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Defining the Relationship Between Plasma Glucose and HbA_{1c}

Analysis of glucose profiles and HbA_{1c} in the Diabetes Control and Complications Trial

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ANALYSIS OF GLUCOSE PROFILES AND HBA_{1C} IN THE DIABETES CONTROL AND COMPLICATIONS TRIAL

Abstract

OBJECTIVE— To define the relationship between HbA_{1c} and plasma glucose (PG) levels in patients with type 1 diabetes using data from the Diabetes Control and Complications Trial (DCCT).

RESEARCH DESIGN AND METHODS— The DCCT was a multicenter, randomized clinical trial designed to compare intensive and conventional therapies and their relative effects on the development and progression of diabetic complications in patients with type 1 diabetes. Quarterly HbA_{1c} and corresponding seven-point capillary blood glucose profiles (premeal, postmeal, and bedtime) obtained in the DCCT were analyzed to define the relationship between HbA_{1c} and PG. Only data from complete profiles with corresponding HbA_{1c} were used (n = 26,056). Of the 1,441 subjects who participated in the study, 2 were excluded due to missing data. Mean plasma glucose (MPG) was estimated by multiplying capillary blood glucose by 1.11. Linear regression analysis weighted by the number of observations per subject was used to correlate MPG and HbA_{1c}.

RESULTS— Linear regression analysis, using MPG and HbA_{1c} summarized by patient (n = 1,439), produced a relationship of MPG (mmol/l) = (1.98 ○1 HbA_{1c}) - 4.29 or MPG (mg/dl) = (35.6 ○1 HbA_{1c}) - 77.3, r = 0.82). Among individual time points, afternoon and evening PG (postlunch, predinner, postdinner, and bedtime) showed higher correlations with HbA_{1c} than the morning time points (prebreakfast, postbreakfast, and prelunch).

CONCLUSIONS— We have defined the relationship between HbA_{1c} and PG as assessed in the DCCT. Knowing this relationship can help patients with diabetes and their healthcare providers set day-to-day targets for PG to achieve specific HbA_{1c} goals.

ADA, American Diabetes Association BG, blood glucose DCCT, Diabetes Control and Complications Trial MPG, mean plasma glucose PG, plasma glucose

The results of the Diabetes Control and Complications Trial (DCCT), published in 1993, and the U.K. Prospective Diabetes Study, published in 1998, established the relationship between HbA_{1c} levels and risks for diabetic complications in patients with type 1 and type 2 diabetes, respectively. Based on the results of the DCCT, the American Diabetes Association (ADA) has published recommendations for HbA_{1c} and plasma glucose (PG) levels that are widely used (1,2). However, it is important that the relationship between daily patient-monitored blood glucose determinations and HbA_{1c} be clearly defined to enable patients and their health care providers to set appropriate daily PG testing goals to achieve HbA_{1c} levels representing low risks for adverse outcomes.

Several previous studies have analyzed the relationship between blood glucose (BG) and HbA_{1c}. Svendson et al. (3) assessed 15 subjects with type 1 diabetes who collected seven-point BG profiles over a 5-week period (three profiles per week) and used a curvilinear equation to correlate BG and HbA_{1c}. Nathan et al. (4) obtained repeated preprandial and postprandial BG samples from 21 subjects with type 1 diabetes over an 8-week period and used a linear regression equation to describe the relationship between BG and HbA_{1c}. In the DCCT, the correlation between HbA_{1c} and mean BG was initially determined in a limited number of patients (n = 278) for the feasibility study (5). However, a comprehensive analysis of the relationship of BG and HbA_{1c}, examining BG at different time points and using the entire data set, was never performed. Here, we examine, in detail, the relationship between BG (converted to PG) and HbA_{1c}, using data obtained from the entire DCCT data set to better define this relationship.

RESEARCH DESIGN AND METHODS

The DCCT data set was provided by the National Institutes of Diabetes, Digestive, and Kidney Diseases of the National Institutes of Health and was prepared by the Data Coordinating Center at George Washington University. The DCCT was a multicenter, randomized clinical trial designed to compare intensive and conventional therapies and their relative effects on the development and progression of diabetic complications in patients with type 1 diabetes (1). The study population consisted of 1,441 patients with type 1 diabetes recruited by 29 centers located throughout the U.S. and Canada. Patients were between 13 and 39 years of age and did not show evidence of severe diabetic complications at the time of admission into the study. Intensive therapy consisted of three or more insulin injections daily or use of an insulin pump with the intent of achieving BG values as close to the normal range as possible. Conventional therapy consisted of one or two insulin injections per day. Mean duration of participation was 6.5 years (range 3–9 years).

