Complications in Infants of Diabetic Mothers Related to Glycated Albumin and Hemoglobin Levels During Pregnancy

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Received Aug 21, 2015; received in revised form Dec 3, 2015; accepted Feb 5, 2016
Available online 2 April 2016

**Background:** This study was conducted to investigate whether glycated albumin is a useful glycemic marker from the point of view of infant complications for monitoring glycemic control in pregnant women with diabetes or gestational diabetes mellitus.

**Methods:** We retrospectively studied 42 Japanese infants of diabetic mothers and their mothers at our facility between May 2010 and July 2013. The mean glycated albumin and glycated hemoglobin levels were compared between mothers of infants with complications and those without complications. We used 15.8% as the cutoff value of glycated albumin and calculated the sensitivity and specificity of items that were significantly different between the two groups.

**Results:** Glycated albumin was significantly higher in mothers of infants with hypoglycemia (15.5 ± 1.8 vs. 13.8 ± 1.2%, p = 0.001), respiratory disorders (15.6 ± 1.8 vs. 13.9 ± 1.2%, p < 0.001), hypocalcemia (15.7 ± 2.1 vs. 14 ± 1.2%, p = 0.004), myocardial hypertrophy (15.2 ± 1.9 vs. 13.7 ± 1%, p = 0.007), and large-for-date status (15.8 ± 1.9 vs. 14 ± 1.3%, p = 0.002). By contrast, considering hypoglycemia, glycated hemoglobin was not significantly different between the two groups. The sensitivity and specificity with 15.8% as the cutoff value of glycated albumin were as follows: hypoglycemia (70% and 81.2%), respiratory disorders (61.5% and 82.8%), hypocalcemia (62.5% and 84.4%), myocardial hypertrophy (87.5% and 79.4%), and large-for-date status (75% and 85.3%).

**Conclusion:** Glycated albumin is a useful marker of glycemic control considering infant complications during pregnancy. This study also suggests that evaluating both glycated hemoglobin and glycated albumin levels can lead to better glycemic control in pregnant women.

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http://dx.doi.org/10.1016/j.pedneo.2016.02.003
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1. Introduction

Infants of diabetic mothers (IDMs) often have complications associated with fetal hyperinsulinemia induced by maternal hyperglycemia.1 In the first trimester, maternal hyperglycemia can cause diabetic embryopathy, which results in major birth defects and spontaneous abortions. In the second and third trimesters, maternal hyperglycemia can cause fetal hyperglycemia, hyperinsulinemia, hypercalcaemia, polycythemia, hyperbilirubinemia, myocardial hypertrophy, delayed lung maturation, and large-for-date status.2

Glycated hemoglobin (HbA1c), the current gold standard marker for glycemic control, reflects blood glucose levels over the previous 2–3 months. However, the HbA1c level is affected by an abnormal erythrocyte life span, which may occur in iron deficiency anemia.3 Pregnant women with diabetes mellitus or gestational diabetes mellitus (GDM) often develop iron deficiency anemia; therefore, HbA1c may be insufficient for assessing glycemic control in these women.

Recent reports have advocated the use of glycated albumin as a marker of glycemic control.4,5-7 Compared with HbA1c, glycated albumin reflects shorter-term blood glucose levels (the previous 2–3 weeks as opposed to the previous 2–3 months) and is unaffected by the erythrocyte life span.8 Therefore, glycated albumin may be a useful marker for glycemic control during pregnancy. However, few studies have examined the association between glycated albumin in diabetic mothers and complications in IDMs.9 Therefore; we investigated whether glycated albumin as a marker of glycemic control.10

2. Methods

2.1. Study design and participants

We performed a retrospective study of 59 Japanese IDMs and their mothers (including women with GDM), who were admitted to our facility between May 2010 and July 2013. Seventeen cases were excluded because the mother’s glycated albumin level was not measured or because of the presence of hepatic disease, renal disease, or obesity [body mass index (BMI) ≥ 30]; therefore, 42 IDMs were included in the final analysis.

