Evaluation of Conventional Blood Glucose Monitoring as an Indicator of Integrated Glucose Values Using a Continuous Subcutaneous Sensor

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OBJECTIVE — To use a portable continuous glucose monitoring system (CGMS) to evaluate how well the customary intermittent self-monitoring of blood glucose (SMBG) correlates with integrated values during the surrounding time periods in ambulatory patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — In the study, 18 young patients with type 1 diabetes were monitored with CGMS for up to 72 h, during which they continued to perform the four standard SMBG tests (preprandial and bedtime). Correlations were examined between each of the four standard SMBG tests and the mean CGMS values from defined periods that preceded and followed. We also tested how well a low bedtime SMBG predicted nocturnal hypoglycemia.

RESULTS — Strong correlations were found between 1) SMBG at breakfast and the mean CGMS value for the preceding 8 h ($r = 0.7514$), 2) SMBG at dinner and the CGMS from lunch to dinner ($r = 0.7538$), 3) SMBG at bedtime and the CGMS from dinner to bedtime ($r = 0.8145$), and 4) SMBG at bedtime and the CGMS from bedtime to breakfast ($r = 0.6463$).

The remaining correlations were weak and not statistically significant. These correlations seem independent of insulin-delivery method as virtually identical results were obtained when data from patients on conventional versus intensive regimes were separately analyzed. A bedtime SMBG <7 mmol/l did not predict nocturnal hypoglycemia (defined as at least one CGMS value <3).

CONCLUSIONS — The breakfast and dinnertime SMBG values are good indicators of integrated glucose values in the time period preceding them, while the bedtime test correlates well with the integrated values both preceding and following it. This information should aid in the meaningful use of SMBG to evaluate glycemic control and make insulin dose adjustments.

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The Diabetes Control and Complications Trial (DCCT) established that a concerted effort to optimize intermittently tested blood glucose levels was effective in both decreasing levels of HbA1c and preventing long-term complications of type 1 diabetes (1). Because there is no reason to believe that the effect of hyperglycemia at the testing times chosen is more relevant to these end points than at any other time, it is widely assumed and supported by the DCCT results that the most meaningful short-term indicator of long-term outcome would be the patient’s integrated blood glucose level (IBGL). Unfortunately, the four customary testing times in conventional glucose self-monitoring (premeal breakfast, lunch and dinner, and bedtime) provide only four narrow windows into a patient’s continuum of glycemic control. Their use as a realistic compromise is based on the assumption that they reflect, to a useful extent, integrated levels surrounding each testing time. Confirmation of this assumption in ambulatory patients in the course of their usual daily life has not been possible until recently.

The newly developed Minimed Continuous Glucose Monitoring System (CGMS), a device that monitors serum glucose on a continuous basis, provides information on glucose levels throughout the interval between these discrete windows. Preliminary studies have shown the device to have sufficient accuracy and precision for clinical purposes (2–5,7). Early studies with this device have also shown it to be useful in detecting periods of unrecognized nocturnal hypoglycemia (6,7) and postprandial hyperglycemia not reflected in the patient’s HbA1c (7). The device has also been shown to be useful in making therapeutic adjustments that, in pilot studies, have translated into improved glycosylated hemoglobin in both adult (8) and pediatric (6) populations.

Despite these advantages, CGMS in its current form is an impractical tool for day-to-day management of diabetes. The device is cumbersome, expensive, and still requires the input of a minimum of four capillary blood test results to calibrate its measurements. For the foreseeable future we must continue to rely upon self-monitoring of blood glucose (SMBG) to assess diabetes control and, more importantly, to adjust management; therefore, it is important to understand the significance of the blood glucose values obtained from specific SMBG time points.
Integrating versus continuous glucose testing

American Diabetes Association guidelines recommend a minimum of three to four tests per day without specifying timing (9). The Canadian Diabetes Association guidelines similarly reflect a lack of evidence-based consensus on which time points are optimally informative for insulin-dose adjustments (10).