Quarterly HbA_{1c} measurements (n = 37,058) and corresponding BG profiles were obtained from 1,441 subjects. After exclusions due to incomplete profiles, there were 26,056 HbA_{1c} values with corresponding seven-point profiles from 1,439 subjects (an average of 18 HbA_{1c} values and corresponding profiles per patient).

For the seven-point BG profiles, capillary blood hemolysates were collected before meals, 90 min after meals, and at bedtime by patients in the home (6). BG was measured in a central laboratory using a hexokinase enzymatic method (7). Blood for HbA_{1c} analysis was collected by venipuncture. HbA_{1c} was measured in a central laboratory using an ion-exchange high-performance liquid chromatography method (8,9).

Statistical analysis was performed using SAS and SPSS (Chicago, IL). Mean BG was determined using area-under-the-curve analysis (10). For each profile, the seven time points were connected by straight lines over time for a 24-h period, and then the trapezoidal areas under each curve were determined, added together, and divided by time. A constant BG level between bedtime and the following morning was assumed. Mean plasma glucose (MPG) was estimated by adding 11% to mean BG estimates (11). Mean MPG and HbA_{1c} were calculated for each subject and used to perform least-squares linear regression analysis. Due to variation in the number of observations per subject, the regression analysis was weighted to account for this. The relationships between individual PG time points and HbA_{1c} were also examined.

RESULTS

The results of linear regression analysis are summarized in Fig. 1. The Pearson correlation coefficient (*r*) was 0.82; change in MPG per increase of 1% HbA_{1c} was 1.98 mmol/l (35.6 mg/dl). The 95% prediction interval for a subject with 18 observations (the average number of profiles per patient in this study) was ±3.81 mmol/l (69 mg/dl) at levels of 6–9% HbA_{1c}. Within-subject (intraindividual) variation in HbA_{1c} was much lower than for seven-point PG (mean intraindividual coefficient of variation = 9.7 vs. 29.8%, respectively).

MPG at increasing levels of HbA_{1c} is shown in Table 1. Along with regression-estimated MPG, the table shows approximate MPG based on increments of 2 mmol/l or 35 mg/dl per 1% change in HbA_{1c} to facilitate clinical interpretation and use of these data.

Results of regression analyses correlating HbA_{1c} with individual premeal and postmeal PG are summarized in Figs. 2 and 3. All individual time points showed lower correlations than the seven-point profiles. Prelunch and earlier PG time points showed lower correlations with HbA_{1c} than postlunch and later PG time points.

CONCLUSIONS

The increasing use of HbA_{1c} to monitor long-term glycemic control in diabetic patients is largely the result of data from the DCCT and the U.K. Prospective Diabetes Study showing that HbA_{1c} is strongly correlated with adverse outcome risks. For patients and health care providers, a clear understanding of the relationship between PG and HbA_{1c} is necessary for setting appropriate day-to-day PG testing goals with the expectation of achieving specific HbA_{1c} targets.

The relationship between HbA_{1c} and PG is complex. Many studies have shown that HbA_{1c} is an index of MPG over the preceding weeks to months. Erythrocyte life span averages ~120 days. The level of HbA_{1c} at any point in time is contributed to by all circulating erythrocytes, from the oldest (120 days old) to the youngest. However, recent PG levels (i.e., 3–4 weeks earlier) contribute considerably more to the level of HbA_{1c} than do long- past PG levels (i.e., 3–4 months earlier). Therefore, HbA_{1c} is a “weighted” average of BG levels during the preceding 120 days; PG levels in the preceding 30 days contribute ~50% to the final result, and PG levels from 90–120 days earlier contribute only ~10% (12,13). This explains why the level of HbA_{1c} can increase or decrease relatively quickly with large changes in PG; it does not take 120 days to detect a clinically meaningful change in HbA_{1c} after a change in MPG.

