The Clinical Usefulness of Glycated Hemoglobin in Monitoring Diabetes Mellitus: A Long-Term Study

Silvia Lenzi, Ottavio Glampietro, Giovanna Giovannitti, Tiziana Sampietro, Roberto Miccoli, and Renzo Navalesi

To assess the long-term clinical usefulness of measuring glycated hemoglobin (Hb A1), we carried out a two-year longitudinal study involving 234 diabetic patients (116 males, 118 females; 139 with type I diabetes mellitus, 95 with type II). Hb A1 values correlated significantly (p < 0.001) with a score index based on plasma glucose in a specimen collected after overnight fasting, and urinary glucose, and ketones in a 24-h specimen. However, we found that one of every three well-controlled patients (both type I and II subjects) had high values for Hb A1. Among poorly controlled patients, only those with "brittle" diabetes had good values for Hb A1.

Additional Keyphrases: plasma and urinary glucose • monitoring therapy

Good long-term metabolic control is believed to influence the development and severity of late complications of diabetes mellitus. The effort to maintain concentrations of blood glucose as near to normal as possible requires a reliable index of long-term glucose control. Glycated hemoglobin (Hb A1) measurement is an excellent marker of long-term glucose control in diabetic patients (I–II). Many investigations have shown its correlation with mean plasma glucose (5), 24-h urinary output (5), and other indexes of metabolic control (II), averaged over two or three months.

However, the perceived clinical value of measuring Hb A1 has been derived mainly from short-term rather than long-term studies (II–I4). We report here the results of a longitudinal study performed to evaluate the clinical value of Hb A1 measurements as compared with a "score" index calculated from measurements of plasma and urinary glucose and of urinary ketones.

Materials and Methods

We studied 234 patients (Table 1), of whom 139 were type I diabetics: 60 males, 79 females, ages 13–69 (mean 45, SD 1) years, with diabetes ranging in duration from a month (new diagnosis) to 47 years (median 10 y). The other 95 patients were type II diabetics (56 males, 39 females), ages 20–70 years (mean 51.8, SD 10.9, median 55) with diabetes ranging in duration from four months to 31 years (median 8 y). Of these 95 patients, 47 were overweight (i.e., >110% of Ideal Body Weight). Each patient was studied for nine to 27 months (mean 16.5, SD 5.9 for type I patients; 13.5, SD 2.4 for type II patients), undergoing four or five laboratory examinations each, at least once every three months. Patients with renal failure, hemolytic anemia, or hemoglobinopathies were excluded from the study.

Table 1. Data on Patients

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>p</th>
</tr>
</thead>
</table>
| n (M/F) | 60/79    | 56/39| 0.005
| Age, y  | 45.2 ± 16.8 | 51.8 ± 10.9 |<0.005
| Diabetes duration, y | 10* (0.1–47) | 8* (0.4–31) |<0.001
| Examinations: b | 16.5 ± 5.9 | 13.5 ± 2.4 |<0.005
| No.      | 7.5 ± 3.7  | 5.3 ± 1.6  |<0.01
| Mean R.I. | 3.9 ± 1.5 | 2.7 ± 1.3 |<0.001
| Hb A1, % | 10.7 ± 1.7 | 9.1 ± 1.2 |<0.001

R.I. = Regulation Index (see text).

b This indicates the time interval (time, in months) during which, and how many times ("No.") in this interval, patients had been examined for the score index (R.I.) determination and for Hb A1 evaluation.

For all subjects we measured plasma glucose after fasting, 24-h urinary glucose, and urinary ketones. Glucose was measured by the glucose oxidase method with a Glucose Analyzer (Beckman Instruments, Fullerton, CA). Hb A1 was measured with a commercial kit (Bio-Rad Labs., Richmond, CA); erythrocytes were washed three times before hemolysis and incubated with saline solution to eliminate the labile Hb A1 fraction (15, 16).

For quality control of Hb A1, we used a standard sample, prepared according to Trivelli et al. (17) and stored at –20 °C; this standard was stable for six months. The intra-assay CV was 3% (n = 44), the inter-assay CV 5% (n = 78). The mean normal value, obtained from data on 40 healthy volunteers, for Hb A1 was 6.7 (SD 0.7)% of total hemoglobin. Short-term metabolic control was evaluated by the Regulation Index (R.I.), an index determined by the sum of the plasma glucose concentration after fasting, the 24-h urinary glucose concentration, and the presence or absence of ketonuria (see Table 2). For each patient we calculated the mean R.I. and the mean Hb A1 value over the duration of the study.

