed to determine MBG. The estimated HbA1c and GA were calculated from the MBG, and the measured values were compared with the estimated values. Correlations between Mean Corpuscular Hemoglobin (MCH), an index of iron-deficiency, and continuous variables were examined.

Results: HbA1c was not significantly correlated with GA. The measured GA was not significantly different from the estimated GA (16.0 ± 2.7% vs. 16.0 ± 1.8%, P=0.982). On the other hand, the measured HbA1c was significantly higher than the estimated HbA1c [6.4 ± 0.9% (46.3 ± 10.3 mmol/mol) vs. 5.6 ± 0.5% (38.2 ± 5.4 mmol/mol), P<0.001]. The measured HbA1c (R= –0.598, P=0.005) and the measured HbA1c/estimated HbA1c ratio (R= –0.566, P=0.009) showed significant inverse correlations with MCH.

Conclusions: HbA1c overestimates glycemic control due to iron deficiency in pregnant women with diabetes, whereas GA accurately reflected their glycemic control. Therefore, GA is a better index of glycemic control than HbA1c in pregnant women with diabetes.

Keywords: Glycated albumin; Hba1c; Pregnancy; Iron deficiency; Glycemic control

Abbreviations: HbA1c: Hemoglobin A1c; GA: Glycated Albumin; MBG: Mean Blood Glucose; CGM: Continuous Glucose Monitoring; MCH: Mean Corpuscular Hemoglobin

Introduction

In pregnant women with diabetes mellitus and women with gestational diabetes, intensive glycemic control during pregnancy is necessary in order to lower the risk of intrauterine fetal death, fetal growth disorders and maternal complications [1,2]. The extent of nonenzymatic glycation of proteins increases in patients with diabetes. Of these glycated proteins, hemoglobin A1c (HbA1c) is widely used as the current standard marker for monitoring chronic glycemic control [3,4], and represents an important target for treatment of patients with diabetes [5].

HbA1c measurements are known to be profoundly influenced by erythrocytes turnover, in addition to plasma glucose levels [6,7]. Blood dilution-related anemia is known to be frequently observed in pregnancy. Iron-deficiency anemia is also often observed, caused by the increased demands for iron in pregnancy [8]. HbA1c levels have been shown to be higher in relation to glycemia in patients with iron deficiency anemia [9-11]. We have shown that HbA1c, but not Glycated Albumin (GA), is elevated due to iron deficiency in pregnant women with or without diabetes [12,13].

It has been shown that continuous glucose monitoring (CGM) is useful for evaluating glycemic control during pregnancy [14]. In the present study, we determined the mean blood glucose (MBG) by conducting CGM in pregnant women with diabetes to examine whether HbA1c and GA show a close correlation with MBG or not.

Methods

Study patients

Twenty pregnant women with diabetes (7 patients with type 1 diabetes mellitus and 13 patients with type 2 diabetes mellitus) whose glycemic control was stabilized by treatment at the Department of Endocrinology, Diabetes and Metabolism in Kitasato University Hospital from March 2007 to July 2011 were included (Table 1). Patients with more than a 0.5% change in HbA1c in the 2-month period preceding the CGM and patients complicated with hepatic diseases, renal diseases or thyroid diseases were excluded. Pregnant women who used the iron supplement or received the iron preparation were also excluded.

The reported investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000. The institutional review board approved this study, and all patients provided written informed consent.

***Corresponding author:** Masafumi Koga, Department of Internal Medicine, Kawanishi City Hospital, 5-21-1 Higashi-Uneno, Kawanishi, Hyogo 666-0195, Japan, Tel: +81-72-794-2321; Fax: +81-72-794-6321; E-mail: m-koga@kawanishi-city-hospital.com

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n	20
Type 1 diabetes/type 2 diabetes	7/13
Age (years)	33.6 ± 3.7
Body mass index (kg/m^2)	26.2 ± 5.2
Diabetes duration (years)	4.2 ± 3.4
Gestational age (weeks)	19.3 ± 8.6
Diabetes therapy (diet/insulin)	3/17
MBG (mg/dl)	110 ± 14
HbA1c (%)	6.4 ± 0.9
HbA1c (mmol/mol)	46.3 ± 10.3
GA (%)	16.0 ± 2.7
RBC (x10^6/μl)	4.26 ± 0.43
Hb (g/dl)	12.4 ± 1.0
Ht (%)	36.8 ± 2.8
MCH (pg)	29.2 ± 2.3

MBG: Mean Blood Glucose; Hba1c: Hemoglobin A1c; GA: Glycated Albumin; RBC: Red Blood Cell; Hb: Hemoglobin; Ht: Hematocrit; MCH: Mean Corpuscular Hemoglobin

Table 1: Clinical characteristics of the study patients.

