Usefulness of HbA1c to diagnose diabetes among Japanese children detected by a urine glucose screening program in the Tokyo Metropolitan Area

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Abstract. We examined the correlation between plasma glucose (PG) and hemoglobin A1c (HbA1c) to evaluate the usefulness and limitations of applying the new diagnostic criteria for diabetes to Japanese pediatric patients. Data were collected from 298 school children who took an oral glucose tolerance test (OGTT) at a school-based urinary glucose screening program in the Tokyo Metropolitan Area between 1988 and 2009. Mean (SD) age of the children was 11.9 (2.5) years. Male-to-female ratio was 1:1.1. Children were diagnosed with renal glucosuria (n=146), diabetes mellitus (n=133), or the Japan Diabetes Society (JDS) “borderline type” (n=19). Median (range) values of fasting plasma glucose (FPG), 2-h plasma glucose in an OGTT (OGTT-2h), and HbA1c were 101 (76-378) mg/dL, 146.5 (57-563) mg/dL, and 6.05 (4.7-14.1) %.

The correlation between PG and HbA1c was analyzed using least squares regression, and HbA1c was found to highly correlate with PG. From estimated regression equations, mean values of FPG and OGTT-2h corresponding to an HbA1c of 6.5% were calculated to be 111.4 mg/dL and 170.4 mg/dL. The mean values of HbA1c corresponding to an FPG of 126 mg/dL and OGTT-2h of 200 mg/dL were calculated to be 7.5% and 7.8%. The mean values of PG corresponding to HbA1c of 6.5% were lower than found in adults as analyzed by JDS. The mean values of HbA1c corresponding to diabetic type PG were higher than found in adults.

Key words: Hemoglobin A1c (HbA1c), Plasma glucose, Oral glucose tolerance test (OGTT), Diagnostic criteria, Correlation

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Material and Methods

Subjects
Data from school children who took an OGTT at a school-based urine glucose screening program for diabetes in the Tokyo Metropolitan Area between 1988 and 2009 were collected. Children were selected to take an OGTT if they had glucosuria for two consecutive occasions. The test was cancelled if they had ketonuria, or if they had an extremely high FPG. Data collected were as follows: gender, age, FPG, OGTT-2h, HbA1c, and diagnoses. Gender, age composition, and diagnoses are shown in Table 1. The mean (SD) age was 11.9 (2.5) years. The male-to-female ratio was 1:1.1. Diagnoses were made based on additional informations including the presence of diabetes-related autoantibodies. Those diagnosed with renal glucosuria, an isolated disorder of proximal tubular glucose transport characterized by abnormal urinary excretion of glucose despite normal or low PG levels, constituted the largest group (n=146). There were 133 subjects diagnosed with diabetes mellitus. Of these, 19 were diagnosed with type 1 diabetes (T1DM), whereas 110 were diagnosed with type 2 diabetes (T2DM). Four were diagnosed as undefined type. Children with T1DM showed low levels of serum insulin, low insulin response to OGTT, and most (more than 80%, data not shown) were positive for diabetes-related autoantibodies. Insulin response of T1DM were generally <5 to 10 microU/mL (in case of slowly progressive type, <20 microU/mL)[8, 9]. Children with T2DM were negative for diabetes-related autoantibodies and showed a higher insulin response to OGTT. Nineteen children were diagnosed as having impaired glucose tolerance (IGT) or JDS “borderline type” plasma glucose. A “borderline type” is defined as a PG that does not satisfy either of the definitions of diabetic or normal type PG. A diabetic type PG is defined as one of the following: (1) FPG ≥126mg/dL, (2) OGTT-2h ≥200mg/dL, or (3) casual PG ≥200mg/dL. Normal type is defined as FPG <110mg/dL and OGTT-2h <140mg/dL. A “borderline type” means “neither diabetic nor normal,” and it corresponds to a combination of IGT and impaired fasting glucose as defined by ADA or WHO [1].

An OGTT was conducted by administering glucose at 1.75 g/kg per standard body weight (maximum 75 g). HbA1c was measured by high-performance liquid chromatography (HPLC). It has been calibrated against the whole blood standard of JDS since 1993.

