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# Estimated Average Glucose: New Way to Assess Glucose Control

## *Introduction*

Recently, the American Diabetes Association, European Association for the Study of Diabetes, International Diabetes Federation, and the International Federation of Clinical Chemistry and Laboratory Medicine convened and recommended a number of changes in the reporting system for long-term glycemic control. They suggested that a new value for assessing long-term glucose control, the A1c-derived Average Glucose (ADAG) or estimated average glucose (eAG), will be reported (in units of either mg/dL or mmol/L) in addition to the A1c value. It is hoped that with this new system, patient understanding of their long-term glucose control will be enhanced.[1] A comparison of A1c and eAG is examined in the following document. A patient handout explaining the various methods to assess glucose control is also included.

## *Why the Change?*

The hemoglobin A1c assay is the recommended measurement for assessing long-term glucose control. An increase in A1c has been correlated with an increase in the risk of microvascular complications associated with diabetes. In order to reduce the complications associated with diabetes, the American Diabetes Association, the Canadian Association of Diabetes and the European Association for the Study of Diabetes, recommended that the A1c value be maintained below 7% for most patients.[2,3]

Despite the A1c being recognized as the standard measure of long-term glucose control, a number of general issues with the assay exist.[4,5]

First, many patients do not understand how to interpret an A1c value because it is expressed as a percentage value, while they are more comfortable with glucose values expressed in mg/dL or mmol/L. Second, the National Glycohemoglobin Standardization Program defines the reference method to measure A1c as high-performance liquid chromatography or HPLC. However, the HPLC method is somewhat nonspecific in that it measures other glycated hemoglobin components. In addition, although most methods used worldwide are certified by the National Glycohemoglobin Standardization Program, some countries such as Japan and Sweden use other standardization programs.[4,5]

These issues led the International Federation of Clinical Chemistry and Laboratory Medicine to develop a reference method that is more specific to A1c and could be standardized worldwide. But, the method developed by this group is complicated, expensive, and requires specialized equipment. Thus, it cannot be routinely incorporated into clinical practice. In addition, because the newly developed reference method is more specific, there is a 1.5 percent to two percent downward shift in the normal values. In addition, in order to be metrologically correct, the A1c should be expressed as mmol A1c/mol total hemoglobin resulting in a reference range of 29 to 43 mmol A1c/mol hemoglobin.[4,5]

It was thought that these changes would lead to significant confusion and likely a deterioration of glycemic control. In response, the American Diabetes Association, European Association for the Study of Diabetes, and the International Diabetes Federation convened and decided that the National Glycohemoglobin Standardization Program reference method be maintained, but an eAG be determined so that long-term glycemic control could be reported in units of mg/dL or mmol/L. This idea was agreed upon by the American Diabetes Association, European Association for the Study of Diabetes, International Diabetes Federation, and the International Federation of Clinical Chemistry and Laboratory Medicine and formed the basis for the A1c-derived Average Glucose (ADAG) trial discussed below.[4,5]

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### *What is an Estimated Average Glucose?*

The American Diabetes Association and the European Association for the Study of Diabetes sponsored the A1c-derived Average Glucose (ADAG) trial, to determine whether there is a correlation between A1c values and blood glucose measurements. In April 2006, this study began recruiting patients at 11 international sites (including U.S.). The goal was to enroll 700 patients including those with type 1 diabetes, type 2 diabetes, and healthy subjects of various ethnicities between 18 and 70 years old. Patients with diabetes were required to have stable glycemic control in the six months prior to recruitment. Patients received frequent glucose monitoring using continuous interstitial glucose monitoring which measures glucose levels every five minutes for two days at baseline, and then for one day every four weeks and home finger capillary glucose monitoring on other days. In addition, monthly monitoring of A1c values for three months was performed. Approximately 2700 glucose values per patient were obtained during the three month period. Using linear regression, A1c levels were compared with average glucose levels during the three month study period.[4,5] The equation which the authors identified was as follows:

Average glucose (mg/dL) =
28.7 x A1c - 46.7
or
Average glucose (mmol/L) =
1.59 x A1c – 2.59

The linear regression equations did not differ in subgroups based on age, sex, diabetes type, race, or smoking status.

Prior to the determination of this new equation, clinicians often used a conversion of an A1c of 6% approximately equal to an average glucose of 135 mg/dL. But this was based on old data which studied small numbers of patients, the majority of whom had type 1 diabetes. These studies utilized a limited number of blood samplings, usually during the daytime only, and most studies were short induration. Use of the new equation, derived from the correlation of thousands of glucose measurements to A1c values, provides the following eAG values:[4,5]

| A1c value | Estimated Average Glucose |
|---|---|
| 5% | 97 mg/dL (5.4 mmol/L) |
| 6% | 126 mg/dL (7 mmol/L) |
| 7% | 154 mg/dL (8.5 mmol/L) |
| 8% | 183 mg/dL (10.1 mmol/L) |
| 9% | 212 mg/dL (11.7 mmol/L) |
| 10% | 240 mg/dL (13.3 mmol/L) |
| 11% | 269 mg/dL (14.9 mmol/L) |
| 12% | 298 mg/dL (16.5 mmol/L) |

There are a number of limitations with the use of this equation. In the study used to determine the equation, many populations were not studied (children, Asians, Pacific Islanders). While it is unlikely that the physiology of glycation differs in these populations, the possibility exists. In addition, although the differences between the ethnic groups were not found to be statistically significant, the study was not adequately powered to detect such difference. Finally, patients with stable glycemia were studied. The effects of erratic glucose concentrations over the three month period are not known.[5]

### *Problems with the A1c*

It is important to note that although it is hoped that the new reporting system will improve patient understanding of their long-term glucose control, the equation utilizes a laboratory reported A1c, and there are a number of factors which can lead to inaccurate results.[6] Inaccurate A1c values (and therefore inaccurate eAG concentrations) should be considered when the patient's recorded self-monitoring blood glucose values do not appear to reflect the measured A1c or eAG value.

The A1c test measures the concentration of glycated hemoglobin or glycohemoglobin over the past two to three months. Glycated protein concentrations are proportional to the concentration of glucose in the blood over the typical life span of a red blood cell, or 120 days. However, it is more heavily weighted to the prior thirty days because blood cells glycated earlier in the 120 day time period may have been replaced with newer, non-glycated blood cells.[7]

There are a number of factors which can reduce the life span of a red blood cell.[6] Factors which falsely lower A1c include:

- recent acute blood loss
- hemolytic anemia
- chronic blood loss

*More. . .*

- hemoglobinopathies such as the presence of hemoglobin S, hemoglobin C, hemoglobin E, hemoglobin SC, or hemoglobin F

Factors which falsely increase A1c include:

- iron deficiency anemia
- patients without a spleen

A number of factors have inconsistent effects on A1c and include:

- high vitamin C intake
- high vitamin E intake
- chronic renal failure

In patients with a condition that leads to false results of the A1c, alternative methods of measuring average blood glucose should be considered. For example, the fructosamine test, also known as the glycated serum protein or glycated albumin, has been shown to be accurate in patients with hemoglobinopathies. The fructosamine test assesses glucose control over a two- to three-week period. However, the fructosamine test has not been standardized and values have not been correlated to the risk of complications associated with hyperglycemia.[6]

## *Conclusion*

A1c-derived average glucose or eAG is a new value which is used to assess long-term glucose control. The new system correlates A1c values with long-term control of glucose and is reported in units of mg/dL or mmol/L rather than a percentage value. It is hoped the new system will allow patients to better understand the measurement of their long-term glucose control.

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