Glycated (Glycosylated) Hemoglobin: HbA1c

New directions to diagnose diabetes

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Also known as hemoglobin A1c, HbA1c, A1C or Hb1c, Glycated (Glycosylated) Hemoglobin is a form of hemoglobin used primarily to identify the average plasma glucose concentration over a prolonged period of time. Increased levels of glycated hemoglobin has been associated with cardiovascular disease, nephropathy, and retinopathy in diabetes mellitus. Monitoring the level of HbA1c in juvenile onset (type 1– autoimmune) diabetes may improve treatment.1

Background

In 1958, hemoglobin A1C was first separated from other forms of hemoglobin (Huisman and Metering) using a chromatographic column.2 Ten years later, hemoglobin A1C was characterized as a glycoprotein (non-enzymatic attachment of glucose to protein) by Bookchin and Gallop.3 Ralibar and coworkers4 wrote that the blood level of A1C is found to be elevated in diabetes and seven years thereafter, formally recommended its use to monitor the degree of control of glucose metabolism in diabetic patients (Cerami, Koenig, et al.).5

Principle and Measures

During the normal 120-day life span of the red blood cell (RBC), glucose molecules react with hemoglobin, forming glycated hemoglobin. Once a hemoglobin molecule is glycated, it remains in this form. In people without diabetes, about 4% to 6% of their hemoglobin is glycosylated. Red blood cells (RBCs) that contain the hemoglobin circulate in the bloodstream for three to four months before being broken down and replaced. During that time, the RBC can bond, irreversibly, to glucose in the bloodstream. A buildup of glycated hemoglobin within the red blood cell therefore reflects the average level of glucose to which the cell has been exposed during its life cycle. Thus, A1C readings higher than about 6% indicate higher than normal amounts of glucose roaming the blood stream in the past 120 days.

Other studies state that the major proportion of its value is related to a rather shorter period of two to four weeks.4 Measuring glycated hemoglobin assesses the effectiveness of therapy by monitoring long-term serum glucose regulation. In individuals with poorly controlled diabetes, the quantities of this glycated hemoglobin are much higher than in healthy people.

Using the conversion table (See table 1) from the American Diabetes Association’s (ADA) 2005 position statement on Standards of Medical Care in Diabetes, the 7.5% A1C reading would equate to an average blood glucose of about 168mg/dL. Bear in mind that the correlation between mean plasma glucose levels and A1C levels is an estimation only, dependent on methodology used for the calculation as well as other factors, such as the red blood cells’ life span. A 1 percent change in an A1C result reflects a change of about 30mg/dL (1.67 mmol/L) in average blood glucose.

Table 1

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Estimated Average Glucose (EAG)</th>
<th>Mean Plasma Glucose (MPG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>mg/dL</td>
<td>Mmol/L</td>
</tr>
<tr>
<td>5</td>
<td>97 (76-120)</td>
<td>5.4</td>
</tr>
<tr>
<td>6</td>
<td>126 (100-152)</td>
<td>7.0</td>
</tr>
<tr>
<td>7</td>
<td>154 (123-185)</td>
<td>8.6</td>
</tr>
<tr>
<td>8</td>
<td>183 (147-217)</td>
<td>10.2</td>
</tr>
<tr>
<td>9</td>
<td>212 (170-249)</td>
<td>11.8</td>
</tr>
<tr>
<td>10</td>
<td>240 (193-282)</td>
<td>13.4</td>
</tr>
<tr>
<td>11</td>
<td>269 (217-314)</td>
<td>14.9</td>
</tr>
<tr>
<td>12</td>
<td>298 (240-347)</td>
<td>16.5</td>
</tr>
</tbody>
</table>

Adapted: American Diabetes Association Standards of Medical Care in Diabetes- 2009, Diabetes Care;32: Suppl 1:S13-S61.14
Recommendations for the diagnosis of diabetes are based on the relations of fasting glucose and glycated hemoglobin with microvascular disease, typically retinopathy. Nonetheless, cardiovascular disease is the leading cause of illness, death, and hospitalization in persons with diabetes. In a recent study by Selvin et al., it was suggested that glycated hemoglobin values in the normal range can identify persons at increased risk for coronary heart disease, stroke, and death before the diagnosis of diabetes, indicating that glycated hemoglobin is a useful marker of cardiovascular risk and death from any cause.

There is a significant proportion of people who are unaware of their elevated HbA1C level before they have blood lab work. For a single blood sample, it provides far more revealing information on glycemic behavior than a fasting blood sugar value. That being said, fasting blood sugar tests are crucial in making treatment decisions. The American Diabetes Association guidelines are similar to others in advising that the glycosylated hemoglobin test be performed at least twice a year in patients with diabetes who are meeting treatment goals, with stable glycemic control, and quarterly in patients with diabetes whose therapy has changed or who are not meeting glycemic goals. Glycated hemoglobin measurement is not appropriate where there has been a change in diet or treatment within 6 week. Likewise, the test assumes a normal blood cell aging process and mix of hemoglobin subtypes, predominantly HbA in normal adults. Hence, people with recent blood loss, donated blood recently or have hemolytic anemia or genetic differences in the hemoglobin molecule (hemoglobinopathy) such as sickle-cell disease and other conditions, are not suitable for this test.

