Estimated average glucose and self-monitored mean blood glucose are discordant estimates of glycemic control

Running Title: eAG bias

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Objective - The A1c-derived Average Glucose study recommended reporting A1c in estimated average glucose (eAG) equivalents. We compared eAG with self-monitored mean blood glucose (MBG) to determine if eAG is systematically biased due to biological variation in the relationship between MBG and A1c.

Research Design and Methods - MBG and A1c were recorded from charts of 202 pediatric type 1 diabetes patients at 1612 clinic visits. Patients were divided into groups with low, moderate, or high A1c bias based on a hemoglobin glycation index (HGI).

Results - MBG vs. eAG (mg/dl, mean±SD): total population, 194±34 vs. 196±36; low HGI group, 186±31 vs. 163±20; moderate HGI group, 195±28 vs. 193±19; high HGI group, 199±42 vs. 230±31.

Conclusions – eAG underestimated MBG in low HGI patients and overestimated MBG in high HGI patients. Disagreement between eAG and MBG downloaded from patient glucose meters will cause confusion if eAG is implemented for clinical use.
The A1c-derived Average Glucose (ADAG) study (1) recommended translating A1c into estimated average glucose (eAG) equivalents for monitoring glycemic control. Controversy persists over the underlying assumption that A1c levels depend exclusively on long-term previous blood glucose concentration (2-6). A number of studies have shown that biological variation in A1c is influenced by factors other than blood glucose concentration (7-13). This suggests that eAG may be a systematically biased estimate of self-monitored mean blood glucose (MBG).

RESEARCH DESIGN AND METHODS

Subjects - This study is an extension of a report on patients with type 1 diabetes at Children’s Hospital of New Orleans (14) and was approved by the Institutional Review Board at Louisiana State University Health Sciences Center, New Orleans, LA. Patients attended diabetes clinics approximately every three months. Data were collected from an average of eight clinic visits per patient.

Glycemic variables - MBG and A1c were transcribed from patient charts as entered by clinic personnel. Glucose data were downloaded from patient meters at each clinic visit. Meter model and sampling protocols varied by patient preference and insurance provider. MBG were calculated over periods of at least 30 days. An average of three glucose measurements per day were recorded in a study using a similar self-monitoring protocol (7). A1c was measured by National Glycohemoglobin Standardization Program (NGSP) (15) approved immunoassays at Children’s Hospital (184 patients) or by commercial laboratories that presumably also used NGSP approved methods (18 patients, including four low, seven moderate and seven high HGI subjects).

Hemoglobin glycation index (HGI) - A population regression equation (A1c (%) = (0.021 × MBG (mg/dl)) + 4.3, r=0.57) was derived using mean MBG and mean A1c from 202 patients collected at 1612 clinic visits as described elsewhere (14). The same data were used to calculate HGI and divide patients into low, moderate and high HGI groups. Predicted A1c were calculated at each clinic visit by inserting MBG into the regression equation. HGI were calculated by subtracting predicted A1c from observed A1c measured at the same clinic visit. Patients were divided into low, moderate and high HGI groups based on mean HGI tertile (33%) rank (low HGI< -0.41, n=67; moderate HGI= 0.41 to 0.26, n=68; high HGI>0.26, n=67).

Estimated average glucose (eAG) - eAG was calculated by inserting observed A1c into the ADAG linear regression equation (eAG (mg/dl) = (28.7 × A1c (%)) - 46.7, r=0.92) (1). A mean blood glucose index (MBGI) that quantifies the difference between MBG and eAG was calculated by subtracting observed MBG from eAG.

Statistical analysis - Descriptive statistics and linear regression analyses were generated using GraphPad Prism v. 4.03 (GraphPad Software, San Diego, CA).

RESULTS

In our original description of this study population (14) we reported that values of glycemic variables for the low, moderate and high HGI groups, respectively, were (mean±SD): MBG, 186±31, 195±28 and 199±42 mg/dl; A1c, 7.6±0.7, 8.4±0.7 and 9.6±1.1%; HGI, -1.0±0.4, -0.1±0.2 and 1.1±0.9%. The present analysis used A1c from that study to calculate mean eAG for the low, moderate and high HGI groups which were (mean±SD): 163±20, 193±19 and
230±31 mg/dl, respectively. Figure 1 compares eAG and MBG in the population and in the different HGI groups and shows that mean eAG and mean MBG were similar when compared in the population or in the moderate HGI group. In contrast, eAG underestimated MBG by an average of 12% (23 mg/dl) in the low HGI group and overestimated MBG by 16% (31 mg/dl) in the high HGI group. The average difference between eAG and MBG in these groups represented an A1c difference of about 1% based on the slope of the ADAG regression equation. Linear regression analysis of HGI vs. MBGI for all 202 patients showed that MBGI (the mean difference between eAG and MBG) for individual patients was significantly positively correlated with mean HGI (MBGI (mg/dl) = (28.7 × HGI (%) + 1.9, r=0.91, p<0.0001).

CONCLUSIONS
The ADAG study concluded that A1c could be reliably translated into eAG based on the linear relationship between A1c and mean blood glucose measured by continuous glucose monitoring in a mixed population of diabetic and non-diabetic subjects (1). This conclusion assumes that all population variation in A1c is either random or due to variation in blood glucose concentration. However, numerous reports of biological variation in A1c (7-13) indicate that this assumption is false. We previously developed HGI to quantify biological variation in A1c due to factors other than blood glucose concentration and showed that HGI was quantitatively consistent within individuals over time, different between individuals, normally distributed and positively correlated with risk for complications (7,8,14). The fact that many patients have HGI values that are always positive or always negative indicates that HGI measures systematic A1c bias between individuals. The present study clearly demonstrates that this systematic A1c bias makes eAG a systematically biased estimate of MBG downloaded from patient glucose meters in high and low HGI patients.

It is important to emphasize that the present study used routine A1c and MBG data typical of that available in most diabetes clinics. If A1c is reported as eAG, patients and clinicians will be confronted with significant discrepancies between eAG and self-monitored MBG which will confound interpretation of glycemic control. Furthermore, treating patients based on eAG alone could result in inappropriate medical decisions (2). Based on Figure 1, if low HGI patients are intensively managed to a low eAG target their MBG would presumably remain above the target, inadvertently leaving these patients at unnecessary risk for chronic complications. Conversely, intensive management could drive MBG in high HGI patients below the eAG target which presumably would increase their risk for hypoglycemia.

We conclude that translating A1c into eAG produced biased estimates of MBG downloaded from patient glucose meters in low and high HGI patients. However, since MBGI (the difference between eAG and MBG) was positively correlated with HGI, eAG derived using the carefully determined ADAG regression equation may have clinical value for assessing biological variation in A1c. Either HGI or MBGI could prove clinically useful for more comprehensive risk assessment and personalized patient care.

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FIGURE LEGENDS

Figure 1 – Disagreement between eAG and MBG. Mean eAG and mean self-monitored MBG were compared in all 202 patients in the population and separately by HGI group. Values are group means ±SD. MBG was similar to eAG in the population and in the moderate HGI group, higher than eAG in the low HGI group and lower than eAG in the high HGI group. Dividing the study population into HGI groups automatically produces subpopulations with similar MBG but different A1c. Since eAG is calculated from A1c it is not surprising that eAG systematically under- or over-estimates MBG in some patients.