Hemoglobin A_{1c} and Mean Glucose in Patients With Type 1 Diabetes

Analysis of data from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial

JUVENILE DIABETES RESEARCH FOUNDATION CONTINUOUS GLUCOSE MONITORING STUDY GROUP*

OBJECTIVE—To determine the relationship between mean sensor glucose concentrations and hemoglobin A_{1c} (HbA_{1c}) values measured in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications laboratory at the University of Minnesota in a cohort of subjects with type 1 diabetes from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial.

RESEARCH DESIGN AND METHODS—Near-continuous glucose sensor data (≥4 days/week) were collected for 3 months before a central laboratory–measured HbA_{1c} was performed for 252 subjects aged 8–74 years, the majority of whom had stable HbA_{1c} values (77% within ±0.4% of the patient mean).

RESULTS—The slope (95% CI) for mean sensor glucose concentration (area under the curve) versus a centrally measured HbA_{1c} was 24.4 mg/dL (22.0–26.7) for each 1% change in HbA_{1c}, with an intercept of −16.2 mg/dL (−32.9 to 0.6). Although the slope did not vary with age or sex, there was substantial individual variability, with mean sensor glucose concentrations ranging from 128 to 187 mg/dL for an HbA_{1c} of 6.9–7.1%. The root mean square of the errors between the actual mean sensor glucose concentration versus the value calculated using the regression equation was 14.3 mg/dL, whereas the median absolute difference was 10.1 mg/dL.

CONCLUSIONS—There is substantial individual variability between the measured versus calculated mean glucose concentrations. Consequently, estimated average glucose concentrations calculated from measured HbA_{1c} values should be used with caution.

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Hemoglobin A_{1c} (HbA_{1c}) is a time-honored gold standard measure of overall diabetes control, and HbA_{1c} values serve as the targets for diabetes management (1). The chemistry of glycation predicts a straightforward relationship between mean glucose concentrations and HbA_{1c} values over the average lifespan of a patient's red cells (2). Because the Diabetes Control and Complications Trial (DCCT) (3) demonstrated that improved glycemic control, measured as HbA_{1c}, decreased the risk of long-term diabetic complications, most HbA_{1c} measurements have been standardized to the DCCT values via the National Glycohemoglobin Standardization Program. Current HbA_{1c} assays can be fast, precise, and accurate (4).

Determining the true relationship between mean glucose concentrations and HbA_{1c} values has been hampered by limitations in accessing mean glucose concentrations in groups of patients over a period of ≥3 months. Discrete glucose measurements obtained infrequently over the day often fail to capture the true magnitude of glycemic excursions commonly found in patients with type 1 diabetes (5) and underestimate the extent and frequency of nocturnal hypoglycemia (6).

In contrast, the recently completed Juvenile Diabetes Research Foundation (JDRF)-sponsored continuous glucose monitoring (CGM) trial provided data to closely examine the relationship between mean glucose concentrations, measured in a near-continuous fashion for 3 months, and the subsequent HbA_{1c} values measured centrally in the DCCT/Epidemiology of Diabetes Interventions and Complications (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 at least 1 year, use of either an insulin pump or at least three daily insulin injections, and an HbA_{1c} value <10.0%. Subjects were randomly assigned to either a CGM group or a control group that used standard home blood glucose monitoring for the first 6 months. After 6 months, both groups used CGM.

Subjects received one of the following CGM devices: the DexCom SEVEN (DexCom, San Diego, CA), the MiniMed Paradigm REAL-Time insulin pump and continuous glucose monitoring system (Medtronic MiniMed, Northridge, CA), or the FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA). Each subject was instructed to wear the sensor on a continuous basis.

HbA_{1c} values were measured at the University of Minnesota using the Tosoh HbA_{1c} 2.2 Plus Glycohemoglobin Analyzer (10). The cohort did not contain enough non–white or Hispanic subjects to evaluate race/ethnicity.