Table 1 Characteristics of 298 subjects

<table>
<thead>
<tr>
<th>Age</th>
<th>11.9±2.5yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male-Female ratio</td>
<td>1:1.1</td>
</tr>
<tr>
<td>Diagnoses</td>
<td></td>
</tr>
<tr>
<td>Renal glucosuria</td>
<td>146</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>133</td>
</tr>
<tr>
<td>T1DM</td>
<td>19</td>
</tr>
<tr>
<td>T2DM</td>
<td>110</td>
</tr>
<tr>
<td>undefined</td>
<td>4</td>
</tr>
<tr>
<td>IGT/borderline</td>
<td>19</td>
</tr>
</tbody>
</table>

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; IGT, impaired glucose tolerance

Statistical analysis
Standard procedures were used to calculate the median, mean, and SD. To show the correlation between PG and HbA1c, least squares regression was used. Spearman’s rank correlation was used for statistical analysis. \( P < 0.05 \) was considered statistically significant. Prediction intervals were calculated to represent the range of predicted PG at a given HbA1c level and vice versa. Analyses were conducted using Microsoft Excel and add-in softwares ystat2008 and Statcel2.

Results

Distribution of HbA1c
The distribution of HbA1c is shown in Fig. 1. There were 143 children who showed normal PG levels, meaning they satisfied both criteria of FPG <110 mg/dL and OGTT-2h <140 mg/dL. Most of the children had HbA1c below 6.4%, but 2 (1.4%) had HbA1c higher than 6.5%. A total of 135 children had “diabetic type” PG, meaning they had either FPG ≥126 mg/dL or OGTT-2h ≥200 mg/dL, or both. They exhibited a wide range of HbA1c from 5.9% to 15.4%, with 6 subjects (4.2%) having HbA1c below 6.5%. Five out of these 6 subjects were eventually diagnosed as having diabetes. There were 14 children with HbA1c above 6.5% but FPG lower than 126 mg/dL. Nine of these 14 were diagnosed as having diabetes as a result of an OGTT. The sensitivity of HbA1c to correctly diagnose diabetes was estimated to be 0.95, and the specificity to correctly rule out those with normal glucose metabolism was estimated to be 0.99.

Correlation between PG and HbA1c
The correlation between PG and HbA1c was analyzed using least squares regression. As shown in
HbA1c to diagnose pediatric diabetes

To diagnose pediatric diabetes, the HbA1c level was measured, and it was found to be 124.4 mg/dL, and OGTT-2h corresponding to the same HbA1c was calculated to be 199.3 mg/dL, which were very close to the current diagnostic criteria of “diabetic type.” They also found from an analysis of data from 36,267 adults that the risk for developing retinopathy increased significantly with HbA1c >6.5% in a Japanese population. Based on these findings, the JDS Committee concluded that HbA1c ≥6.5%, which was recommended by the International Expert Committee and ADA as the cutoff point for diagnosing diabetes, was appropriate to apply to the Japanese population.

The JDS Committee also recommended that HbA1c alone was insufficient to diagnose diabetes. One must suffice also either one of the criteria FPG ≥126 mg/dL, OGTT-2h ≥200 mg/dL, or casual PG ≥200 mg/dL simultaneously or on another occasion, because patients diagnosed as “diabetic type” by PG are known to exhibit a wide range of HbA1c values [1].

Fig. 2(A) and (B), HbA1c was highly correlated with PG (FPG: rs=0.86, P<0.0001; OGTT-2h: rs=0.87, P<0.0001). Mean FPG for an HbA1c of 6.5% was calculated from regression to be 111.4 mg/dL. Mean OGTT-2h for an HbA1c of 6.5% was calculated from regression to be 170.4 mg/dL. Regression equations are shown in the figures.

Correlation between HbA1c and PG

Fig. 3(A) and (B) show the correlations between HbA1c and FPG and OGTT-2h. Mean HbA1c for an FPG of 126 mg/dL was calculated from regression to be 7.5%. Mean HbA1c for an OGTT-2h of 200 mg/dL was calculated from regression to be 7.8%.

