

Translating Hemoglobin A_{1c} into Average Blood Glucose: Implications for Clinical Chemistry

David B. Sacks¹

Measurement of hemoglobin A_{1c} (Hb A_{1c})² is a fundamental component of the management of patients with diabetes mellitus. Hb A_{1c} measurement provides an indication of chronic exposure to glucose and is extensively used for both monitoring long-term glycemic status and evaluating whether an individual patient has attained adequate metabolic control. The patient's Hb A_{1c} value is used by clinicians to determine whether glucose-lowering therapy is adequate. A recent report (1) establishes a mathematical relationship between Hb A_{1c} and the average glucose (AG) concentration in blood. The findings presented are likely to have considerable impact on the way Hb A_{1c} is reported by clinical laboratories and used by healthcare providers (and patients). The importance and potential consequences of the study are the focus of this Perspective.

Monitoring Glucose Control

The efficacy of therapy to lower blood glucose in patients with diabetes mellitus is assessed by 2 complementary methods, glucose measurement, which is performed by patients, and Hb A_{1c} measurement. Patients perform self-monitoring of blood glucose (SMBG) by using hand-held meters to measure their own blood glucose concentrations. It is recommended that patients on insulin perform SMBG 4 times a day. The dose of the insulin injection is determined by the glucose value. Many modern meters store the results of all the glucose measurements, which can be downloaded and accessed by the physician during the patient's visit.

The second method for monitoring therapy to lower blood glucose is measurement of glycohemoglobin, most commonly performed by assaying Hb A_{1c}. Glycohemoglobin is formed by the attachment of glu-

cose to hemoglobin by a nonenzymatic process, termed glycation. The erythrocyte membrane is permeable to glucose, which enters the cell, where it binds to hemoglobin. The unstable product, termed an aldimine, undergoes an Amadori rearrangement to form a stable ketoamine (glycohemoglobin), which persists for the lifespan of the erythrocyte (typically 120 days). The concentration of glycohemoglobin is relatively consistent and does not exhibit the wide diurnal fluctuations seen with blood glucose, which varies substantially with exercise, food ingestion, and other factors. Because the rate of formation of glycohemoglobin is directly proportional to the glucose concentration in the blood, the glycohemoglobin concentration represents the integrated values for glucose over the preceding 8–12 weeks (2). Interpretation of glycohemoglobin depends on the erythrocyte having a normal lifespan. Any conditions that shorten erythrocyte survival will decrease the concentration of glycohemoglobin.

Several forms of glycohemoglobin have been identified. These include Hb A_{1c}, Hb A₁ (Hb A₁ consists of Hb A_{1a}, Hb A_{1b}, and Hb A_{1c}), and total glycohemoglobin (Hb A₁ and other hemoglobin-glucose adducts). Hb A_{1c} is formed by the attachment of glucose to the N-terminal valine of the β -chain of Hb A. The clinical value of Hb A_{1c} was unequivocally documented by the Diabetes Control and Complications Trial, which established a direct relationship between blood glucose concentration (assessed by Hb A_{1c}) and risk of microvascular complications in patients with type 1 diabetes (3). A subsequent study revealed analogous correlations between Hb A_{1c} and microvascular complications in patients with type 2 diabetes (4). The American Diabetes Association and other clinical organizations recommend routine (at least twice a year) measurement of Hb A_{1c} in all persons with diabetes.

Hb A_{1c} and AG

In the Diabetes Control and Complications Trial, retrospective analysis of data derived from SMBG measurements made by patients identified a linear correlation between Hb A_{1c} and AG concentrations (5). Although the study population was large (1441 patients), the Diabetes Control and Complications Trial

¹ Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.

Address correspondence to the author at: Brigham and Women's Hospital, Department of Pathology, 75 Francis Street, Thorn 530, Boston, MA 02115. Fax (617) 278-6921; e-mail dsacks@rics.bwh.harvard.edu.

Received August 12, 2008; accepted August 13, 2008.

Previously published online at DOI: 10.1373/clinchem.2008.113282

² Nonstandard abbreviations: Hb A_{1c}, hemoglobin A_{1c}; SMBG, self-monitoring of blood glucose; AG, average glucose; eAG, estimated AG.

was not designed to determine AG, and the correlation was based on only 7 glucose measurements. A few other studies have examined the relationship, but the limited number of glucose assays raises questions about the assessment of chronic glycemia in these studies. To ascertain the relationship between Hb A_{1c} concentration and long-term glucose values, a multinational study was conducted. The findings were published recently (1). Study participants were recruited at 11 centers in the US, Europe, Africa, and Asia to obtain diverse racial and ethnic representation. The final study population included 268 patients with type 1 diabetes, 159 patients with type 2 diabetes, and 80 individuals without diabetes. Hb A_{1c} was measured at baseline and monthly for 3 months. To minimize assay variation, all Hb A_{1c} analyses were performed in a single laboratory with 4 different assays certified by the National Glycohemoglobin Standardization Program. AG is more difficult to measure accurately than Hb A_{1c}. For AG evaluation, participants underwent continuous glucose monitoring for 48 h at baseline and monthly for the duration of the study. The monitoring was performed with a MiniMed device, which measures interstitial glucose concentration every 5 min. During the 2 days of continuous glucose monitoring, study participants performed an 8-point assessment of blood glucose with a HemoCue meter. A third measure of glycemia employed SMBG (using the OneTouch Ultra) 7 times per day for at least 3 days per week, for the entire study period. Over the course of the 12-week study, approximately 2700 glucose measurements were performed on each participant.

