Glycohemoglobin and Glucose Tolerance Tests Compared as Indicators of Borderline Diabetes

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We concurrently measured glycohemoglobin and performed 3-h oral (100 g) glucose tolerance tests on 69 ambulatory patients suspected of having abnormal carbohydrate metabolism. The patients were divided into two groups: (a) The 37 patients for whom the results were normal had plasma glucose concentrations of 0.70–1.15 g/L during fasting and 0.70–1.23 g/L 2 h after glucose ingestion. (b) Borderline diabetics exceeded one or both of these limits. The range of glycohemoglobin in the normal group was 3.0–4.7% of total hemoglobin. Of the 21 borderline diabetics, 11 had increased glycohemoglobin (4.8–8.0%). The difference in tolerance test results between borderline diabetics with and without increased glycohemoglobin was insufficient to predict the status of glycohemoglobin. We suggest a tentative definition for latent diabetes: increased glycohemoglobin in the presence of normal or borderline-abnormal glucose concentration in plasma collected during fasting.

It has been suggested that the diagnosis of diabetes be made only when the patient exhibits reproducible plasma glucose concentrations greater than 1.40 g/L during fasting (1). The practice of diagnosing latent diabetes on the basis of glucose intolerance in the presence of normal or borderline-abnormal fasting plasma glucose concentration has been found to vastly overestimate the presence of disease (1–3). Some investigators have suggested that missing the diagnosis of true latent diabetes is unimportant, because they believe that the hypertrophy of the capillary basement membrane that is characteristic of diabetes begins independently of hyperglycemia (1, 4, 5). However, others have suggested that at least some diabetic lesions are a consequence of hyperglycemia and can be prevented or reduced by controlling plasma glucose concentration (5–7). If latent diabetes as a true precursor stage of overt diabetes could be diagnosed with confidence, it would be possible to test the hypothesis that some diabetic lesions could be prevented or reduced by early intervention. Thus a test is needed that better discriminates latent diabetes than does the glucose tolerance test.

There is reason to believe that the glycohemoglobin test might serve this function, because glycosylation of hemoglobin is increased as a consequence of extended hyperglycemia (8–13). To test this use of the glycohemoglobin test, we compared glycohemoglobin and glucose tolerance tests in 69 ambulatory patients who were suspected by their physicians of having abnormal carbohydrate metabolism.

Materials and Methods

Glycohemoglobin (hemoglobin A1A + A1B + A1C) was measured by the Fast Hemoglobin Test System (Isolab, Inc., Akron, OH 44321). Hemolysates were prepared from blood collected with ethylenediaminetetraacetate as anticoagulant, stored at 5–10 °C, and analyzed within a week. The hemolysates were applied to cation-exchange columns and eluted sequentially with two buffers. Glycohemoglobin is defined as the percentage of the total hemoglobin that is eluted by the first buffer. We included a certified standard glycohemoglobin sample (Isolab, Inc.) in every run of assays and normalized all values in that run to the standard value (14). The hemoglobin eluted by each buffer was measured both by absorbance at 415 nm (Model M Photometer; Leitz, Inc., Rockleigh, NJ 07647) and by the difference between absorbance at 415 nm and at 450 nm (with an ABA-100; Abbott Laboratories, North Chicago, IL 60064). We then averaged these two measurements. The mean difference between them was 0.3% glycohemoglobin, with a range of 0–1.0%. There was complete agreement between the two measurements in the classification of all patients with normal glycohemoglobin, but they disagreed in the classification of two of the 11 patients with above-normal glycohemoglobin (Figure 1). Lactescent plasma can show a much greater percentage of glycohemoglobin when measured monochromatically than when measured bichromatically (15). No such samples were included in this study.

All glucose tolerance tests were performed in the morning. Patients were instructed to fast during and for at least 8 h previous to testing. As part of the test, patients should consume at least 150 g of carbohydrate per day for at least three days before a tolerance test (1), but we found it impossible to ensure patient compliance in this matter and thus accepted diet as a variable intrinsic to the tolerance test. However, all patients were ambulatory at the time of testing.

