Persistence of Individual Variations in Glycated Hemoglobin

Analysis of data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Trial

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OBJECTIVE—To determine the individual persistence of the relationship between mean sensor glucose (MG) concentrations and hemoglobin A_{1c} (A1C) from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring (CGM) Randomized Trial.

RESEARCH DESIGN AND METHODS—MG was calculated using CGM data for 3 months before A1C measurements at 3, 6, 9, and 12 months for the CGM group and at 9 and 12 months for the control group. An MG-to-A1C ratio was included in analysis for subjects who averaged ≥4 days/week of CGM use.

RESULTS—Spearman correlations of the MG-to-A1C ratio between consecutive visits 3 months apart ranged from 0.70 to 0.79. The correlations for children and youth were slightly smaller than those for adults. No meaningful differences were observed by device type or change in A1C.

CONCLUSIONS—Individual variations in the rate of hemoglobin glycation are persistent and contribute to the inaccuracy in estimating MGs calculated from A1C levels.

Hemoglobin A_{1c} (A1C) is a time-honored gold standard measure of overall diabetes control, and A1C measurements serve as the targets for diabetes management (1). More recently, elevated A1C has been proposed as a more facile method for diagnosing diabetes (2). Additionally, A1C forms the basis for calculating the synthetic estimated average glucose (eAG) (3). Both of these uses of A1C implicitly assume a consistent ratio between A1C and mean glucose (MG) over 2–3 months across individual subjects. Although the chemistry of glycation predicts a straightforward relationship between MG concentrations and A1C, many investigators have reported persistent individual variations in the rate of glycation among both subjects with and without diabetes. Investigators have described fast or high glycators as well as slow or low glycators. Twin studies suggest a substantial heritable component (4).

Quantifying both the magnitude and the degree of persistence of the individual variation in the rate of erythrocyte glycation, however, has been hampered by limitations in accessing MG concentrations in groups of patients over a long period of time (5,6). In contrast, the recently completed Juvenile Diabetes Research Foundation (JDRF) Continuous Glucose Monitoring (CGM) trial provided data to closely examine the relationship between MG concentrations, measured in a near continuous fashion for 6–12 months, and the A1C values measured centrally in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) laboratory in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS
—The JDRF CGM randomized trial protocol has been described in detail previously (7–9). Major eligibility criteria included age ≥8 years, type 1 diabetes for ≥1 year, use of either an insulin pump or at least three daily insulin injections, and A1C <10.0%. Subjects were randomly assigned to either a CGM group or a control group for the first 6 months after which both groups used CGM for an additional 6 months. A1C was measured, and CGM data were downloaded at study visits occurring at 3, 6, 9, and 12 months from baseline. Thus subjects in the CGM group could contribute up to four A1C/CGM data points over 12 months, whereas those in the original control group could contribute two data points (when they had been using CGM at the 9- and 12-month visits).

All three commercially available glucose sensors were used, and subjects were instructed to wear the sensor on a continuous basis (7,8). A new sensor was inserted every 3–7 days with 4–15 calibrations over the sensor use according to the manufacturer's recommendations. A1C values were

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measured at the University of Minnesota using the Tosoh A1C 2.2 Plus Glycohemoglobin high-performance liquid chromatography analyzer (9).

MG was calculated using CGM data over the 91-day span before each visit, giving equal weight to each of the 24 h of the day. A data point was included in the analysis if the subject averaged ≥4 days per week of CGM use over the 91-day period and the subject had at least two 3-month CGM epochs followed by an A1C value. This criterion was met for 889 epochs in 311 of the 451 randomized subjects (153 had two epochs, 49 had three epochs, and 109 had four epochs). Within-subject persistency of the ratio of MG to A1C at different time points was assessed using Spearman correlation. A correlation coefficient based on ranks using the method of Magee (10) to account for repeated measures was computed. Results were similar using the hemoglobin glycation index (11) as an alternate measure of glycation, using both the regression equations from the JDRF randomized clinical trial data (7,8) and the American Diabetes Association Equation (12) (Supplementary Figs. A1 and A2). Subgroup analyses were performed by age, sex, device type, and change in A1C over the previous 3 months. The cohort did not contain enough non-White or Hispanic subjects to evaluate race/ethnicity.

RESULTS—The 311 subjects ranged in age from 8 to 73 years (mean ± SD: 28 ± 17) at study entry, with 28% of subjects aged 8 to <15 years, 26% between 15 and <25 years, and 46% ≥25 years. Median (25th, 75th percentiles) duration of diabetes was 6 (3, 7), 8 (5, 12), and 23 (16, 32) years for these age-groups, respectively. Baseline A1C values ranged from 4.7 to 9.8% (mean ± SD: 7.4 ± 0.8), and 56% were female.