Statistical analysis

We limited our analysis to subjects who averaged ≥4 days per week of CGM use in the 3 months before an HbA_{1c} measurement. To minimize the impact of

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*Members of the writing committee are listed in APPENDIX. A full listing of the members of the study group is included in the Supplementary Data online.

changing glycemic control after the introduction of CGM, we only analyzed the 3 months of CGM data collected before the 12-month (end-of-study) HbA_{1c} measurement. An HbA_{1c} value was obtained for 436 subjects who completed the 12-month visit. Of these, 252 subjects had worn their CGM device for an average of ≥4 days per week during the prior 3 months and were included in these analyses.

Mean glucose concentrations were calculated over the 91-day period before the HbA_{1c} measurement, giving equal weight to each of the 24 h of the day. Similar calculations were done for the mean glucose values during the 1-month (30-day) and 2-month (61-day) intervals before the HbA_{1c} measurement. Least–squares regression analysis was performed using mean glucose concentration as the dependent variable and HbA_{1c} as the independent variable (linear term). Fitting higher order polynomial terms showed no deviation from linearity. Residual values were examined to verify that they followed an approximate normal distribution. No outliers or overly influential data points were identified. A plot of residuals against predicted values showed no meaningful deviation from the assumption of homoscedasticity.

RESULTS—At the 12-month visit, the 252 subjects in analysis ranged in age from 9 to 74 years (mean ± SD: 32 ± 17), with 21% of subjects <15 years, 24% between 15 and 24 years, and 55% ≥25 years. Median duration of diabetes was 7 years (25th to 75th percentile, 4–9) for children, 8 years (5–10) for adolescents, and 24 years (17–32) for adults; 54% were female and 94% were white. HbA_{1c} values ranged from 5.1 to 9.6% (7.1 ± 0.8%). Approximately half of subjects had a stable HbA_{1c} value, with 55% being within ±0.2% of the HbA_{1c} value measured 3 months prior, 21% improving ≥0.3%, and 24% worsening ≥0.3% over the last 3 months. In total, 346,434 h of CGM glucose values (median 1,433 h per subject) were analyzed.

The slope (95% CI) for mean sensor glucose concentration (area under the curve) versus a centrally measured HbA_{1c} was 24.4 mg/dL (22.0–26.7) for each 1% change in HbA_{1c} with an intercept of −16.2 mg/dL (−32.9 to 0.6) (Fig. 1 and Table 1). Using only 1 or 2 months of glucose data before the HbA_{1c} measurement did not alter the slope (Table 1).

The slope of mean glucose concentration versus HbA_{1c} value did not vary meaningfully by age, sex, or type of CGM device (Table 1). Although only 42 of the 252 subjects were not insulin pump users, the mode of insulin delivery did not materially alter the slope. Reanalyzing the data using only the 195 subjects whose HbA_{1c} remained within ±0.4% of the value obtained 3 months earlier or the 138 subjects whose HbA_{1c} remained within ±0.2% did not materially alter the slopes.

Substantial individual variability existed in the relationship between HbA_{1c} and mean glucose concentration. For HbA_{1c} values between 6.9 and 7.1% (n = 46), the average sensor mean glucose concentrations ranged from 128 to 187 mg/dL. For HbA_{1c} values between 7.9 and 8.1% (n = 16), the average sensor mean glucose concentrations ranged from 154 to 223 mg/dL (Fig. 1). The root mean square of the errors between the actual mean sensor glucose concentration versus the value calculated using the regression equation was 14.3 mg/dL, whereas the median absolute difference was 10.1 mg/dL. A total of 91% of subjects had mean glucose concentrations within ±15% of the calculated average glucose concentrations (calculated from HbA_{1c}).

CONCLUSIONS—The estimated slope of the relationship between mean glucose concentration and HbA_{1c} has varied from study to study (Table 2). In studies that used infrequent discrete blood glucose testing, Hempe et al. (11) found a slope of 18.5 mg/dL for each unit (%) change in HbA_{1c}, whereas Rohlfing et al. (12) and Makris et al. (13) found slopes of ~35 mg/dL for each unit (%) change in HbA_{1c}, a number that was used to describe the relationship for a decade. These investigators also found wide variability between measured mean glucose concentrations and estimated average glucose values calculated using their regression equations.