Glucose (“Dextrol”; Sherwood Medical Industries, Inc., St. Louis, MO 63103), 100 g, was administered orally. Blood and urine were collected from the fasting patients and at 0.5, 1, 2, and 3 h after they took the Dextrol.

Blood was collected from an arm vein (oxalate-fluoride anticoagulant) and glucose was measured in the plasma by a glucose oxidase method (with a kit from Sclavo, Inc., Wayne, NJ 07470). This method is reported by the manufacturer to be unaffected by the oxalate–fluoride mixture. Urinary glucose concentration was estimated semiquantitatively with Benedict's reagent (Clinistest Tablets; Ames Co., Elkhart, IN 46514). Urine volume or total glucose excretion were not recorded during the tolerance test.

The patients studied consisted of 44 females ranging in age from 13 to 82 (mean age, 43) and 25 males of age 25 to 72 years.

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assayed in plasma from 12 overt diabetics. The fasting plasma glucose concentration in this group ranged from 1.69 to 4.66 g/L and the glycohemoglobin ranged from 5.1 to 9.6%. The correlation between fasting plasma glucose concentration and percentage glycohemoglobin in this combined population (n = 83) was good (r = 0.86, p < 0.001) and agrees with published reports (16–19).

However, when overt diabetics were excluded from the calculation, there was no correlation between fasting plasma glucose concentration and percentage glycohemoglobin, or between plasma glucose concentration during fasting and the sum or peak of plasma glucose concentration during the tolerance test. There was a weak but significant correlation between percentage glycohemoglobin and the sum (r = 0.57, p < 0.001) (Figure 1) and the peak of plasma glucose concentration during the tolerance test.

We divided the data on the patients into two groups according to plasma glucose concentration (20). The “normal” group had plasma glucose concentrations of 0.70–1.15 g/L fasting and 0.70–1.23 g/L 2 h after glucose. The “borderline-abnormal” group exceeded one or both of these limits.

The normal group had glycohemoglobin values of 3.0–4.7% (Table 1). Various normal ranges between 3 and 12% have been reported for glycohemoglobin (9, 12, 16–18, 21–25). Our range (3.0–4.7%) compares well with the quantitative analysis of McDonald et al. (25). The width of our normal range (1.7%) equals our limit of a significant change within a single patient (14) and suggests that there is little or no substantive difference in glycohemoglobin among normal patients.

The borderline-abnormal group was divided into two subgroups, 21 with normal and 11 with above-normal glycohemoglobin values (Table 1). The ranges for plasma glucose concentration in borderline-abnormal patients with normal glycohemoglobin showed extensive overlap with the ranges in borderline-abnormal patients with increased glycohemoglobin. Of the 21 borderline-abnormal patients with normal glycohemoglobin, 11 shared a common range for the sum of plasma glucose concentration during the tolerance test with nine of the 11 patients with increased glycohemoglobin (Figure 1). Any difference in plasma glucose concentration between borderline-abnormal patients with and without above-normal glycohemoglobin is deprived of clinical utility by the normal deterioration in glucose tolerance with advancing patient age (1, 26).

The presence of glucose in the urine during the tolerance test was an indication that the patient belonged to the borderline-abnormal group; four of the 37 normal patients, and 21 of the 32 borderline-abnormal patients had detectable

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**Results**

Glycohemoglobin assays were performed on these 69 patients. The plasma glucose concentration during fasting ranged from 0.70 to 1.48 g/L and the percentage glycohemoglobin ranged from 3.0 to 8.0%. Glycohemoglobin was also

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**Table 1. Results for the 37 “Normal” Patients, 32 “Borderline-Abnormal” Patients**