We retrieved the mother’s age, gestational week, number of previous pregnancies, BMI (prior to the pregnancy), glycated albumin level, HbA1c, diabetes type, family history of diabetes mellitus, systolic and diastolic blood pressure, infant birth weight, and infant complications. The glycated albumin and HbA1c values measured within 1 month prior to birth were used in the analyses. The complications assessed were hypoglycemia, respiratory disorders, hypocalcemia, polycythemia, hyperbilirubinemia, myocardial hypertrophy, and large-for-date status. Malformations were excluded from the analysis owing to their occurrence prior to the 7th gestational week.10 Maternal diabetes mellitus was diagnosed according to the Japan Diabetes Society (JDS) criteria.11 Mothers with preexisting diabetes mellitus were treated with insulin subcutaneous injections. GDM was diagnosed according to the criteria of the International Association of Diabetes and Pregnancy Study Groups.12 Infant complications were defined as follows: hypoglycemia = blood glucose < 1.9 mmol/L; respiratory disorders = infants that required oxygenation; hypocalcemia = serum calcium levels < 2.0 mmol/L; polycythemia = serum hematocrit levels > 0.65/L; hyperbilirubinemia = infants that required phototherapy; myocardial hypertrophy = interventricular septum thickness > 5 mm on ultrasound; and large-for-date status = birth weight > 90th percentile for gestational age.

2.2. Laboratory analysis

HbA1c (%) was measured by high-performance liquid chromatography and was calibrated using JDS Lot 2. HbA1c was estimated as the National Glycated Hemoglobin Standard Program (NGSP) equivalent value and the estimated Internal Federation of Clinical Chemistry (IFCC) equivalent value using the following formulae: $HbA1c = HbA1c~(JDS) + 0.4$ (%) and $NGSP = (0.9148 × IFCC) + 2.152$, respectively.11,13 Glycated albumin was measured enzymatically using ketamine oxidase, an albumin-specific proteinase, and albumin assay reagent (Lucica GA-L; Asahi Kasai Pharma Co., Tokyo, Japan).14

2.3. Statistical analysis

We checked whether any factors (mother’s age, BMI, gestational week, systolic blood pressure, diastolic blood pressure, or type of delivery) were significantly different in IDMs with and without complications (hypoglycemia, respiratory disorders, hypocalcemia, polycythemia, hyperbilirubinemia, myocardial hypertrophy, and large-for-date status). Then, multivariable regression analysis was performed to determine whether glycated albumin is an independent predictor of neonatal complications of IDM. We compared the mean glycated albumin and HbA1c values between IDMs with and without complications. We conducted the post hoc test to calculate the sample power of adequate equations by adopting an error probability of 5% for the sample size used. The sample power (1 − β error probability) was 0.831. We used 15.8% as the cutoff value for glycated albumin and calculated the sensitivity and specificity of items that were significantly different between the two groups. We also calculated the odds ratios and 95% confidence intervals for the prevalence of each complication at the determined cutoff value. All data are presented as mean ± standard deviation. The Kolmogorov-Smirnov goodness-of-fit test was performed to determine whether data were normally distributed. Two-sided Student t tests or Welch t tests were used to determine possible differences between the two groups. Sample power calculations were performed using the G*Power software version 3.0.10 (Franz Faul, University of Kiel, Kiel, Germany).15 and other statistical analyses were performed using EZR 1.10 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan).16 The level of significance was set at $p < 0.05$ in all analyses. This study was approved by the Ethics Review Board of our facility.
3. Results

Baseline characteristics of the study population are shown in Table 1. Glycated albumin and HbA1c were significantly different between cases and controls (15.3 ± 1.6 vs. 13.3 ± 1.1%, p < 0.01 and 5.9 ± 0.3 vs. 5.6 ± 0.4%, p = 0.03, respectively). Twenty-five IDMs presented with complications; 17 (40.4%) had myocardial hypertrophy; 13 (30.9%) had hypoglycemia; 11 (26.1%) had respiratory disorders; nine (21.4%) had hypocalcemia; eight (19%) were large for date; six (14.2%) had hyperbilirubinemia; and four (9.5%) had polycythemia. There were no cases of myocardial hypertrophy combined with heart failure. All infants with hypoglycemia improved following intravenous glucose infusion. One infant required ventilation after the diagnosis of respiratory distress syndrome. None of the infants had hypoglycemia-induced convulsions. All of the infants with hyperbilirubinemia and polycythemia showed improvements following phototherapy and intravenous glucose infusion, respectively.