"Satisfactory" metabolic control was defined as a value of <3 for the R.I. and <9% for Hb A1.

Results

In type I diabetic patients the mean R.I. (3.9, SD 1.5) and the mean Hb A1 (10.7, SD 1.7)% were significantly higher than in type II patients: 2.7 (SD 1.3) and 9.1 (SD 1.2)% respectively. These results were positively correlated in type I patients (type I: Hb A1 = 7.9 + 0.59 R.I., r = 0.58, p <0.001) and type II patients (type II: Hb A1 = 7.6 + 0.57 R.I., r = 0.61, p <0.001).

No correlation was found between the patients' age or duration of diabetes and either R.I. or Hb A1.

Table 3 lists the patients, divided into two groups according to the control of their diabetes as evaluated both by the
Table 2. Score Index (R.I.) Calculated from Results of the Usual Laboratory Tests of Diabetes Control

<table>
<thead>
<tr>
<th>Urinary glucose, g/L</th>
<th>0–5</th>
<th>6–10</th>
<th>11–20</th>
<th>21–40</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score S1</td>
<td>0.5</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Plasma glucose, g/L</td>
<td>1.10</td>
<td>1.11–12.5</td>
<td>1.26–1.50</td>
<td>1.51–2.00</td>
<td>2.00–2.50</td>
</tr>
<tr>
<td>Score S2</td>
<td>0</td>
<td>0.5</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Urine ketones</td>
<td>Absent</td>
<td>Present</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score S3</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Regulation Index (R.I.) = S1 + S2 + S3.

Table 3. Comparison between Well- and Poorly Controlled Diabetics as Defined by Mean R.I. and Hb A1

<table>
<thead>
<tr>
<th>Patients</th>
<th>Hb A1, %</th>
<th>Mean R.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 9</td>
<td>24</td>
<td>6</td>
</tr>
<tr>
<td>&gt; 9</td>
<td>17</td>
<td>92</td>
</tr>
<tr>
<td>Type II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 9</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>&gt; 9</td>
<td>19</td>
<td>32</td>
</tr>
</tbody>
</table>

For both type I (n = 139) and type II (n = 95) diabetics, the difference was highly significant ($x^2$, $p < 0.01$).

R.I. and by the values for Hb A1. Among patients with R.I. ≤ 3, 40% (n = 17) of the patients with type I diabetes and 30% (n = 19) of those with type II had Hb A1 > 9%. The differences were highly significant ($p < 0.001$, $x^2$ test) in both groups. Among patients with R.I. > 3, 7% (n = 6) of the type I group had Hb A1 < 9%. All of these patients had frequent and severe hypoglycemic episodes.

Discussion

For patients with either type I or type II diabetes, we found that when the index based on the traditional methods of glucose control (the R.I. value) suggested satisfactory control, 30 to 40% of the patients did not have acceptable metabolic control as assessed by the Hb A1 value.

Others have shown a significant correlation of glycated hemoglobin with mean blood glucose concentrations (13, 14). The fact that one of three patients (either treated with oral antidiabetic agents or with insulin) may be erroneously considered well controlled by conventional laboratory methods, points out the clinical usefulness of the Hb A1 assay. More-intensive monitoring—for instance, by the patient testing blood sugar at home—may be of benefit.

Only 7% of type I patients with a "bad" score index showed a discrepancy between the score index and the Hb A1 results. They were all "brittle" diabetics, with normal values for Hb A1 and either high values for 24-h urinary glucose output or nocturnal symptomatic hypoglycemic reactions followed by rebound hyperglycemia, which are frequent in patients who are being overtreated with insulin.

Under these conditions, the score indexes were high, with normal values for Hb A1. A significant linear correlation has been reported between the incidence of severe hypoglycemias and Hb A1 values that are artifactually near normal (12).

In the type II diabetics with poor control, the score index and the Hb A1 value agreed well. Assay of glycated hemoglobin does not appear to provide additional information in comparison with conventional methods of metabolic assessment in these patients (12).

Our data suggest that Hb A1 measurement is clinically useful in patients with apparently satisfactory metabolic control as assessed by fasting plasma glucose and urinary glucose, because it may reveal insufficient control. It is of less value in poorly controlled patients and in "brittle" diabetics.

References