New Directions

In July 2009, an international expert committee (appointed by the American Diabetes Association (ADA), International Diabetes Federation (IDF) and the European Association for the Study of Diabetes (EASD) published a report that made the case for using HbA1C assay to diagnose type 2 diabetes. Although met with road blocks and controversies, in January 2010, the ADA now includes A1C as an appropriate diagnostic test, reversing its previous position that recommended against it.

Chronic diseases imply damaged or dysfunctional body parts. In the case of diabetes, the dysfunction is in the body’s ability to make or use insulin. Whether diabetes begins with the inability to properly use insulin (insulin resistance) or with inadequate production of insulin (beta-cell failure) is controversial but most diabetic patients experience both problems earlier rather than later in the disease. From the standpoint of diagnosis, however, the origin of diabetes is an academic debate because the use or production of insulin cannot realistically be measured on a population-wide basis. Thus, we rely on the result of the dysfunction-hyperglycemia to characterize and diagnose diabetes. In the United States, diagnosis is typically made on the basis of fasting plasma glucose (FPG), while in Europe and in clinical trials, an oral glucose tolerance test (OGTT) is the preferred method. Unfortunately, both tests have rather limited overlap, meaning that most persons diagnosed by an FPG would not be diagnosed by an OGTT and vice-versa. Furthermore, the two tests can produce different results for the same person on different days. As if that weren’t sufficiently confusing, consider that the level of hyperglycemia necessary to diagnose diabetes, by either test, is somewhat arbitrary. Because it is not clear what level of hyperglycemia represents a given level of insulin use or production, once diagnosed, we rely on A1C.

Use of A1C to diagnose diabetes has been considered by the expert panels in the past, but the idea has been rejected. The primary obstacle was a lack of standardization of the assay, but that is no longer the case. In fact, A1C is better standardized than other measurements of glucose. Other advantages of A1C include the fact that it is a better indication of overall glycemic exposure over time and that there is substantially less day-to-day variability. From a practical standpoint, A1C is much easier to measure because it does not require fasting or timed samples, and it is currently used to manage diabetes. The attractiveness of a single test to both diagnose and manage diabetes, especially while the test is easy to administer and largely reproducible, suggests that greater reliance on the A1C assay is inevitable.

The expert panel followed the methods used to define diagnostic thresholds for the FPG and OGTT, identifying 6.5% as the A1C level at which the prevalence of diabetic retinopathy begins to rise above that of nondiabetic patients.

The purpose in making diagnosis is to initiate treatment. Whether early treatment reduces the risk for microvascular and macrovascular complications associated with diabetes has not yet been determined but knowing that early treatment can reduce those complications, diagnosis of diabetes must be done sooner. Even it complications aren’t avoided with early treatment, other benefits of lifestyle can certainly accrue. Thus, there is little reason to delay diagnosis and treatment until A1C reaches 6.5%.

In summary, the expert panel has suggested that the A1C assay may be used to diagnose diabetes, recommending 6.5% as the diagnostic threshold, and the ADA has now accepted the suggestion. Regardless of which test one decides to use, it is apparent that
many factors play into account than just the result of the test in assessing a patient’s health risk and in selecting the next treatment approach. If an expert panel wanted to take on the topic of diagnosing diabetes, perhaps it is time to run away from the glucose-centric definition to one that more clearly represents the full cardiometabolic risk of the individual patient.

References
Questions for STEP Participants

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In the following, choose the one best answer for each question.

1. Glycated hemoglobin is also known as
   A. HbA1C
   B. Hb1c
   C. Hemoglobin A1c
   D. All of the above

2. Normal life span of an erythrocyte
   A. 30 days
   B. 24 hours
   C. 120 days
   D. 3–6 months

3. For people without diabetes, the average level of glycylated Hb is:
   A. below 4 %
   B. 4 to 6 %
   C. Above 10%
   D. 70 to 120 mg%

4. A 1 percent change in an A1C result reflects a change of about ________ in average blood glucose.
   A. 5.5 %
   B. 30 mg/dl
   C. 5.4 Mmol/l
   D. 120 mg %

5. Glycated hemoglobin values reflect the two to three month average endogenous exposure to glucose including postprandial spikes in the blood glucose level.
   A. True
   B. False

6. The leading cause of illness, death, and hospitalization in persons with diabetes is:
   A. nephropathy
   B. cardiovascular disease
   C. retinopathy
   D. liver disease

7. A person is not suitable to test for HbA1c when the individual has:
   A. recent blood loss
   B. hemoglobinopathy (variant Hgb molecule)
   C. sickle-cell disease
   D. All of the above

8. In January 2010, the American Diabetes Association (ADA) includes A1C assay as an appropriate diagnostic test for type 2 diabetes.
   A. True
   B. False

9. Laboratory diagnosis of diabetes is obtained by:
   A. FPG
   B. OGTT
   C. HBA1c
   D. All of the above

10. Advantages of A1C assay:
    A. does not require fasting
    B. used to diagnose diabetes
    C. used to manage diabetes therapy
    D. All of the above