Another factor that complicates efforts to describe an accurate and precise relationship between PG and HbA_{1c} is that, for practical reasons, previous studies and our present study have attempted to define this relationship using a limited number of PG levels measured over a limited time period (in this case, 1 day every 3 months) to estimate HbA_{1c}. Short-term PG levels can fluctuate markedly, particularly in patients with type 1 diabetes; this can result in significant discrepancies when attempting to estimate HbA_{1c} based on a single PG measurement or even a series of measurements on a single day. In this study, the time between sampling also contributes to intraindividual variation, especially for PG. However, we have achieved greater certainty in our estimates of the relationship between PG and HbA_{1c} than was possible in previous studies by using a considerably larger number of patients and observations obtained over a longer period of time. The resulting strong correlation suggests that, although a single PG measurement or a single daily profile may not reliably predict HbA_{1c}, PG levels measured over time can provide a reasonably accurate estimation of HbA_{1c}.

Several studies have suggested that, although intraindividual variation in HbA_{1c} is minimal, there is evidence of wide fluctuations in HbA_{1c} between individuals that are unrelated to glycemic status, suggesting that there are “low glycators” and “high glycators” (14–16). However, a recent study showed that when multiple observations per patient are used to minimize the effects of assay variation, the interindividual range of HbA_{1c} results in nondiabetic individuals is actually quite narrow, <1% HbA_{1c} (17). Therefore, for any individual patient, a consistent discrepancy between patient-monitored PG determinations and estimated HbA_{1c} should be investigated; there may be other factors causing this discrepancy, such as improper meter use, laboratory error, a physical condition that alters red cell life span, or a variant hemoglobin interfering with the HbA_{1c} assay method. With the advent of new technologies that are capable of monitoring PG on a 24-h basis (18), it will be interesting to see how our estimate of the relationship between PG and HbA_{1c} compares with estimates obtained using these technologies.

Our data indicate that fasting PG alone should be used with caution as a measure of long-term glycemia. Fasting PG tended to progressively underestimate HbA_{1c} (and seven-point MPG) at increasing PG levels. The data also suggest that postmeal PG contributes appreciably to HbA_{1c}; however, all postmeal times are not equal in their contribution. We found that compared with the seven-point profiles, postbreakfast levels markedly overestimate HbA_{1c}, whereas postlunch levels show a relationship to HbA_{1c} that is very similar to that of MPG. A previous study of patients with type 2 diabetes also found that postlunch PG is a better indicator of glycemic control than fasting PG (19). However, that study did not examine bedtime PG, which we found also shows a relationship to HbA_{1c} that is very similar to that of MPG.

The ADA currently recommends that patients with diabetes attempt to achieve average preprandial PG levels of 5.0–7.2 mmol/l (90–130 mg/dl) and average bedtime PG levels of 6.1–8.3 mmol/l (110–150 mg/dl) as well as HbA_{1c} <7% (2). Our results show estimated average preprandial PG and bedtime PG levels of 8.7 and 9.2 mmol/l (157 and 166 mg/dl), respectively, at 7% HbA_{1c}. These data suggest that patients who consistently achieve ADA-recommended BG and PG targets will also achieve an HbA_{1c} level <7%.

In summary, there is a predictable relationship between PG and HbA_{1c}. Understanding this relationship will allow patients with diabetes and their healthcare providers set appropriate day-to-day PG targets based on HbA_{1c} goals. It is important to note that the relationship between PG and HbA_{1c} defined in this study only applies when HbA_{1c} is measured using assay methods that are certified by the National Glycohemoglobin Standardization Program as traceable to the DCCT reference method, as recommended by the ADA (20). Fasting PG should be used with caution as a surrogate measure of MPG because it may significantly underestimate HbA_{1c} and, therefore, risks for complications at increasing HbA_{1c} levels.

