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Clinically Significant Disagreement between Mean Blood Glucose and Estimated Average Glucose in Two Populations: Implications for Diabetes Management

Stuart A. Chalew, M.D.,[1,2] James M. Hempe, Ph.D.,[1,2] and Robert McCarter, Sc.D.[3]

Abstract

Background:

Hemoglobin A1c (HbA1c) is highly correlated with mean blood glucose (MBG) levels and widely used in assessment of diabetes therapy. It has been proposed to report HbA1c in terms of an estimated average glucose (eAG) derived from the population regression of MBG on HbA1c. Pertinent to the clinical utility of eAG would be the degree of agreement between eAG and MBG estimated from multiple sampled glucose measurements over time.

Methods:

We examined agreement between eAG and MBG by Bland–Altman analysis from two different populations of type 1 diabetes patients: 150 children at our clinic in New Orleans and publicly available data from 1440 participants in the Diabetes Control and Complications Trial (DCCT). In New Orleans, MBG was derived from the mean of each patient's self-monitored glucose records over the 3 months before the HbA1c was obtained at the patient's clinic visit. Hemoglobin A1c was traceable to the DCCT. In DCCT participants, MBG was calculated from the patient's seven-sample glucose profile set submitted during each quarterly visit. Estimated average glucose was calculated from each individual's HbA1c using a previously reported regression equation of MBG versus HbA1c, eAG = (HbA1c $*$ 28.7) - 47.7, derived from a continuous glucose monitoring protocol over a 12-week period.

Results:

The analysis showed that there is frequent and clinically significant disagreement between MBG and eAG. Estimated average glucose over or under estimated MBG by 28.7 mg/dl or greater (HbA1c difference of 1% or greater) in approximately 33% of patients from both populations. The eAG overestimation of MBG was highest at lower MBG. The difference between eAG and MBG was skewed upward with increasing mean of eAG and MBG in the DCCT.

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Author Affiliations: [1]Pediatric Endocrinology/Diabetes and Research Institute for Children, Children's Hospital of New Orleans, New Orleans, Louisiana; [2]Louisiana State University Health Sciences Center, New Orleans, Louisiana; and [3]Bioinformatics and Statistics Unit, National Children's Medical Center, Washington DC

Abbreviations: (ADAG) A1c-derived average glucose, (CHNOLA) Children's Hospital of New Orleans, (DCCT) Diabetes Control and Complications Trial, (eAG) estimated average glucose, (HbA1c) hemoglobin A1c, (LOA) limits of agreement, (MBG) mean blood glucose, (SD) standard deviation

Keywords: estimated average glucose, glycated hemoglobin, hemoglobin A1c, mean blood glucose

Corresponding Author: Stuart A. Chalew, M.D., Pediatric Endocrinology/Diabetes Children's Hospital of New Orleans and the LSU Health Sciences Center, 200 Henry Clay Ave., New Orleans, LA 70118; email address schale@lsuhsc.edu

Abstract cont.

Conclusions:

Frequent discordance between eAG and MBG in clinical practice will likely be confusing to patients and clinicians. In patients where eAG overestimates MBG, intensive management based on eAG alone will likely lead to greater frequency of hypoglycemic episodes. To overcome these limitations of eAG, a customized assessment of HbA1c with respect to a patient's MBG should be performed using directly monitored patient glucose levels over time.

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Introduction

Numerous studies have documented that hemoglobin A1c (HbA1c) is highly correlated with a patient's directly measured blood glucose levels averaged over time.[1–3] One of the most widely cited of these studies, the Diabetes Control and Complications Trial (DCCT), also demonstrated that treatment of type 1 diabetes patients that lowered the mean blood glucose (MBG) level to as close to normal as possible prevented the development and progression of long-term microvascular complications of diabetes.[3,4] The HbA1c achieved by patients during the DCCT was an important predictor of risk for microvascular complications.[4] The findings of the DCCT as well as the relative ease of measurement led to the widespread clinical use of HbA1c for monitoring the efficacy of diabetes management. The relationship between HbA1c and MBG derived from the DCCT data became widely cited, and HbA1c levels reported by clinical labs were often accompanied by an estimated MBG based on the DCCT linear regression formula.[5] Tandem reporting of an estimated MBG together with the directly measured HbA1c gave the impression that a patient's HbA1c level was reliably interchangeable with an MBG derived by the regression equation of MBG on HbA1c.