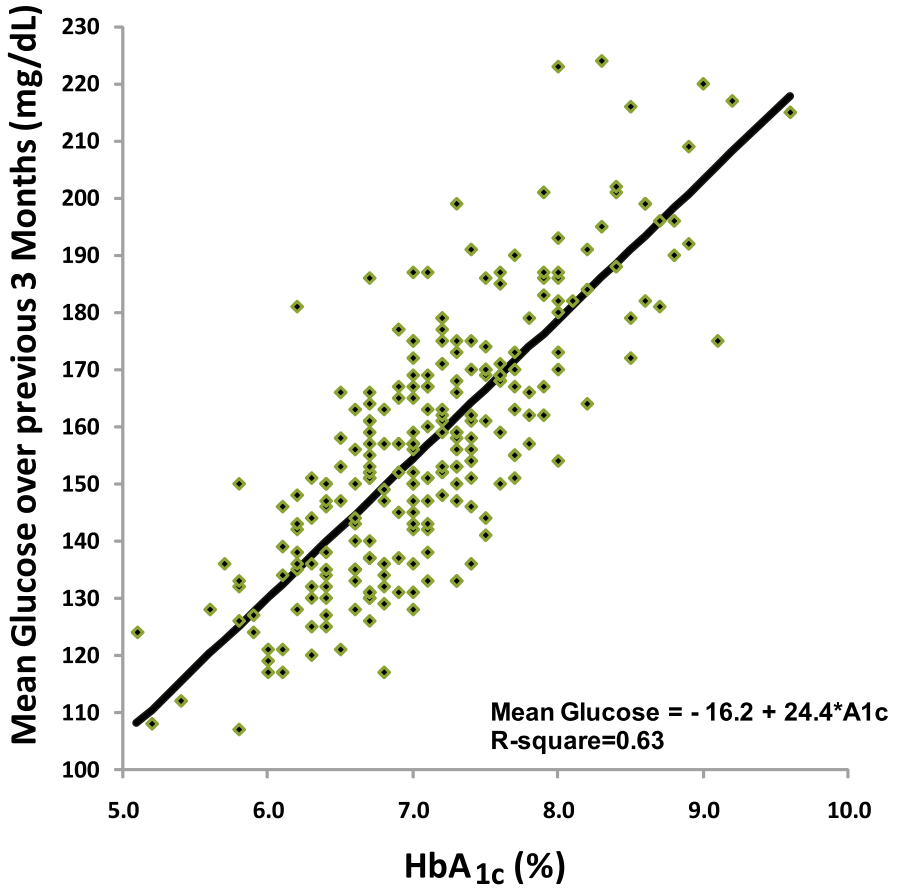

Figure 1—*Mean glucose versus HbA_{1c}: mean glucose measured by the CGM device over 3 months (91 days) before the HbA_{1c} measurement* (n = 252). *Regression line was calculated using least squares. (A high-quality color representation of this figure is available in the online issue.)*

Table 1—*Mean glucose versus HbA$_{1c}$ in subgroups*

	Subjects (*n*)*	Slope for mean glucose versus HbA$_{1c}$ (mg/dL per 1%)		
		3 months†	2 months†	1 month†
Overall	252	24.4 ± 2.3	25.4 ± 2.4	25.7 ± 2.9
Age (years)				
8–14	54	25.0 ± 3.7	26.3 ± 4.1	26.6 ± 4.9
15–24	60	24.6 ± 4.8	25.1 ± 5.3	26.3 ± 6.9
≥25	138	20.7 ± 3.5	21.8 ± 3.6	20.9 ± 4.1
Treatment group				
Control	122	22.5 ± 3.7	24.2 ± 4.0	22.8 ± 4.8
RT-CGM	130	25.7 ± 2.9	26.1 ± 3.1	27.9 ± 3.6
Sex				
Female	137	24.8 ± 3.0	25.8 ± 3.2	25.9 ± 3.9
Male	115	23.5 ± 3.6	24.5 ± 3.8	25.0 ± 4.5
Insulin delivery				
Multiple daily injections	42	25.8 ± 6.0	26.8 ± 6.1	29.3 ± 8.0
Pump	210	23.5 ± 2.5	24.3 ± 2.7	24.0 ± 3.2
CGM device				
DexCom	53	25.8 ± 4.9	27.5 ± 5.3	29.5 ± 7.2
Navigator	52	20.7 ± 4.3	22.0 ± 4.8	21.1 ± 5.8
Paradigm	147	24.8 ± 3.3	25.4 ± 3.4	25.4 ± 3.8
Change in HbA$_{1c}$ over the prior 3 months				
Improved ≥0.5%	26	26.4 ± 5.7	25.3 ± 5.7	25.2 ± 6.4
Within ±0.4%	195	24.2 ± 3.0	24.6 ± 3.2	25.5 ± 3.8
Worsened ≥0.5%	31	25.7 ± 5.8	27.1 ± 6.1	23.6 ± 7.5