Statistical analysis of the study data revealed that linear regression between Hb A_{1c} and AG provides the tightest correlation ($AG_{mg/dL} = 28.7 \times Hb A_{1c} - 46.7$; $AG_{mmol/L} = 1.59 \times Hb A_{1c} - 2.59$). For example, an Hb A_{1c} value of 6% (equivalent to the upper limit of the reference interval) translates into an estimated AG (eAG) of 7.0 mmol/L (126 mg/dL). A widely used target for therapy, Hb A_{1c} of 7%, corresponds to an eAG of 8.6 mmol/L (154 mg/dL) (1). Subgroup analysis indicates essentially uniform results. No significant differences in the regression equation were observed for variations in individuals tested, including sex, presence or absence of diabetes, type of diabetes, age, race, and ethnicity. Thus a single equation can be used for the majority of individuals.

Some caveats to the study require consideration. The inherent limitation to accurate measurement of glucose with meters and continuous monitors necessitated a wide acceptance range ($\geq 90\%$ of the values fall within $\pm 15\%$ of the regression line) (1). Although the data meet these a priori criteria for acceptance, the AG varies among individuals with the same Hb A_{1c} value. Several factors could account for the scatter. These in-

clude measurement error, interindividual variation, imperfect correlation between Hb A_{1c} and AG, and differences in glycation or heterogeneity in erythrocyte lifespan. Further analysis of selected subgroups in the study may yield insight. Another limitation is the low number of Asian individuals included in the study population (the planned participation of a subgroup of individuals from India did not occur). Therefore, India and China, the 2 countries with the largest numbers of individuals with diabetes, are not represented in the study population. Although no statistically significant differences were detected among ethnic groups, the study was not powered to identify possible differences. The absence of children and pregnant women from the study limits extrapolation of the findings to these groups. Another study constraint was that only diabetic patients with stable glycemic control were included, so the results are confined to this population.

The study is likely to impact both patients and all healthcare workers—ranging from clinicians and nurses to educators and laboratory personnel—who contribute to the management of patients with diabetes. The American Diabetes Association has initiated an extensive campaign to educate clinicians and patients. This education plan includes the establishment of an Estimated Average Glucose Steering Committee, which is working with diverse groups to facilitate implementation. Clinical laboratory personnel will have an important role. It is likely that many laboratories will use the regression equation provided above to calculate an eAG based on the Hb A_{1c} result. This eAG value would not replace the measured Hb A_{1c} concentration, which would still be reported, but could be provided in addition to the Hb A_{1c}. The concept is somewhat analogous to the reporting by many laboratories of eGFR (estimated glomerular filtration rate), which is calculated from the measured serum creatinine concentration. Laboratory information systems will perform the conversion from Hb A_{1c}, and eAG will be reported in International System of Units values (mmol/L) or mg/dL, consistent with the units used to report glucose in the specific laboratory. Some clinicians and numerous diabetes educators have expressed the belief that the concept of AG will be easier to explain to patients than Hb A_{1c}. Many patients with diabetes do not know whether they had a recent Hb A_{1c} measurement or its value, and the hope is that an explanation of eAG will replace this lack of knowledge with an indicator of glycemic control that is understandable to patients.

Notwithstanding the limitations mentioned above, the data generated by this study enhance our comprehension of the relationship between Hb A_{1c} and AG. Measurement of glycohemoglobin is an accepted

and integral part of the management of patients with diabetes. It is anticipated that in many laboratories Hb A_{1c} will continue to be reported, using the same units and reference range currently employed, along with eAG. I sincerely hope that the additional information will facilitate communication between clinicians and patients and improve glycemic control in individuals with diabetes.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting

or revising the article for intellectual content; and (c) final approval of the published article.

Authors' Disclosures of Potential Conflicts of Interest: Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. The following authors reported a potential conflict of interest:

Employment or Leadership: None declared.

Consultant or Advisory Role: None declared.

Stock Ownership: None declared.

Honoraria: The author is the recipient of an honorarium from Bio-Rad.

Research Funding: None declared.

Expert Testimony: None declared.

Role of Sponsor: The funding organizations played no role in the design of study, choice of enrolled patients, review and interpretation of data, or preparation or approval of manuscript.

References

1. ADAG Study Group. Translating the hemoglobin A_{1c} assay into estimated average glucose values. *Diabetes Care* 2008;31:1473–8.
2. Sacks DB, Bruns DE, Goldstein DE, Maclaren NK, McDonald JM, Parrott M. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 2002;48:436–72.
3. DCCT. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–86.
4. U.K. Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *UK Prospective Diabetes Study (UKPDS) Group. Lancet* 1998;352:837–53.
5. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA(1c): analysis of glucose profiles and HbA(1c) in the Diabetes Control and Complications Trial. *Diabetes Care* 2002;25:275–8.