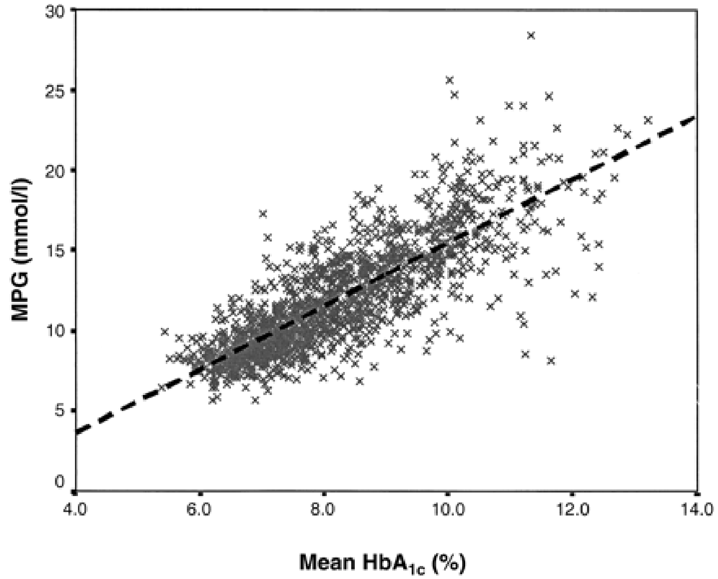

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Figure 1—

MPG versus HbA_{1c}: n = 1,439; r = 0.82; PG (mmol/l) = (1.98 ·1 HbA_{1c}) – 4.29. The dashed line indicates the regression line.

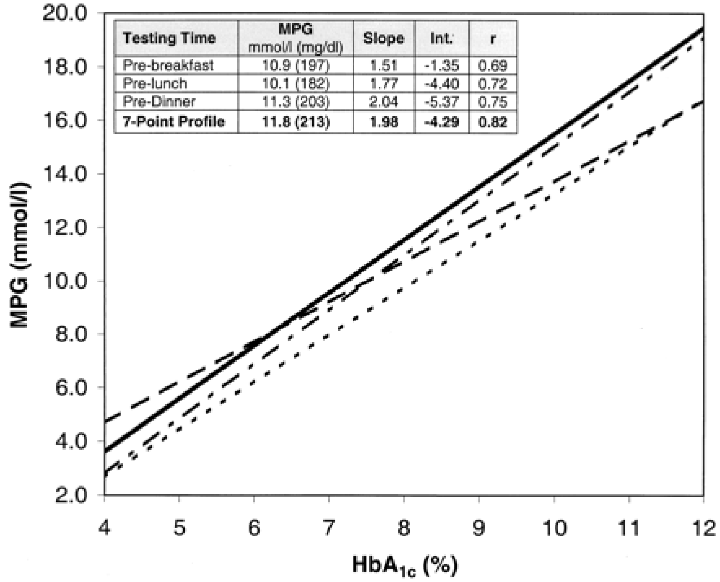

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Figure 2—

Premeal MPG and *r* at different testing times. — —, Prebreakfast; -----, prelunch; — - —, predinner; ——, seven-point.

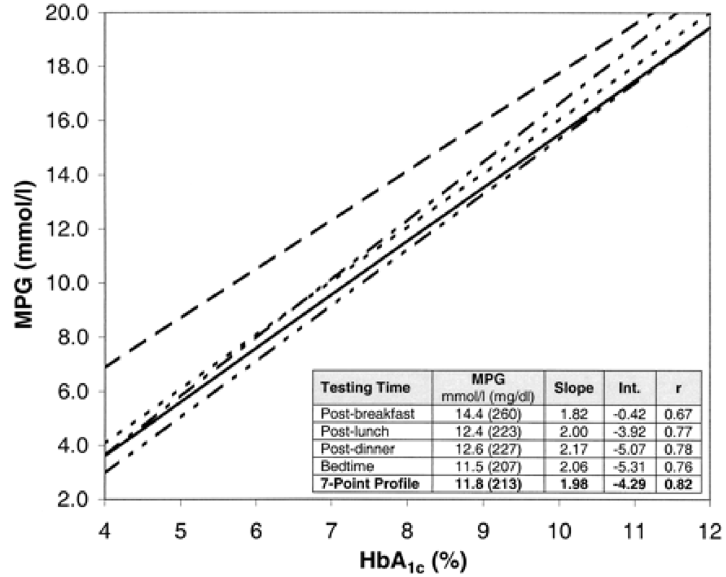

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Figure 3—

Postmeal MPG and *r* at different testing times. — —, Postbreakfast; -----, Postlunch; — - —, postdinner; — -- —, bedtime; ——, seven-point.

Table 1—

View inline

MPG as estimated from the regression line and approximate MPG (based on MPG change of 35 mg/dl or 2 mmol/l per 1% change in HbA_{1c}) at different HbA_{1c} levels

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Footnotes

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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