Discussion

In order to adopt HbA1c as one of the diagnostic criteria for diabetes, the JDS have appointed a committee to consider its use and to make recommendations. The committee analyzed data from 6,658 adults who received an OGTT at their regular health check-ups, and found a strong correlation between PG and HbA1c. From estimated regression equations, the JDS Committee demonstrated that an HbA1c of 6.5% corresponded to an FPG of 126 mg/dL, and that an HbA1c of 6.4% corresponded to an OGTT-2h of 200 mg/dL [1]. Thus the Committee concluded that HbA1c ≥6.5% corresponded to FPG of 126 mg/dL or OGTT-2h of 200 mg/dL in a Japanese population. At the same time, the FPG corresponding to HbA1c of 6.5% was calculated to be 124.4 mg/dL, and OGTT-2h corresponding to the same HbA1c was calculated to be 199.3 mg/dL, which were very close to the current diagnostic criteria of “diabetic type.” They also found from an analysis of data from 36,267 adults that the risk for developing retinopathy increased significantly with HbA1c >6.5% in a Japanese population. Based on these findings, the JDS Committee concluded that HbA1c ≥6.5%, which was recommended by the International Expert Committee and ADA as the cutoff point for diagnosing diabetes, was appropriate to apply to the Japanese population.

With regard to pediatric patients, the diagnosis of diabetes, including HbA1c, is the same as for adults [1]. As neither the JDS Committee nor any other previous study focused on the correlation between PG and HbA1c levels in the Japanese pediatric population, we analyzed data from a school-based urinary glucose screening program to investigate the correlation between FPG or OGTT-2h and HbA1c.

In the present study, HbA1c was highly correlated with FPG or OGTT-2h, as shown in the figures. The correlation was highly significant (FPG: rs=0.86, P<0.0001; OGTT-2h: rs=0.87, P<0.0001). The FPG corresponding to HbA1c of 6.5% was calculated to be 124.4 mg/dL, and OGTT-2h corresponding to the same HbA1c was calculated to be 199.3 mg/dL, which were very close to the current diagnostic criteria of “diabetic type.”
the present study were different from those derived in the JDS report. In the present study, the mean value of FPG corresponding to an HbA1c of 6.5% as defined as “diabetic type” was 111.4 mg/dL, which was lower than the value of 124.4 mg/dL derived from data in adults [1]. The mean value of OGTT-2h corresponding to an HbA1c of 6.5% was 170.4 mg/dL in the present study, which was also lower than the value of 199.3 mg/dL derived from the same adult data. In contrast, the mean value of HbA1c corresponding to an FPG of 126 mg/dL was 7.5% and that corresponding to an OGTT-2h of 200 mg/dL was 7.8%, both of which were higher than in the JDS report.

There are several factors to be considered to explain the difference in correlation between PG and HbA1c among pediatric and adult subjects. Firstly, one must consider the difference in the composition of the data set between the present study and the JDS report. Secondly, the level of hemoglobin might have influenced the level of HbA1c. Thirdly, racial disparity and the influence of age on the glycation of hemoglobin must also be considered.

Children in the present study mainly had normal PG and diabetic type PG in almost a 1:1 ratio, and IGT or borderline types constituted less than 10% of the whole population (Table 1). FPG, OGTT-2h, and HbA1c were not normally distributed in the present study, and the median (range) values of FPG, OGTT-2h, and
HbA1c were 101 (76-378) mg/dL, 146.5 (57-563) mg/dL, and 6.05 (4.7-14.1) %, respectively. The dataset discussed in the JDS report might have included more IGT or borderline types than the present data. The reason for this speculation is that the mean (SD) values of FPG, OGTT-2h, and HbA1c available for the JDS data were much lower than the corresponding values for the present data, calculated for the purpose of comparison. Namely, the mean (SD) values of FPG, OGTT-2h, and HbA1c for the JDS data were 118.1 (36.7) mg/dL, 181.8 (94.6) mg/dL, and 6.2 (1.4) %, respectively, whereas the corresponding values for the present data were 126.9 (55.7) mg/dL, 206.7 (127.6) mg/dL, and 7.2 (2.3) %, respectively. These data suggest that there might have been a difference in the composition of the dataset between the present study and the JDS report. As a result, correlations in the present study might have been influenced more by diabetic types than in the JDS report. Diabetic types exhibit a much wider range of HbA1c than normal children, as shown in Fig. 1, and this might be one of the reasons for higher HbA1c corresponding to a given level of PG.

