EDUCATIONAL COMMENTARY- ESTIMATED AVERAGE GLUCOSE (eAG)

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Learning Outcomes
Upon completion of this exercise, the participant will be able to:

• describe the clinical study that demonstrated a linear correlation between hemoglobin A1C levels and the estimated average glucose (eAG).
• calculate the eAG from the hemoglobin A1C level.
• discuss the pros and cons of reporting an eAG in conjunction with a hemoglobin A1C level.

The incidence of diabetes is growing rapidly worldwide. The Centers for Disease Control and Prevention estimates that 24 million people in the United States have diabetes, with approximately 25% of them undiagnosed and an additional 57 million considered to be prediabetic. Globally, the World Health Organization estimates 175 million people have diabetes and projects that by 2030 this number will double. Diagnosis is based on a fasting (no caloric intake for 8 hours) plasma glucose concentration of 126 mg/dL (7.0 mmol/L) or higher, a casual or a random glucose concentration of >200 mg/dL (11.1 mmol/L) plus symptoms, or a 2-hour oral glucose tolerance test of 200 mg/dL or higher. Whichever test is used, the results should be confirmed by repeat testing on a subsequent day unless unequivocal symptoms of hyperglycemia are present. Laboratory testing is crucial in the diagnosis and monitoring of patients with diabetes (see “Update on Diabetes Testing,” API Chemistry Educational Commentary, 2006, 2nd Test Event, for a detailed discussion).

Monitoring Diabetes
Self-monitoring of blood glucose by diabetics followed by adjustment of medication is considered an essential component of preventing long-term effects of hyperglycemia, and patients are familiar with target blood glucose levels. Prolonged hyperglycemia has been shown to result in non-enzymatic glycation of several proteins including hemoglobin. The glycohemoglobin level, expressed as a percent of total hemoglobin and referred to as hemoglobin A1C or simply A1C, is a reflection of the mean blood glucose concentration for the previous 1 to 3 months and is considered the best assay for monitoring glycemic control over time (see “Glycohemoglobin,” API Chemistry Educational Commentary, 2002, 2nd Test Event). Current recommendations for frequency of A1C testing are: at least twice a year in patients with stable glycemic control who are meeting treatment goals, and quarterly in patients who are not meeting glycemic goals or whose therapy has changed. Recommended A1C levels are <6% to <6.5%.

Estimated Average Glucose (eAG)
Equations that correlate A1C levels to average glucose levels were developed as early as 1993 based on clinical studies. In June 2008, the American Diabetes Association (ADA) recommended that laboratories report estimated average glucose (eAG) values alongside A1C values, and numerous professional organizations have endorsed the recommendation.
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The recommended equation for calculating eAG is:

\[ 28.7 \times A1C - 46.7 = eAG \text{ (in mg/dL)} \]

The Table lists the calculated A1C values from 6% to 10% to eAG using this formula. Unlike implementation of the estimated glomerular filtration rate (eGFR) calculation (with which eAG is sometimes compared and which contains several variables in addition to the serum creatinine level), incorporating the eAG into laboratory information systems should be much easier because of the simplicity of the formula. One way to quickly estimate the eAG is to remember that 6% A1C correlates to 126 mg/dL (the diagnostic cutoff for diabetes) and then to add 28 mg/dL for each 1% increase in A1C. This estimation gives eAG values within 1 mg/dL of those in the Table. (An online calculator is available at: http://professional.diabetes.org/GlucoseCalculator.aspx.)

<table>
<thead>
<tr>
<th>Hemoglobin A1C, %</th>
<th>eAG, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>126</td>
</tr>
<tr>
<td>6.5</td>
<td>140</td>
</tr>
<tr>
<td>7</td>
<td>154</td>
</tr>
<tr>
<td>7.5</td>
<td>169</td>
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<td>8</td>
<td>183</td>
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<td>8.5</td>
<td>197</td>
</tr>
<tr>
<td>9</td>
<td>212</td>
</tr>
<tr>
<td>9.5</td>
<td>226</td>
</tr>
<tr>
<td>10</td>
<td>240</td>
</tr>
</tbody>
</table>

*The formula is eAG = 28.7 × A1C − 46.7.

Source: American Diabetes Association.