In practice, most compliant type 1 diabetic individuals test preprandially and at bedtime. Though many clinicians customarily assign more value to AC breakfast and AC dinner SMBG test times, and less to the AC lunchtime test, no clinical research has substantiated the worth of one testing time over another using the integrated values surrounding these points as the gold standard. For the first time, the CGMS has provided the opportunity to assess the validity of SMBG in field conditions. It has already been demonstrated that SMBG underestimates IBGL (7), not a surprising finding given that SMBG is concentrated on fasting time points. That study, however, did not attempt to evaluate SMBG-IBGL correlation of individual data points. The purpose of our study was to evaluate how well each of the four custom SMBG values reflects a patient’s integrated blood glucose over four defined pre-SMBG and four post-SMBG periods of the day. We stress that in this study we did not evaluate the technical validity of CGMS. Rather, based on previous validating literature, we took its measurements as the gold standard against which capillary testing was assessed as a proxy for integrated values in the intervals between testing times.

RESEARCH DESIGN AND METHODS

Participants
The study consisted of 21 type 1 diabetic patients. Data from three patients were rejected a priori before any analysis was done because no technically reliable tracings were obtained based on the following exclusion criteria 1) less than three SMBG tests in a 24-h period and 2) >30% difference between any of the patient’s SMBG value and the corresponding glucose value recorded by the CGMS at the same time.

If the first criterion was met, then the entire 24-h period was eliminated. If the second criterion was met, then data from the corresponding period were excluded. The three excluded patients had median values for age, duration of disease, and glycosylated hemoglobin that were no different from the group as a whole.

The remaining 18 patients were aged 7–20 years (median age = 14 years) and the duration of their diabetes ranged from 1 to 11 years (median duration = 3 years). The patients showed a wide variation of glycemic control, with HbA1c ranging from 6.2 to 11% (median 8.5%, upper limit of nondiabetic values 6.5%) at the nearest time they participated in the study. Eight of the participants were on a conventional two-injection regime (“conventional” subgroup), nine were using multiple injections, and one used a constant subcutaneous infusion pump (“intensive” subgroup).

Sensor
The CGMS uses a 23-gauge subcutaneous catheter that can be inserted into the patient’s abdomen for a period of up to 72 h and is attached via a wire to a small pager-sized device that acts as a monitor and stores the recorded glucose levels. The sensor samples glucose in the interstitial fluid every 10 s using a glucose oxidase method and then records the average glucose level for a period of 5 min. These results can only be viewed after the 72-h period, a limitation mandated by the approval status of the device. The sensor is calibrated against the patient’s capillary blood glucose measurements, under the reasonable assumption that the correlation with interstitial fluid levels is linear. This also obviates concerns about systematic bias introduced by some meters measuring whole blood versus plasma glucose, for the purpose of correlating meter with sensor.

Procedure
All patients had the sensor inserted by a registered nurse, according to the device’s instructions, at the Montreal Children’s Hospital Diabetes Clinic. Patients wore the CGMS for 24, 48, or 72 h, depending on their personal choice, although they were all encouraged to do so for the full 72 h. During this period, patients continued to perform SMBG at the customary times. These values are entered by the patient into the CGMS apparatus and are used to calibrate the device. Patients also recorded their mealtimes and insulin injection times, either in a log or into the CGMS, directly, using pre-established symbols.

After 1–3 days, patients returned to the clinic with the CGMS, where the data were downloaded directly into the Minimed Solutions Software. The software automatically produced a report including textual and graphical summaries of the patients’ glycemic profile for the given time period, as well as the individual glucose levels recorded every 5 min.
poor, insignificant correlations except between the SMBG for bedtime and the CGMS for the period between bedtime and breakfast ($r = 0.6463, P < 0.0005$). Virtually identical results were obtained when data from patients on a conventional regimen were analyzed separately from those on an intensive regimen. The sole exception was the correlation of the bedtime SMBG value with CGMS during the night, which was significant in the whole group and the conventional subgroup but narrowly failed to reach significance in the intensive subgroup ($P = 0.07$).

Despite its strong correlation with overnight glycaemia, the bedtime test did not prove to be predictive of nocturnal hypoglycaemia. Of 11 cases with SMBG results $<$7 mmol/l at bedtime, only 3 were associated with an overnight sensor value of $<$3 mmol/l, a proportion that was not significantly different from cases with bedtime SMBG result $\geq$7 (4 of 17).