The A1c-Derived Average Glucose (ADAG) Study Group, a consortium of investigators, reevaluated the relationship between HbA1c and MBG using a hybrid protocol of continuous glucose monitoring and intermittent monitoring.[6] The ADAG study population was exclusively adult and primarily Europoid. These investigators again found a strong linear relationship between HbA1c and MBG in their study population. The ADAG group advocated supplementing the current laboratory reporting system for HbA1c with an estimated average glucose (eAG) derived from their population regression equation. One rationale for such a substitution would be presentation of glycemic control to patients and clinicians in terms of more easily understood and familiar units of blood glucose instead of the more abstract units of HbA1c.

The recommendation of the ADAG group implies that eAG is a reliable substitute for MBG, and aside from analytic variation, the only important factor determining HbA1c level is the preceding MBG. Our group and others have provided evidence indicating that HbA1c, in addition to its linear relationship with MBG, is also importantly influenced by consistent, between-individual factors.[7–14] Thus, at any given level of MBG and changes in MBG with therapy, there will be consistent between-patient differences in HbA1c. We have proposed that this between-patient variation (or biological variation) in HbA1c needs to be accounted for in order to provide the most reliable assessment of current patient clinical status as well as for prediction of complications. Potentially, biological variation in HbA1c would cause systematic skewing of individual patient eAG and clinically significant discrepancy between MBG and eAG. As most diabetes patients now have immediate access to updated MBG from their personal capillary glucose monitoring devices, considerable disparity between MBG and eAG may prove confusing for patients to understand and interpret. Furthermore, for eAG to be clinically relevant, the validity of the ADAG population relationship between HbA1c and MBG should be evaluated in other patient populations.

In order to assess the practical clinical impact that might occur with routine use of eAG, we undertook a comparison study of MBG derived from directly obtained patient glucose sampling with the corresponding eAG derived from HbA1c. If eAG is a reliable substitute

for MBG, then there should be negligible clinically significant difference between eAG and MBG in practice. Thus we sought in this project to examine the degree of agreement between eAG and MBG from patients in a typical pediatric diabetes clinic environment. In addition, we also compared eAG with MBG from publicly available DCCT data, which has multiple paired patient measures of HbA1c and MBG for up to 9 years.

Methods

Participants

Data were obtained from two populations. Population 1 was composed of patients from the Diabetes Clinic at the Children's Hospital of New Orleans (CHNOLA). Participants were restricted to children with type 1 diabetes regularly testing capillary blood glucose. Patients were at least 3 months past initial diagnosis of diabetes. Children with medical conditions known to alter HbA1c not due to changes in MBG were excluded from the study. Mean blood glucose and HbA1c data were collected during a retrospective review of charts.

In addition, publicly available data from the DCCT was evaluated. Extensive detail on this population and DCCT study design is available elsewhere.[3–4] In brief, participants were adolescents and adults with type 1 diabetes. Participants had samples for MBG and HbA1c obtained at least quarterly throughout the study. In one DCCT patient, there was insufficient MBG data to match with HbA1c, and information from this patient was not included in the analysis.

Hemoglobin A1c Assays

The CHNOLA HbA1c was assayed by a commercial immunoassay (DCA2000+, Bayer Diagnostics, Tarrytown, NY), which is traceable to the DCCT. The DCCT assayed HbA1c using a cation exchange high-performance liquid chromatography method.[15]

Mean Blood Glucose Assessment

The CHNOLA MBG was calculated for each patient at the clinic visit as the mean of all blood glucose levels collected and stored from the preceding 3 months in the patient's personal glucose monitoring device. The DCCT MBG was calculated from a seven-sample glucose profile set, which was obtained over the course of 1 day prior to the study visit. Mean blood glucose for that visit was the mean of the individual glucose values for that profile set.