We checked whether any factors (mother’s age, BMI, gestational week, systolic blood pressure, diastolic blood pressure, or type of delivery) were significantly different in IDMs with and without each complication (hypoglycemia, respiratory disorders, hypocalcemia, polycythemia, hyperbilirubinemia, myocardial hypertrophy, and large-for-date status), and there were no significant differences between these two groups. Multivariable regression analysis revealed glycated albumin to be a significant independent predictor of neonatal complications of IDMs (R² = 0.572, standard error = 0.15%, t = 3.8, p < 0.01). We compared mean glycated albumin and HbA1c values for each complication between IDMs with and without complications (Table 2). Glycated albumin differed significantly between the mothers of infants with versus without hypoglycemia (15.5 ± 1.8 vs. 13.8 ± 1.2%, p = 0.001), respiratory disorders (15.6 ± 1.8 vs. 13.9 ± 1.2%, p < 0.001), hypocalcemia (15.7 ± 2.1 vs. 14 ± 1.2%, p = 0.004), myocardial hypertrophy (15.2 ± 1.9 vs. 13.7 ± 1%, p = 0.007), and large-for-date status (15.8 ± 1.9 vs. 14 ± 1.3%, p = 0.002). By contrast, HbA1c differed significantly between mothers of infants with respiratory disorders (6.4 ± 0.8 vs. 5.7 ± 0.4%, p = 0.002), myocardial hypertrophy (6.2 ± 0.7 vs. 5.7 ± 0.4%, p = 0.009), and large-for-date status (6.6 ± 0.8 vs. 5.7 ± 0.4%, p < 0.001). As for hypoglycemia, HbA1c was not significantly different between the two groups (6.1 ± 0.4 vs. 5.8 ± 0.6%, p = 0.2).

Table 1 Baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of mothers, n</td>
<td>25</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Age, y ± SD</td>
<td>35.1 ± 4.6</td>
<td>34.9 ± 3.5</td>
<td>0.78</td>
</tr>
<tr>
<td>BMI prior to pregnancy, kg/m² ± SD</td>
<td>22.8 ± 2.4</td>
<td>23.8 ± 2.8</td>
<td>0.69</td>
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<tr>
<td>Gestational week, wk ± SD</td>
<td>38.2 ± 1.4</td>
<td>38.1 ± 1.0</td>
<td>0.85</td>
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<tr>
<td>Previous pregnancy</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Baby’s birth weight, g ± SD</td>
<td>3211 ± 434</td>
<td>2977 ± 463</td>
<td>0.11</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg ± SD</td>
<td>113.7 ± 9.7</td>
<td>109.3 ± 8.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg ± SD</td>
<td>75.1 ± 8.4</td>
<td>74.2 ± 8.2</td>
<td>0.72</td>
</tr>
<tr>
<td>Glycated albumin, % ± SD</td>
<td>15.3 ± 1.6</td>
<td>13.3 ± 1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HbA1c, % ± SD (NGSP)</td>
<td>5.9 ± 0.3</td>
<td>5.6 ± 0.4</td>
<td>0.03</td>
</tr>
<tr>
<td>HbA1c, mmol/mol ± SD (IFCC)</td>
<td>40.8 ± 3.7</td>
<td>37.8 ± 4.5</td>
<td>0.03</td>
</tr>
<tr>
<td>Family history of diabetes mellitus</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Type of mother’s diabetes mellitus</td>
<td>Type 1 diabetes mellitus</td>
<td>4</td>
<td>2</td>
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<tr>
<td></td>
<td>Type 2 diabetes mellitus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gestational diabetes mellitus</td>
<td>19</td>
<td>16</td>
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</tbody>
</table>

BMI = body mass index; HbA1c = glycated hemoglobin; IDMs = infants of diabetic mothers; IFCC = Internal Federation of Clinical Chemistry; NGSP = National Glycated Hemoglobin Standard Program; SD = standard deviation.
The sensitivity, specificity, and odds ratios for the glycated albumin cutoff values (15.8%) are shown in Table 3. The odds ratios for all parameters were statistically significant, and the sensitivity and specificity were relatively high.