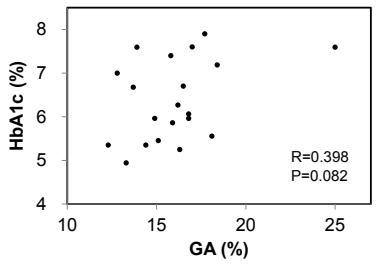

Figure 1: Correlation between GA and HbA1c in 20 pregnant women with diabetes.

Measurements

Blood samples were taken at overnight fasting in the early morning and were measured immediately. HbA1c was measured by High Performance Liquid Chromatography (HPLC). HbA1c as a Japan Diabetes Society (JDS) value (%) was converted to a National Glycohemoglobin Standardization Program (NGSP) value or an International Federation of Clinical Chemistry (IFCC) value (%) in accordance with the official equation [15]. GA was determined by enzymatic methods using albumin-specific protease, ketoamine oxidase and albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan) [16]. Blood cell counts, hematocrit, hemoglobin, and mean corpuscular hemoglobin (MCH) were measured by an automated hematology system. Inter-assay coefficient variations (CVs) of HbA1c and GA were 0.49% and 1.35%, respectively.

CGM (CGMS® System Gold manufactured by Medtronic MiniMed) was performed for about 72 hours, and the data of two days were averaged using the data collected for 48 hours on Days 2 and 3 after wearing [17]. Calibration during wearing was performed four times or more a day using MediSafe Mini® (TERUMO Corporation, Tokyo, Japan). The estimated HbA1c values were calculated using MBG obtained by CGM according to the following conversion formula established by Nathan et al. [18].

Estimated HbA1c (%)=[MBG (mg/dl) + 46.7] / 28.7

Since the GA/HbA1c ratios in patients with type 1 and type 2 diabetes mellitus were 3.1 and 2.7, respectively [19], the estimated GA was determined by multiplying the estimated HbA1c by 3.1 and 2.7 for patients with type 1 and type 2 diabetes mellitus, respectively.

Statistical analyses

The data were expressed as mean ± SD. Paired Student's t tests were used to estimate the level of significance of differences between measured values and estimated values. To analyze the effects of explanatory variables, single linear univariate regression analyses were performed. The StatView computer program (version 5.0 for Windows; Abacus Concepts, Berkeley, CA) was used for all statistical analyses. The level of statistical significance was established as less than 5%.

Results

In 20 pregnant women with diabetes, the age was 33.6 ± 3.7 years old, the body mass index was 26.2 ± 5.2 kg/m^2, the diabetes duration was 4.2 ± 3.4 years, and the gestational period was 19.3 ± 8.6 weeks (Table 1). Three patients with type 2 diabetes mellitus underwent diet therapy, and the other patients underwent insulin therapy. The MBG obtained by CGM, HbA1c and GA were 110 ± 14 mg/dl, 6.4 ± 0.9% (46.3 ± 10.3 mmol/mol) and 16.0 ± 2.7%, respectively. RBC, Hb, Ht and MCH were 4.26 ± 0.43×106/μl, 12.4 ± 1.0 g/dl, 36.8 ± 2.8% and 29.2 ± 2.3 pg, respectively.,

HbA1c was not significantly correlated with GA (R=0.398, P=0.082) (Figure 1). The measured GA showed a significant correlation with the estimated GA (R=0.707, P<0.001, y=1.03x–0.53), and there was no significant difference between the measured GA and the estimated GA (16.0 ± 2.7% vs. 16.0 ± 1.8%, P=0.982) (Figure 2A). The regression line between the measured GA and the estimated GA was almost consistent with the straight line of y =x. On the other hand, the measured HbA1c showed no significant correlation with the estimated HbA1c (R= 0.422, p=0.064), and the measured HbA1c was significantly higher than the estimated HbA1c [6.4 ± 0.9% (46.3 ± 10.3 mmol/mol) vs. 5.6 ± 0.5% (38.2 ± 5.4 mmol/mol), P<0.001] (Figure 2B). The regression line between the measured HbA1c and the estimated HbA1c shifted upwards compared with the straight line of y=x.