The median (25th, 75th percentiles) of the MG-to-A1C ratio among all 889 epochs was 22.2 mg/dL per 1% (20.8, 23.5) ranging from 17.2 to 31.6. This distribution was steady over the 12-month course of the study (median values 22.4, 22.1, 22.1, and 22.1 at 3, 6, 9, and 12 months, respectively). Children and youth had larger ratios compared with adults (median 23.0 vs. 22.3 vs. 21.4 for subjects aged 8 to <15, 15 to <25, and ≥25 years, respectively; *P* < 0.001). As shown in Fig. 1, subjects who were high glycators (low MG-to-A1C ratio) during one 3-month epoch tended to be high glycators during the subsequent
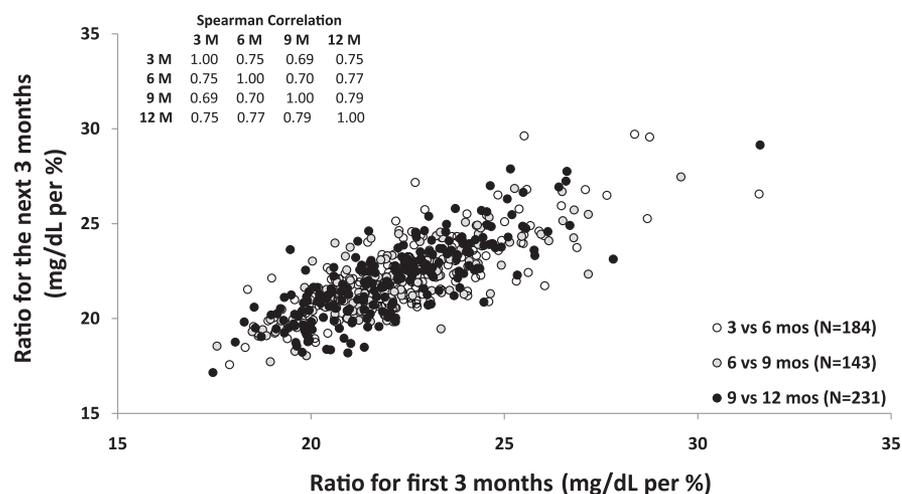
Figure 1—*Comparison of the MG-to-A1C ratio from the same subject at different times. The MG-to-A1C ratios of subjects in 3-month periods were compared. The ratio at the earlier time is on the* x-axis, *and the ratio 3 months later is on the* y-axis. *Spearman correlation values are given for all four times.*

3-month epoch. Correlations of the MG-to-A1C ratio between consecutive epochs ranged from 0.70 to 0.79. The correlation value from the repeated-measures model was 0.67. The correlation was comparable (*r* = 0.75) over a 9-month span from 3 to 12 months. Correlation values for children and youth were smaller than those in adults ranging from 0.57 to 0.71, 0.46 to 0.65, and 0.75 to 0.78 between consecutive epochs, for subjects aged 8 to <15, 15 to <25, and ≥25 years, respectively. All *P* values were < 0.001. Correlations of the ratio of change in MG to change in A1C between successive visits ranged from 0.50 to 0.58 (Supplementary Fig. A3). No meaningful differences were observed by sex, device type, and treatment group (Supplementary Table A1 and Fig. A4).

CONCLUSIONS—Our results confirm the finding of others that individuals with type 1 diabetes persistently glycate hemoglobin at different rates. Many factors have been proposed to explain this (13,14), including conditions impacting erythrocyte life span, variation in erythrocyte glucose transport, and deglycation within the erythrocytes. In a recent meta-analysis of 10 genome-wide association studies examining nearly 15,000 nondiabetic adults of European descent, Wheeler et al. (15) found 10 loci associated with A1C, 2 of which were associated with iron homeostasis, perhaps altering erythrocyte life span.

Factors that alter the rate of hemoglobin glycation may be associated with the rate of glycation of other proteins, thus impacting the likelihood of diabetes complications. Additionally, these persistant differences in the MG-to-A1C ratio imply that the MG concentration calculated from A1C measurement should be used with caution.

The study was designed and conducted by the investigators. The writing group collectively wrote the manuscript and vouch for data. The investigators had complete autonomy to analyze and report the trial results. There were no agreements concerning confidentiality of data between the Juvenile Diabetes Research Foundation, Inc., the authors, or their institutions. The Jaeb Center for Health Research had full access to all data in the study and takes responsibility for the integrity of data and the accuracy of data analysis.

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