4. Discussion

The results of the present study showed that glycated albumin was a useful glycemic marker from the point of view of infant complications for monitoring glycemic control in pregnant women with diabetes or gestational diabetes. It was recently reported in Japan that glycated albumin is a more useful marker for glycemic control during pregnancy than HbA1c. Glycated albumin is a ketoamine formed by nonenzymatic glycation of serum albumin.14 Glycated albumin is a more useful marker than HbA1c for several reasons. First, the half-life of albumin is approximately 15 days; therefore, glycated albumin increases in the presence of hyperglycemia and reflects mean glycemia over a period of approximately 2 to 3 weeks.17 Thus, glycated albumin is a better index of short-term glycemic control than HbA1c.

Table 3

<table>
<thead>
<tr>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Odds ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>70</td>
<td>81.2</td>
<td>3.7 (1.6–8.5)</td>
</tr>
<tr>
<td>Respiratory disorder</td>
<td>61.5</td>
<td>82.8</td>
<td>3.5 (1.4–8.3)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>62.5</td>
<td>84.4</td>
<td>4 (1.5–7.2)</td>
</tr>
<tr>
<td>Myocardial hypertrophy</td>
<td>87.5</td>
<td>79.4</td>
<td>4.2 (2–8.6)</td>
</tr>
<tr>
<td>Large for date</td>
<td>75</td>
<td>85.3</td>
<td>5.1 (2–12.5)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

There were several cases in this study in which HbA1c levels were within the normal range, but glycated albumin levels were high. This might have been caused by glycated albumin reflecting more short-term glycemic control. Second, glycated albumin is unaffected by iron metabolism. Iron deficiency anemia is often observed in late pregnancy because of increased iron demand, and HbA1c levels are higher relative to the actual glycemic state in patients with iron deficiency anemia. Because glycated albumin is not correlated with hemoglobin, it is not affected by iron deficiency anemia.5,18 There were several cases in this study in which HbA1c levels were high but glycated albumin levels were within the normal range. Thus, we can better determine the blood sugar status of pregnant women by evaluating both HbA1c and glycated albumin levels. Hiramatsu et al19 reported that glycated albumin levels in healthy pregnant Japanese women ranged from 11.5% to 15.7%. Meanwhile, Shimizu et al1 reported that hypoglycemia, respiratory disorders, and polycythemia were significantly more frequent in infants of mothers (including those with GDM) with an HbA1c level >15.8% than in infants of mothers with a glycated albumin level <15.8%.9 They also reported that the frequency of complications did not differ significantly between infants whose mothers (including those with GDM) had an HbA1c level ≥5.8% (40 mmol/mol) and those with HbA1c levels ≤5.8% (40 mmol/mol).9 Our study results confirmed that glycated albumin is useful from the point of view of infant complications for monitoring glycemic control in pregnant women with diabetes or gestational diabetes, consistent with the results reported by Shimizu et al.9

This study has several limitations. First, this was a single-center study, so the number of participants was small. Larger studies are recommended to confirm our results. Second, we studied only Japanese IDMs and their mothers. There might be ethnic differences in glycated albumin, but the reference range of glycated albumin in an
American population is 11.9—15.8%, which is close to the reference range for Japanese women. Furthermore, glycated albumin is affected by albumin metabolism. Glycated albumin is artificially low relative to glycemic status in conditions associated with increased albumin metabolism, such as hyperthyroidism, nephrotic syndrome, steroid use, and obesity. We must be aware of the limitations of this test in those patients. There were no patients with hyperthyroidism, nephrotic syndrome, or steroid use in our study, and we excluded obese patients. In conclusion, our study has shown that glycated albumin is a useful marker of glycemic control in pregnant diabetic women. Because the glycated albumin level can be measured easily and accurately using an enzymatic method, it can be measured without pretreatment alongside common biological markers, such as glucose, which should encourage wider use. This study also suggests that evaluating both HbA1c and glycated albumin levels can lead to better glycemic control in pregnant women. Nevertheless, further studies are required to confirm the utility of glycated albumin as a marker of glycemic control during pregnancy.

Conflict of interest

The authors declare no conflict of interest. The authors received no support for this work in the form of grants, equipment, or drugs.

References