MCH, an index of the iron deficiency, showed no significant correlation with MBG (R=–0.136, P=0.568) and GA (R=-0.289, P=0.217), whereas MCH showed a significant inverse correlation with HbA1c (R=–0.598, P=0.005) (Figure 3). MCH showed no significant

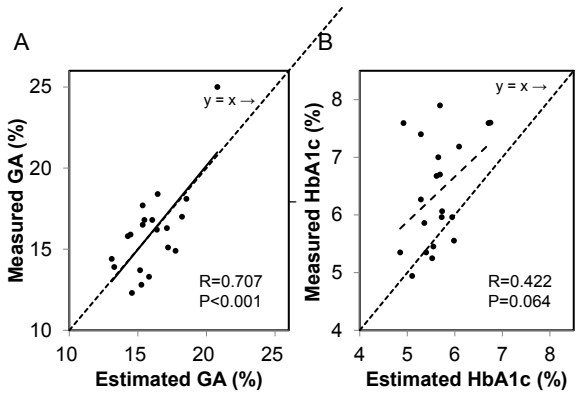

Figure 2: Correlation between the measured values and the estimated values for GA (A) and HbA1c (B) in 20 pregnant women with diabetes The line of y = x is shown with a dotted line and the regression lines between the measured values and the estimated values are shown in a straight line (A) and a dashed line (B).

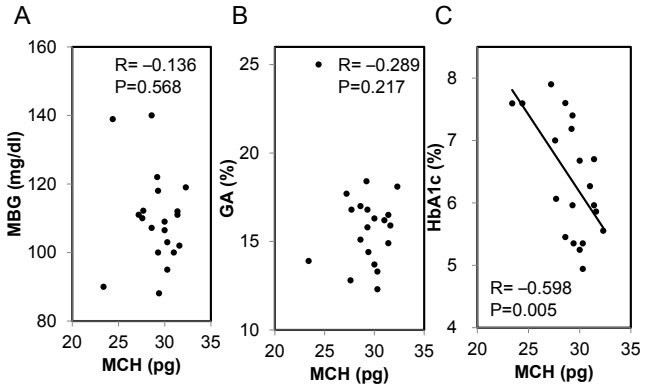

Figure 3: Correlation between mean corpuscular hemoglobin (MCH) and mean blood glucose (MBG) (A), GA (B) and HbA1c (C) in 20 pregnant women complicated with diabetes.

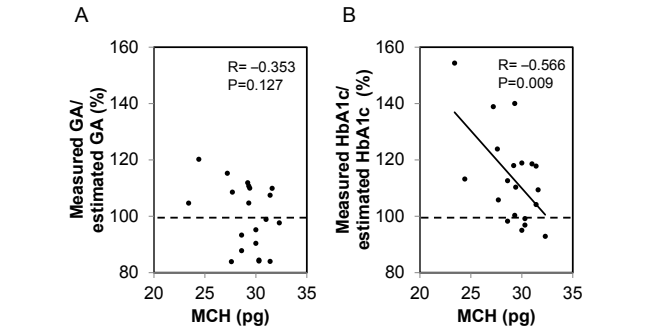

Figure 4: Correlation between mean corpuscular hemoglobin (MCH) and the measured GA/estimated GA ratio (A) and the measured HbA1c/estimated HbA1c ratio (B) in 20 pregnant women with diabetes. The measured GA/estimated GA ratio and the measured HbA1c/estimated HbA1c ratio of 100% is shown with a dashed line.

correlation with the measured GA/estimated GA ratio (R=–0.353, P=0.127), whereas MCH showed a significant inverse correlation with the measured HbA1c/estimated HbA1c ratio (R=–0.566, P=0.009) (Figure 4). The MCH also showed a significant inverse correlation with the measured/estimated HbA1c ratio (R=-0.664, P=0.013), but not the measured GA/estimated GA ratio (R=-0.047, P=0.890) in the pregnant women with type 2 diabetes mellitus. On the other hand, the MCH showed no significant correlations with the both ratios in the pregnant women with type 1 diabetes mellitus (data not shown).