<table>
<thead>
<tr>
<th></th>
<th>Fasting</th>
<th>0.5 h</th>
<th>1 h</th>
<th>2 h</th>
<th>3 h</th>
<th>Sum</th>
<th>GH</th>
<th>Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.92</td>
<td>1.42</td>
<td>1.21</td>
<td>0.97</td>
<td>0.85</td>
<td>5.40</td>
<td>3.9</td>
<td>40</td>
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<tr>
<td>Median</td>
<td>0.91</td>
<td>1.46</td>
<td>1.19</td>
<td>0.96</td>
<td>0.86</td>
<td>5.33</td>
<td>3.9</td>
<td>35</td>
</tr>
<tr>
<td>Range</td>
<td>0.71–1.15</td>
<td>0.79–2.09</td>
<td>0.56–2.11</td>
<td>0.72–1.23</td>
<td>0.50–1.27</td>
<td>3.90–7.18</td>
<td>3.0–4.7</td>
<td>13–77</td>
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<tr>
<td><strong>21 Borderline-abnormal patients with normal glycohemoglobin values</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Mean</td>
<td>1.04</td>
<td>1.80</td>
<td>1.91</td>
<td>1.59</td>
<td>1.08</td>
<td>7.41</td>
<td>4.1</td>
<td>48</td>
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<tr>
<td>Median</td>
<td>1.02</td>
<td>1.77</td>
<td>2.00</td>
<td>1.53</td>
<td>1.16</td>
<td>7.22</td>
<td>4.1</td>
<td>49</td>
</tr>
<tr>
<td>Range</td>
<td>0.79–1.32</td>
<td>0.98–2.63</td>
<td>0.97–2.87</td>
<td>0.88–2.72</td>
<td>0.81–1.63</td>
<td>5.60–9.85</td>
<td>3.2–4.7</td>
<td>27–72</td>
</tr>
<tr>
<td><strong>11 Borderline-abnormal patients with increased glycohemoglobin</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.21</td>
<td>2.26</td>
<td>2.47</td>
<td>1.94</td>
<td>1.43</td>
<td>9.31</td>
<td>5.7</td>
<td>54</td>
</tr>
<tr>
<td>Median</td>
<td>1.23</td>
<td>2.36</td>
<td>2.33</td>
<td>1.88</td>
<td>1.20</td>
<td>8.83</td>
<td>5.4</td>
<td>58</td>
</tr>
<tr>
<td>Range</td>
<td>0.98–1.48</td>
<td>1.80–2.78</td>
<td>1.85–3.28</td>
<td>1.21–3.45</td>
<td>0.77–3.72</td>
<td>7.12–14.71</td>
<td>4.8–8.0</td>
<td>33–82</td>
</tr>
</tbody>
</table>

*a Fasting, hours after glucose ingestion, and sum of these. b Glycohemoglobin.
glucose in their urine during the tolerance test. However, we found no clinically useful difference in urine glucose concentration between borderline-abnormal patients with and without increased glycohemoglobin.

We conclude that the difference in glucose tolerance test results between borderline-abnormal patients with and without increased glycohemoglobin is insufficient to predict the status of glycohemoglobin.

Discussion

The glucose tolerance test more sensitively indicates latent diabetes than does glucose determination during fasting (1). In patients who are possible latent diabetics, glycohemoglobin shows some correlation with the glucose tolerance test, but fasting plasma glucose values show none. This suggests that glycohemoglobin also more sensitively indicates latent diabetes than does measurement of plasma glucose during fasting. The main problem with the tolerance test is its indiscrimination; it results in too many falsely positive diagnoses (1-3). The glycohemoglobin assay seemed to be more discriminating than the glucose tolerance test because increased glycohemoglobin implied abnormal tolerance but abnormal tolerance did not necessarily imply increased glycohemoglobin.

We imagine late-onset diabetes to evolve by gradual extension of postprandial hyperglycemia. In the overt stage, hyperglycemia extends through the fasting state. In the latent stage, the post-prandial plasma glucose concentration would remain increased longer than normal but eventually would return to normal. The glucose tolerance test can demonstrate one instance of postprandial hyperglycemia. But attempts to extrapolate from this one instance of hyperglycemia to the general status of the patient are necessarily subject to wide margins of error. Almost any factor that influences the physiology or psychology of the patient can also influence the tolerance test (1). Many such factors could be negligible in the glycohemoglobin assay, because it reflects long-term time-averaged blood glucose concentration. We therefore suggest a tentative definition for latent diabetes: increased glycohemoglobin in the presence of normal or borderline-abnormal plasma glucose concentration during fasting.

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References