Data are slopes (± margin of error for 95% CI) unless otherwise indicated. *One subject was not included in the 1-month analysis because of insufficient data. †Mean glucose calculated from CGM data taken over 3 months (91 days), 2 months (61 days), and 1 month (30 days) before the HbA$_{1c}$ measurement. To convert slopes to mmol/L per 1%, divide by 18. RT-CGM, real-time continuous glucose monitoring.

In our study, the slope of the regression line was 24–25 mg/dL glucose for every 1% change in HbA$_{1c}$. This value is lower than values reported earlier using six to seven intermittent sample blood glucose profiles (11,12) but similar to the results of other studies that used CGM (14–16). For example, using CGM, Mazze (14) found a slope of 26.3 with mean glucose concentration as the dependent variable.

Nathan et al. (15) and Borg et al. (17) used a combination of both intermittent discrete and intermittent CGM data from adults with and without diabetes. They found a slope of 28.7 mg/dL glucose for every 1% change in HbA$_{1c}$ using CGM data (15), which was also similar to the value in the current study, and a correlation of 0.89 between HbA$_{1c}$ and mean glucose using CGM and self-monitoring blood glucose data combined (17).

It is not surprising that the relationship between measured glucose concentrations and HbA$_{1c}$ differs with the use of CGM compared with episodic blood glucose monitoring. One might expect that the addition of a more complete 24-h measure of glucose concentrations would provide a tighter and more accurate assessment of the relationship between glucose concentrations and HbA$_{1c}$ values. There are limitations to the determination of the relationship between glucose and HbA$_{1c}$ with the current study. However, we did not find any major differences in the relationships between glucose concentrations and HbA$_{1c}$ values when considering patients whose HbA$_{1c}$ was stable and patients whose HbA$_{1c}$ changed over the time interval of observation. Individual biological variation in erythrocyte survival or glycation rates might contribute to the discrepancy between estimated and measured mean glucose concentrations in individual subjects. Future analysis will examine the consistency of the relationship between glucose and HbA$_{1c}$ in the same patient over time.

Subgroup analyses in our study showed that the slope of mean glucose concentration versus HbA$_{1c}$ value was not clinically or statistically different by age-group, sex, or sensor type. In our study, we did not have a sufficient number of non-white subjects to evaluate the relationships of mean glucose concentration versus HbA$_{1c}$ in other ethnic and racial groups.

It is important to note that all studies have reported substantial variability between the measured mean glucose concentrations and the estimated values calculated from regression equations (Table 2). As an example, Nathan et al. (15) reported that only slightly <90% of subjects had measured glucose concentrations within ±15% mean glucose concentrations predicted by HbA$_{1c}$. We found a similar value in the current study (91%).

CGM typically has a relative error ranging from 14 to 20% (18–21). Quality control samples conducted during this study for HbA$_{1c}$, in contrast, showed that 99% of repeat measurements were within ±0.1% of the original value. This result suggests that the measurement error for HbA$_{1c}$ is negligible compared with that for CGM used to calculate the mean glucose in this analysis.