Discussion

In the present study, HbA1c overestimates glycemic control due to iron deficiency in pregnant women with diabetes, whereas GA accurately reflected their glycemic control. MBG as well as GA showed no significant correlation with MCH, but HbA1c showed a significant inverse correlation with MCH. This result was the similar phenomenon in pregnant women without diabetes reported previously [12]. It is known that iron deficiency itself including iron deficiency anemia does not influence glycemic control but makes HbA1c apparently high [9-11,20]. The findings obtained in the present study were compatible with these previous results. It is considered that the measured HbA1c showed no significant correlation with the measured GA or the estimated HbA1c because it is elevated by iron deficiency. As a result, HbA1c may not accurately reflect glycemic control in pregnant women with diabetes.

If GA or HbA1c accurately reflects glycemic control, the measured value/estimated value ratio should become 100%. For GA, this ratio was distributed between 80% and 120%. On the other hand, the measured HbA1c/estimated HbA1c ratio showed markedly high values of 140% to 160% in some patients (Figure 4). Since this ratio showed a significant inverse correlation with MCH, the stronger the degree of iron deficiency, the larger the difference between HbA1c levels and glycemic control state. On the other hand, hemoglobin showed no significant correlation with HbA1c or the measured HbA1c/estimated HbA1c ratio (data not shown). This result suggests that hemoglobin does not necessarily reflect iron deficiency because hemoglobin during pregnancy is also influenced by blood dilution-related anemia.

It is known that hypoglycemia induces perinatal complications together with hyperglycemia [20]. HbA1c in patients with iron deficiency shows apparently high values, so if treatment for diabetes is enforced based on HbA1c levels during pregnancy, it induces overtreatment for diabetes and the risk of hypoglycemia, and hence the frequency of perinatal complications may increase. It was reported that, in pregnant women with diabetes and patients with gestational diabetes, the frequency of perinatal complications in patients with high GA value was significantly higher than in those with low GA value, but there was no significant difference between patients with high HbA1c value and those with low HbA1c value [21]. This result might be explained by that hypoglycemia was induced when overtreatment for diabetes was applied in patients apparently showing high HbA1c.

HbA1c did not reflect glycemic control due to iron deficiency, whereas GA accurately reflected glycemic control because it is not influenced by iron deficiency state [12,13,22]. GA is known to reflect intermediate-term glycemic control in comparison with HbA1c [23,24]. Since it is necessary to improve glycemic control in a short time during pregnancy, the utility of GA as an index of glycemic control during pregnancy has been proposed [22]. In addition, GA reflects glycemic control more accurately than HbA1c during pregnancy, and so it is considered desirable to use GA as an index of glycemic control during pregnancy instead of HbA1c.

The present study has several limitations. First, there were small number of patients; it is necessary to verify the present finding using large number of pregnant women with diabetes in the future. Second, the MCH showed no significant correlation with the measured value/estimated value ratios of HbA1c and GA in pregnant women with type 1 diabetes mellitus. Therefore, it is necessary to verify the present findings using large number of pregnant women with type 1 diabetes. Third, since this was a retrospective study, the gestational period was not constant when CGM was performed; it is necessary to conduct a prospective study in a certain gestational period. Forth, it is considered that HbA1c and GA reflect glycemic control in the past 1 or 2 months and that in the past 2 weeks, respectively; simultaneous determination of these values with CGM is another issue. Fifth, the present study could not examine the relationship between perinatal complications and the indices of glycemic control; it is necessary to perform CGM at a certain time and to examine which of MBG, HbA1c or GA at that time is related to perinatal complications. It is also necessary to examine the relationship between perinatal complications and the variation of blood glucose obtained with CGM including Standard Deviation (SD) or Mean Amplitude of Glycemic Excursions (MAGE).

In conclusion, HbA1c overestimates glycemic control due to iron deficiency during pregnancy. On the other hand, GA accurately reflected glycemic control during pregnancy because it is not influenced by iron deficiency. In order to reduce perinatal complications, it is important to

achieve good glycemic control using GA as an index of glycemic control instead of HbA1c in pregnant women with diabetes.

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