One must take note here that HbA1c in our present study was measured using the HPLC method, which had been calibrated against the whole blood standard of JDS since 1993. Our analysis has a limitation in that calibration status of data taken beforehand, namely from 1988 through 1992, is not available. It is crucial to consider whether this aspect has an influence on our findings. However, calibration status of the data referred in JDS report is also unavailable, and it is impossible to discern each data on their calibration status. We cannot discard the possibility that a difference in calibration status might have influenced our findings, but it is only fair to say there is not enough information to reach at any definite conclusion concerning this point.

Secondly, blood concentration of hemoglobin is known to influence the level of HbA1c. Lower hemoglobin levels have been shown to result in higher HbA1c levels in healthy children [14]. Hemoglobin levels of the subjects are not available in the present study, and such data are not available for the JDS adult population, either. However, since hemoglobin levels in children are generally lower than those in adults, the effect of hemoglobin level on HbA1c cannot be discarded. However, there were no significant differences in FPG, OGTT-2h, or HbA1c between boys and girls in the present study. Since adolescent girls generally have lower hemoglobin levels than adolescent boys, the fact that there were no significant differences between boys and girls might be suggesting that the effect of hemoglobin levels had been limited in the present study.

Racial disparity in HbA1c levels independent of PG has been reported [15-17]. However, both the JDS adult data and the present data are taken from the Japanese population, which is not racially or ethnically diverse. Numerous studies have been done on the correlation between various levels of PG and HbA1c [10-13, 18, 19], but to our knowledge there is no previous study that shows a significant difference in the correlation between different groups of patients. Lastly, one must also consider the possibility that glycation of hemoglobin differs between children and adult. However, we could not find any published evidence to suggest such a difference. Further research is needed to elucidate the reason for the difference in correlation between PG and HbA1c between children and adults.

Many children have been diagnosed with T2DM in the school-based urinary glucose screening program since 1974 [20-22]. Nearly 70% were diagnosed by means of an OGTT (data not shown). Although the OGTT has been routinely used to evaluate glucose intolerance [23], the procedure is time-consuming and costly, and there has recently been a tendency to avoid an OGTT in clinical settings [24]. If the new diagnostic criteria for glucose intolerance are applied with an intention to reduce the burden on pediatric patients, some patients could be overlooked. As one cannot diagnose diabetes with recurrent examination of HbA1c according to the JDS criteria [1], a certain percentage of those with HbA1c above 6.5% would not be diagnosed as having diabetes unless an OGTT was conducted, because an HbA1c of 6.5% corresponds to a mean FPG of 111.4 mg/dL. This demonstrates the importance of performing an OGTT in diagnosing diabetes in a pediatric population also, as demonstrated previously in an adult Japanese population [23].

In using HbA1c as one of the criteria for diagnosing childhood diabetes, one should be aware of the various relationships between PG and HbA1c. Because PG levels and HbA1c levels reflect different aspects of glucose metabolism, one should not expect a perfect concordance between these various measures [3]. It is certain that HbA1c will pick up those who might have been overlooked by an FPG measurement, but at the same time, there is always a risk of missing those who would have been diagnosed through an OGTT.
Conclusion

In Japanese children detected by a urine glucose screening program at schools in the Tokyo Metropolitan Area, both FPG and OGTT-2h strongly correlated to HbA1c, but average PG levels corresponding to a definite HbA1c level were found to be lower than those found in adult data analyzed by the JDS. At the same time, average HbA1c corresponding to a definite PG was much higher in our study. The reason behind this discrepancy is not clear. In cases in which FPG levels were not as high as expected from the level of HbA1c, diagnoses of diabetes were made on the basis of OGTT-2h. In using HbA1c to diagnose diabetes in a similar pediatric population, it may be useful to take note that there might be a lack of concordance between HbA1c and either measurement of glucose levels.

References