Estimated Average Glucose

Estimated average glucose was calculated from patient HbA1c data using the regression equation published by the ADAG study group:[6] eAG = (HbA1c * 28.7) - 46.7. Mean blood glucose in the ADAG study was derived from hybrid continuous glucose monitored and intermittent monitoring protocol. Hemoglobin A1c was a composite of four DCCT traceable assays.[6]

Analysis

Available MBG and HbA1c recorded from CHNOLA charts were paired from each visit. Data were not included from a clinic visit if corresponding HbA1c or MBG was not available from that visit. Estimated average glucose was calculated from HbA1c along with the difference between eAG and MBG and the mean of eAG and MBG calculated for each visit.

For the DCCT data, MBG was paired with the closest HbA1c value dated within the month of the date of glucose profile set. Estimated average glucose was then calculated from HbA1c of each pair. The difference between eAG and MBG, the mean of eAG and MBG, was calculated. The mean for each of these variables for each patient over the course of DCCT participation was then computed. Agreement of the two measures of glycemia (eAG versus MBG) was performed using a Bland–Altman analysis.[16] Limits of agreement (LOA) are defined as +2 (upper LOA) or -2 (lower LOA) standard deviations (SDs) from the mean difference of eAG - MBG.

Results

Data from 150 patients at CHNOLA were available for analysis, and the average number of clinic visits contributing data was 1.5 (range 1 to 4 visits). In the DCCT, the MBG and matching HbA1c was available from 1440 patients. Hemoglobin A1c was highly correlated with MBG from both the CHNOLA ($r = 0.62$, $p < .0001$) and DCCT ($r = 0.82$, $p < .0001$) patient populations. As eAG is derived from the patient's HbA1c, it was correlated identically with MBG as was HbA1c.

Agreement between eAG and MBG was assessed by Bland–Altman analysis. A comparison of the two populations is presented in **Table 1**. The SD of the difference between eAG and MBG was 36.7 and 33.2 mg/dl, respectively, for the CHNOLA and DCCT populations. The Bland–Altman plots, **Figures 1** (CHNOLA) and **2** (DCCT), depict the difference between the two estimates of glycemia (i.e., eAG - MBG) on the y axis compared

Table 1.
Bland–Altman Analysis Summary for the Children's Hospital of New Orleans and Diabetes Complications and Control Trial Populations

Population	HbA1c (%)	MBG (mg/dl)	eAG (mg/dl)	eAG - MBG (mg/dl)	+2 SDs (mg/dl)	-2 SDs (mg/dl)
CHNOLA	8.3 ± 1.5	188 ± 43	192 ± 42	2.9 ± 36.7	76.3	-70.5
DCCT	8.2 ± 1.4	195 ± 53	188 ± 41	-6.7 ± 33.2	58.8	- 74

with the average of the individual's MBG and eAG on the *x* axis. The upper (+2 SD above the mean difference) and lower (-2 SD below the mean difference) LOA are also plotted on the charts. Wide variation or trends in the difference between eAG and MBG indicate lack of agreement between the estimates. The largest differences in eAG - MBG were found when the average of MBG and eAG ranged from 150–300 mg/dl. There was a significant decrease in eAG - MBG with increasing (MBG + eAG)/2 for the DCCT data (r = -0.296, p < .0001). In addition, the figures indicate the presence of clinically important disagreement between eAG and MBG for large numbers of patients in both populations. For both populations, the difference in eAG - MBG was inversely correlated with increasing MBG. Thus eAG tended to overestimate MBG at lower levels of MBG.

We quantified how many patients would be overestimated or underestimated by eAG. For reference, we selected a value of 28.7 mg/dl, as a difference between eAG and MBG of this magnitude would correspond to a difference in HbA1c of 1%. Similarly, a difference of 14.4 and 43 mg/dl between eAG and MBG would represent clinically important differences of a patient's HbA1c of 0.5% and 1.5%, respectively. **Table 2** is a compilation of the percentage of patients who would have differences greater than the absolute value of eAG - MBG at the three reference levels. Also included in the table within parentheses is the percentage of patients where eAG overestimated MBG by the designated thresholds; these patients have been referred to as "high glycators."