Although there are challenges in measuring mean glucose concentrations with CGMS as well, the errors with these devices are generally unbiased, with mean errors typically centered around zero. Moreover, CGMS can provide an unprecedented view across time. In the current study, we had nearly complete glycemic data, day and night, for the entire 3 months of glucose concentrations before an HbA$_{1c}$ measurement. Consequently, our findings of considerable discrepancies between actual and estimated mean glucose concentrations lead us to disagree with the conclusions of Nathan et al. (15) that a calculated mean glucose is clinically equivalent to a measured mean glucose. HbA$_{1c}$ measures are extremely precise, and there are substantial individually persistent variations in the ratio between HbA$_{1c}$ and mean glucose. Thus, estimated mean glucose values calculated from measured HbA$_{1c}$ values should be used with caution.

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Table 2—*Summary of published data*

Source	Type 1, type 2, nondiabetes	Subjects (*n*)	Approximate HbA_{1c} range (National Glycohemoglobin Standardization Program)	Children, adults	Length	Method: discrete or CGM	Curve fit (R^2)	Predict HbA_{1c} slope (95% CI)	Intercept (mg/dL) (95% CI)	Range of actual mean glucose at 6.9–7.1%†
Discrete										
Hempe et al. (11)	Type 1 diabetes	128	6.5–18.7%	Children, adolescents, adults	Up to 2.3 years	Discrete	Linear (0.50)	18.5*	~−4.8*	~90–235
Rohlfing et al. (12)	Type 1 diabetes	1,439	5.3–13.3%†	Adolescents, adults	3–9 years	Discrete 7 point quarterly	Linear (0.67)	35.6	−77.3	~100–250
Makris et al. (13)	Type 2 diabetes and/or metabolic syndrome	140	5.1–10.9%	Adults 41–81 years	1 month	Discrete 6 point 12 times in a month	Linear (0.86)	34.7 (32.5–37.0)	−79.2	~127–207
CGM										
Nathan et al. (22)	Type 1 and type 2 diabetes and nondiabetes	15, 7, and 3	4.6–10.2%†	Adults	3 months	CGM	Linear (0.79)	31.5	−68.6	Too few
Wilson et al. (16)	Type 1 diabetes	48	5.8–8.8%†	Children, adolescents	6 months	CGM	Linear	18 (14–22)	+40	~138–189
Nathan et al. (15)	Type 1 and type 2 diabetes and nondiabetes	268, 159, and 80	3.8–14.3%†	Adults	3 months	Intermittent CGM >7 days over 3 months discrete	Linear (0.84)	28.7	−46.7	~125–205
Mazze (14)	Type 1 and type 2 diabetes and nondiabetes	124	4.9–10.4%†	Adults	8–75 days	CGM	Linear (0.71)	26.3*	−32.7*	~130–150
Current study	Type 1 diabetes	252	5.1–9.7%	Children, adolescents, adults	3-month continuous	CGM	Linear (0.63)	24.4 (22.0−26.7)	−16.2	128–187

*Study originally reported slope from a model with HbA_{1c} as the independent variable (i.e., HbA_{1c} = slope × mean glucose + intercept). Values were converted to equivalent slope and intercept with mean glucose as the dependent variable using the reported R^2 value. †Estimated from graphs.

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D.M.W. researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. D.X. contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. R.W.B. contributed to discussion and reviewed and edited the manuscript. J.B. contributed to discussion. B.B. researched data, contributed to discussion, and reviewed and edited the manuscript. L.A.F. researched data, contributed to discussion, and reviewed and edited the manuscript. I.H. researched data, contributed to discussion, and reviewed and edited the manuscript. C.K. contributed to discussion and reviewed and edited the manuscript. L.L. researched data, contributed to discussion, and reviewed and edited the manuscript. K.J.R. researched data, contributed to discussion, and reviewed and edited the manuscript. M.S. researched data and reviewed and edited manuscript. W.V.T. researched data, contributed to discussion, and reviewed and edited the manuscript.

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

Continuous glucose monitors and sensors were purchased at a bulk discount price from DexCom (San Diego, CA), Medtronic MiniMed (Northridge, CA), and Abbott Diabetes Care (Alameda, CA). Home glucose meters and test strips were provided to the study by LifeScan and Abbott Diabetes Care. The companies had no involvement in the design, conduct, or analysis of the trial or the manuscript preparation.

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