Basis of Recommendation
The ADA recommendation is based on the findings of an international (United States, Europe, Africa) study, the A1C-Derived Average Glucose (ADAG) Study, published in *Diabetes Care* in 2008.¹ The study used continuous glucose monitoring and self-glucose monitoring in 507 patients (268 type 1 diabetics, 159 type 2 diabetics, 80 nondiabetics) and determined that a linear relationship existed between the A1C level and estimated average daily glucose levels. Each subject obtained approximately 2700 glucose values during the 3-month study. An average glucose was calculated and linear regression analysis was used to determine the equation giving the tightest correlation. The priori criterion for establishment of a linear relationship was that 90% of the estimates had to be within 15% of the A1C regression equation, and this criterion was just barely met.

Debate Continues
Even though the ADA recommendation has been accepted in the United States, significant debate continues, and other countries have chosen to either not accept it or delay a decision pending further studies. The ADA’s
primary reason for the recommendation was that patients would have a better understanding of the A1C results if they could correlate them to their daily glucose measurements. Another reason cited by proponents of the recommendation is that because A1C is reported in percent with relatively small numbers, a significant hyperglycemic change is represented by a relatively small change in the A1C. That is, telling a patient that his or her A1C changed by 1% or 2% may not seem as significant as telling the patient that the daily glucose level changed by 56 mg/dL (3.1 mmol/L).

Critics or opponents of implementation often focus their concerns on the ADAG study on which the equation is based. The population studied was non-randomly selected and limited in that ethnic minorities were underrepresented, and other groups such as pregnant women, patients with unstable glucose control, and children were excluded. The authors acknowledged some of these limitations and advocate more studies targeting some of these groups. Perhaps of more significance is the criticism of the acceptance criterion (90% of the values within 15%) of the ADAG study. Critics argue that in approximately 10% of the cases the error limit is >15% and would be even higher when analytical and clinical variability is added. Critics have also pointed out that uncertainty associated with the eAG value itself is acknowledged in the study but is not evident in the formula. Using data from the study, they illustrated this uncertainty by showing that 2 patients with the same true mean glucose level of 170 mg/dL (9.4 mmol/L) could have A1C values as different as 6.5% and 9% and hence be told that their eAG is anywhere between 140 mg/dL (7.8 mmol/L) and 212 mg/dL (11.8 mmol/L). Still another criticism is that the eAG could confuse patients if there is a difference between the eAG and their self-monitored glucose values. The study authors stated that often this difference is due to self-monitoring sampling-time errors such as not testing at bedtime, and that if this is corrected the correlation improves.

Additional Complications

Both proponents and opponents stress that the A1C assay has limitations and that these limitations must be considered when interpreting eAG results. Any condition involving altered RBC turnover such as hemolytic anemia, aplastic anemia, or the removal of a spleen will affect A1C (and hence eAG) levels. Also, any patients with abnormal levels of hemoglobin A will have altered A1C levels.

A separate issue with A1C is that the A1C measurements in the Diabetes Control and Complications Trial (DCCT) published in 1993 did not use pure A1C for calibration and was not a true reference method. These values form the basis for the current targeted cutoff levels. A reference standard and a reference method were developed by an International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) working group. This group also recommended that A1C results be reported 3 ways: in traditional DCCT units (%), in new IFCC units of mmol/mol, and as the eAG. To further complicate the matter, A1C results obtained with instruments calibrated with the IFCC reference standard are 2% lower than those calibrated with the DCCT standard.

In 2008, a panel of diabetes experts proposed using A1C as both a screening and diagnostic tool for diabetes, much as fasting and random plasma glucose levels are currently used. One of the group members stated that
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the intent was to "generate discussion in the community, get people to look objectively at the published data and see if there is a role for HbA1c." The group recommended an A1c level of >6.0% for the initial screening cutoff and ≥6.5% as the diagnostic cutoff. No major organizations have adopted these recommendations to date, but several such as the ADA and the European Association for the Study of Diabetes are currently reviewing data with the intent of making a decision.

Summary and Conclusions
The United States medical community has generally adopted the recommendation from the ADA and clinical organizations that whenever a hemoglobin A1c value is reported, a corresponding estimated average glucose (eAG) is also reported. The eAG is easily calculated using a formula derived from linear regression analysis of extensive data obtained in the international (United States, Europe, Africa) A1c -Derived Average Glucose (ADAG) Study that demonstrated a linear relationship between A1c and eAG values. The debate continues concerning implementation of this recommendation as well as other recommendations about reporting of A1c results and use of A1c for diagnosis of diabetes.

References


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