The DCCT data was further analyzed by treatment group (**Table 3**). There was much greater disagreement between eAG and MBG in the conventionally treated group than in the intensive group. The decrease of eAG - MBG with increasing levels of (MBG + eAG)/2 was apparent in both groups but more marked in the conventionally treated group. There was a greater percentage of high glycators in the intensive patients than in the conventional group. **Table 4** is a compilation of the percentage of patients who would have differences greater than the absolute value of eAG - MBG for the intensive and conventional treatment groups at the three reference levels. Also included in the table within parentheses is the percentage of patients where eAG overestimated MBG by the designated thresholds; these patients have been referred to as "high glycators."

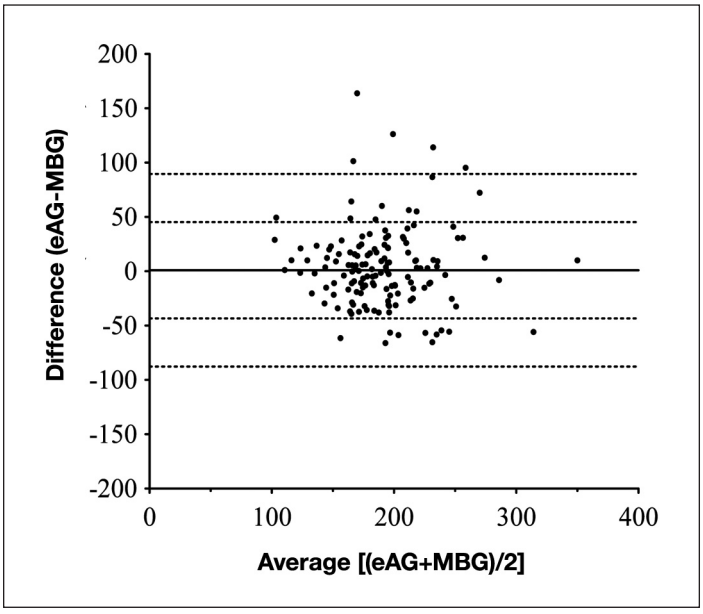

Figure 1. Bland–Altman plot of CHNOLA data.

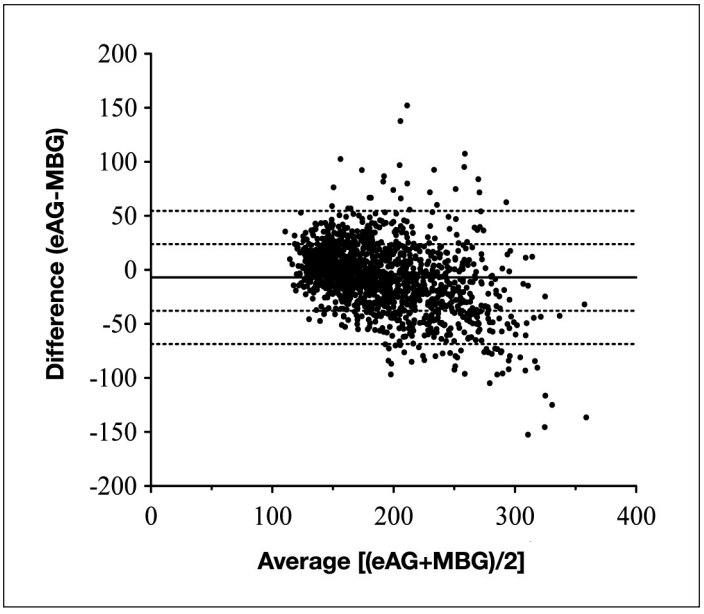

Figure 2. Bland–Altman plot of DCCT data.

