Defining the Relationship Between Plasma Glucose and HbA\textsubscript{1c}  

Analysis of glucose profiles and HbA\textsubscript{1c} in the Diabetes Control and Complications Trial

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OBJECTIVE — To define the relationship between HbA\textsubscript{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\textsubscript{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\textsubscript{1c} and PG. Only data from complete profiles with corresponding HbA\textsubscript{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\textsubscript{1c}.

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

CONCLUSIONS — We have defined the relationship between HbA\textsubscript{1c} and PG as assessed in the entire DCCT data set to better define the relationship between HbA\textsubscript{1c} and mean PG was initially determined in a limited number of patients (n = 278) for the feasibility study (5). However, a comprehensive analysis of the relationship between BG and HbA\textsubscript{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\textsubscript{1c}, using data obtained from the entire DCCT data set to better define this relationship.

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\textsubscript{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\textsubscript{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\textsubscript{1c} be clearly defined to enable patients and their health care providers to set appropriate daily PG testing goals to achieve HbA\textsubscript{1c} levels representing low risks for adverse outcomes.

Several previous studies have analyzed the relationship between blood glucose (BG) and HbA\textsubscript{1c}. Svendsen 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\textsubscript{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\textsubscript{1c}. In the DCCT, the correlation between HbA\textsubscript{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 between BG and HbA\textsubscript{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\textsubscript{1c}, using data obtained from the entire DCCT data set to better define this relationship.

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Abbreviations: ADA, American Diabetes Association; BG, blood glucose; DCCT, Diabetes Control and Complications Trial; MPG, mean plasma glucose; PG, plasma glucose.  
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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 HbA1c measurements (n = 37,056) and corresponding BG profiles were obtained from 1,441 subjects. After exclusions due to incomplete profiles, there were 26,056 HbA1c values with corresponding seven-point profiles from 1,439 subjects (an average of 18 HbA1c 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 HbA1c analysis was collected by venipuncture. HbA1c 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 HbA1c 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 HbA1c 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% HbA1c was 1.98 mmol/l (35.6 mg/dl). The 95% prediction interval for a subject at any point in time is contributed HbA1c to facilitate clinical interpretation and use of these data. Results of regression analyses correlating HbA1c 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 HbA1c than postlunch and later PG time points.

Table 1—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 HbA1c) at different HbA1c levels

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Regression estimated MPG</th>
<th>Approximate MPG for clinical use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mmol/l</td>
<td>mg/dl</td>
</tr>
<tr>
<td>4</td>
<td>3.6</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>5.6</td>
<td>101</td>
</tr>
<tr>
<td>6</td>
<td>7.6</td>
<td>137</td>
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<td>7</td>
<td>9.6</td>
<td>172</td>
</tr>
<tr>
<td>8</td>
<td>11.5</td>
<td>208</td>
</tr>
<tr>
<td>9</td>
<td>13.5</td>
<td>244</td>
</tr>
<tr>
<td>10</td>
<td>15.5</td>
<td>279</td>
</tr>
<tr>
<td>11</td>
<td>17.5</td>
<td>315</td>
</tr>
<tr>
<td>12</td>
<td>19.5</td>
<td>350</td>
</tr>
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</table>

CONCLUSIONS — The increasing use of HbA1c 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 HbA1c is strongly correlated with adverse outcome risks. For patients and health care providers, a clear understanding of the relationship between PG and HbA1c is necessary for setting appropriate day-to-day PG testing goals with the expectation of achieving specific HbA1c targets.

The relationship between HbA1c and PG is complex. Many studies have shown that HbA1c is an index of MPG over the preceding weeks to months. Erythrocyte life span averages ~120 days. The level of HbA1c 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 HbA1c than do long-
past PG levels (i.e., 3–4 months earlier).
Therefore, HbA1c 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 con-
tribute only ~10% (12,13). This explains
why the level of HbA1c can increase or
decrease relatively quickly with large
changes in PG; it does not take 120 days
to detect a clinically meaningful change in
HbA1c after a change in MPG.
Another factor that complicates ef-
forts to describe an accurate and precise
relationship between PG and HbA1c is
that, for practical reasons, previous stud-
ies and our present study have attempted
to define this relationship using a limited
number of PG levels measured over a lim-
ited time period (in this case, 1 day every
3 months) to estimate HbA1c. Short-term
PG levels can fluctuate markedly, partic-
ularly in patients with type 1 diabetes; this
can result in significant discrepancies
when attempting to estimate HbA1c 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 varia-
tion, especially for PG. However, we have
achieved greater certainty in our estimates
of the relationship between PG and HbA1c
than was possible in previous studies by
using a considerably larger number of pa-
tients 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 HbA1c,
PG levels measured over time can provide
a reasonably accurate estimation of
HbA1c.
Several studies have suggested that,
although intraindividual variation in
HbA1c is minimal, there is evidence of
wide fluctuations in HbA1c between indi-
viduals that are unrelated to glycemic sta-
tus, 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
HbA1c results in nondiabetic individuals
is actually quite narrow, <1% HbA1c
(17). Therefore, for any individual pa-
tient, a consistent discrepancy between
patient-monitored PG determinations
and estimated HbA1c should be investi-
gated; 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 HbA1c
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 HbA1c 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 HbA1c (and seven-point MPG) at increasing PG levels. The data also suggest that postmeal PG contributes appreciably to HbA1c; however, all postmeal times are not equal in their contribution. We found that compared with the seven-point profiles, postbreakfast levels markedly overestimate HbA1c, whereas postlunch levels show a relationship to HbA1c 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 level in diabetic patients. Diabetes Care 16:1313–1314, 1993

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 HbA1c <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% HbA1c. These data suggest that patients who consistently achieve ADA-recommended BG and PG targets will also achieve an HbA1c level <7%.

In summary, there is a predictable relationship between PG and HbA1c. Understanding this relationship will allow patients with diabetes and their healthcare providers set appropriate day-to-day PG targets based on HbA1c goals. It is important to note that the relationship between PG and HbA1c defined in this study only applies when HbA1c 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 HbA1c and, therefore, risks for complications at increasing HbA1c levels.

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References
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