Discussion

The ADAG study group has recommended interpreting HbA1c results in terms of an eAG to be calculated by the regression equation derived from their study population.[6] Specifically, a patient's HbA1c would be entered into the equation (eAG = [HbA1c * 28.7] - 46.7) and the eAG mathematically calculated.[6] Their proposal would potentially lead to eAG as the sole representation of HbA1c to patients and clinicians, replacing the more traditional practice of reporting HbA1c levels in terms of percent total hemoglobin. There were a number of limitations of the eAG study that might potentially preclude the implementation of its recommendations. The ADAG subjects were preselected to be representative of ranges of glycemic control. Hemoglobin A1c was a composite of four different assays. As the ADAG investigators limited the study to a single period of observation for their subjects, they never evaluated the consistency of repeated measures of HbA1c and MBG to assess the impact of between and within subject variation on eAG. The ADAG study population was primarily adult Europoids and potentially did not have sufficient power to detect racial differences in HbA1c controlled for MBG. A prior study suggests that there are ethnic differences in HbA1c not due to MBG.[17] The applicability to children was not addressed.[8,14] Neither did the ADAG group validate the application of their regression model in another population. Thus practical aspects of widespread application of eAG in large diverse clinical populations of patients is unclear.

Many diabetes patients, particularly those with type 1 diabetes, are regularly checking their capillary blood glucose levels with personal glucose meters. There is also growing availability and use of continuous glucose monitoring systems among patients. Thus a large group of patients have ready access to their updated MBG calculated from personal glucose data. If the eAG proposal were adopted, these patients would be confronted on a regular basis with two separate-source assessments of diabetes control in terms of glucose units, one being their updated MBG from directly measured glucose and the second an indirect estimate from eAG. In this project, we sought to compare MBG from direct patient monitoring from two different populations with eAG. We used Bland–Altman analysis[16] to examine the degree of agreement between eAG and MBG. For eAG to be a reliable guide for diabetes management, there should be fairly close agreement in most patients between eAG and MBG.

The first study population at the CHNOLA was an unselected group of children with type 1 diabetes.

Table 2.
Percentage of Patients with Absolute Difference between Estimated Average Glucose and Mean Blood Glucose

Absolute difference in eAG - MBG or HbA1c	CHNOLA Patients (%)[a]	DCCT Patients (%)[a]
14.4 (mg/dl) or 0.5%	61 (31)	58 (21)
28.7 (mg/dl) or 1%	37 (18)	31 (9)
43.1 (mg/dl) or 1.5%	18 (9)	15 (3)

[a] High glycators are represented within the parentheses.

Table 3.
Estimated Average Glucose and Mean Blood Glucose Comparison between Diabetes Complications and Control Trial Treatment Groups

DCCT group	*n*	HbA1c (%)	MBG (mg/dl)	eAG (mg/dl)	eAG - MBG (mg/dl)
Conventional	730	9.1 ± 1.3	231 ± 47	213 ± 37	-16 ± 39
Intensive	710	7.3 ± 0.9	158 ± 27	162 ± 26	3.8 ± 21.2

Table 4.
Percentage of Patients with Absolute Differences between Estimated Average Glucose and Mean Blood Glucose for the Diabetes Complications and Control Trial Treatment Groups

Absolute difference eAG - MBG	Conventional group (%)[a]	Intensive group (%)[a]
14.4 (mg/dl)	71 (19)	46 (29)
28.7 (mg/dl)	46 (10)	17 (11)
43.1 (mg/dl)	28 (5)	6 (3)

[a] High glycators are represented within the parentheses.

Glucose data were uploaded from patients' personal glucose meters for estimation of MBG, and at the same clinic visit, a sample for HbA1c was obtained. The data represents typical information about diabetes management that would be available in the routine monitoring and follow-up of pediatric diabetes patients. In this analysis, a considerable number of patients had clinically significant disagreement between their MBG and eAG. Published American Diabetes Association consensus glycemic goals of HbA1c for children cite targets in steps of 0.5% for different age groups.[18] A 0.5% difference in HbA1c would represent a difference between MBG and eAG of 14.4 mg/dl, while a 1% HbA1c difference would correspond to a 28.7 mg/dl difference between MBG and eAG. In our pediatric diabetes clinic, 61% and 37%

of patients had absolute differences between MBG and eAG exceeding 14.4 and 28.7 mg/dl, respectively. If only patients in whom eAG overestimated MBG, so-called "high glycators," were considered, then 31% and 18% of patients would exceed 14.4 and 28.7 mg/dl, respectively. Data from our clinic indicate that such discrepancies between MBG and eAG persist over time with repeated measuring and thus are unlikely to represent random analytic variation.[19]

The second population was the DCCT study group. The majority of the 1441 DCCT participants included were adults. In addition, HbA1c data generated from the DCCT study has been used as a reference guide for many other studies including eAG. The DCCT estimated MBG from a 1-day sampling of glucose levels before and after breakfast, lunch, and dinner and before bed. Thus the average of a single day's glucose sampling was paired with a contemporaneous HbA1c sample. Despite the limited scope of sampling underlying the MBG, HbA1c and MBG are highly correlated (r = 0.82). In addition to the influence of MBG on HbA1c, we have previously shown that there are consistent between-patient differences in HbA1c over time in DCCT patients.[9,10] The large number of repeated measurements per year over multiple years in the DCCT allows the appreciation of the consistency of between-patient variation of HbA1c versus MBG.[9,10]

Between-patient variation of HbA1c independent of MBG is likely the primary cause of disagreement between MBG and eAG found in the CHNOLA and DCCT populations.[10] Potential sources of biologic variation may include race/ethnicity,[17] genetic sources,[20,21] and aging.[22] Lack of appreciation of between-patient variation would lead to consistent overestimation or underestimation of MBG by eAG. Furthermore, the Bland–Altman analysis of the DCCT data shows that eAG - MBG differences are skewed downward with increasing glucose levels (**Figure 2**). This led to eAG underestimating MBG with increasing glucose levels. This bias appeared to occur because of a plateauing of HbA1c at higher MBG levels, thus HbA1c would underestimate MBG at higher levels. Potentially different HbA1c assays will perform differently over the range of clinically experienced MBGs. Such differences may not be appreciated if HbA1c assays are simply compared to each other by correlation analysis. It is unlikely that a rigorous assessment of the relationship between MBG and all clinically available HbA1c assays will be performed in the future. Thus skewing in the relationship between MBG and particular HbA1c methods will further contribute to inappropriate underestimation or overestimation of MBG by eAG in general clinical practice.

The DCCT data also revealed a difference in the frequency of eAG - MBG differences between the intensive and conventionally treated groups. There was greater variation in eAG - MBG with increasing MBG. As would be expected, patients in the conventional group had higher MBGs than the intensive group and thus greater variability in eAG - MBG. Estimated average glucose overestimated MBG more often in the intensive care group.

We consider cases where eAG overestimates MBG, so-called "high glycators," to be particularly problematic. In a considerable number of patients, particularly patients with type 2 diabetes, where personal glucose monitoring is not routine, therapy may be guided by HbA1c results alone. Overestimation of MBG by eAG would put these patients at increased risk for hypoglycemia. This may be a particular problem as noted earlier for patients undergoing intensive management. We estimate from our data that between 9% and 18% of patients would be high glycators and have a consistent discrepancy in which eAG overestimates MBG by 28.7 mg/dl or more. Several published studies of intensive diabetes control in type 2 diabetes treated HbA1c target protocols without consideration of between-patient HbA1c differences not due to MBG.[23–25] In these studies, increasingly aggressive hypoglycemic therapy was prescribed in order to reach a predetermined HbA1c goal. Participants in these studies experienced high occurrence of hypoglycemic episodes, and there was a higher mortality among this patient group, reported from the Action to Control Cardiovascular Risk in Diabetes trial.[23] Potentially, the higher morbidity and mortality described in these studies may have been due to overly aggressive therapy of unrecognized high glycators. Similar increased risk for hypoglycemia would be anticipated with reliance on eAG alone for titration of treatment.

Our findings indicate that patients and health care professionals will encounter frequent and clinically significant dissonance between a population-derived eAG and a patient's own directly monitored MBG. We are particularly concerned that high glycator patients whose eAG routinely overestimates MBG will be unidentified and at potential increased risk for hypoglycemic episodes if eAG is used as the primary criterion for medication adjustment. As sophisticated systems for direct assessment of MBG are now available, it would be prudent for patients to undergo a customized assessment of their own MBG status with HbA1c rather than rely on an eAG

derived from a population regression. Individualized assessment of HbA1c versus MBG would identify high glycator patients who might otherwise be exposed to undue hypoglycemia, especially during intensive management.

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