**CONCLUSIONS**

SMBG has long been the mainstay of evaluating glycemic control for the purpose of making changes in management in the short term. Despite major advances in continuous monitoring, the standard four SMBG tests will likely continue to play this essential role in diabetes care in the foreseeable future. The availability of CGMS now permits rigorous validation and better understanding of SMBG as a proxy for IBGL.

In accordance with our prior hypothesis, both the breakfast and dinner tests correlated well with the defined pre-SMBG time period. The strong correlation between the SMBG for breakfast and the CGMS for 8 h before breakfast was expected because of the minimal level of food intake, physical activity, and variations in emotional status during sleep. The same considerations also explain the excellent correlation between bedtime testing and overnight IBGL.

Of the remaining three periods, two (lunch-to-dinner and dinner-to-bedtime) correlate well with the SMBG level at their end, while the third (breakfast-to-lunch) does not. The reason for this is less clear and needs further study, but it does not seem to be related to mode of insulin delivery, as the lack of correlation was found in both subgroups (Table 1). The failure of the bedtime test to predict nocturnal dips by no means invalidates its use for this purpose. During the study, patients were following the usual clinic routine of doubling their bedtime snack if their SMBG result was $>$7 mmol/l. Rather, it can be taken as evidence that this routine is sufficient to eliminate the additional risk of nocturnal hypoglycaemia posed by a bedtime blood glucose in the normal range, if such additional risk exists. These findings are also consistent with previous studies (7) showing that a bedtime SMBG value $>$7 is no insurance against nocturnal hypoglycaemia.

We do not wish our data to be interpreted as showing that SMBG is equivalent to CGMS, or that it can be used instead. The latter provides information not contained in a simple SMBG value, such as glycemic excursion, which may be important if the relationship between risk of complications and glucose levels is not linear, in which case extreme highs might contribute to complications out of proportion with their contribution to the IBGL. What we propose is that the information derived from this study validates the use of intermittent SMBG as a proxy for IBGL, for as long as the former remains

### Table 1—Correlations between each of the four standard SMBG results and the CGMS average during the period before (top half) and after (bottom half) the test

<table>
<thead>
<tr>
<th>SMBG</th>
<th>CGMS</th>
<th>Conventional</th>
<th>Intensive</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>P</td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td><strong>Breakfast</strong></td>
<td>8 h premeal</td>
<td>0.744</td>
<td>0.00132</td>
<td>0.719</td>
</tr>
<tr>
<td><strong>Lunch</strong></td>
<td>Breakfast to lunch</td>
<td>0.126</td>
<td>0.65</td>
<td>0.378</td>
</tr>
<tr>
<td><strong>Dinner</strong></td>
<td>Lunch to dinner</td>
<td>0.760</td>
<td>0.00225</td>
<td>0.569</td>
</tr>
<tr>
<td><strong>Bedtime</strong></td>
<td>Dinner to bedtime</td>
<td>0.815</td>
<td>0.00015</td>
<td>0.797</td>
</tr>
<tr>
<td><strong>Breakfast</strong></td>
<td>Breakfast to lunch</td>
<td>0.307</td>
<td>0.31</td>
<td>0.224</td>
</tr>
<tr>
<td><strong>Lunch</strong></td>
<td>Lunch to dinner</td>
<td>-0.055</td>
<td>0.85</td>
<td>-0.012</td>
</tr>
<tr>
<td><strong>Dinner</strong></td>
<td>Dinner to bedtime</td>
<td>-0.321</td>
<td>0.31</td>
<td>0.295</td>
</tr>
</tbody>
</table>
| **Bedtime**           | Bedtime to breakfast  | 0.635        | 0.00667 | 0.594  | 0.0728 | 0.6463 | 0.000428 | 0.43 | 5.5     

**Statistics**

The 5-min interval glucose values and the SMBG values were exported into Microsoft Excel. The mean, rather than integrated (area under the curve [AUC]), CGMS values were used in the correlations because they are a precise correlate of the integrated value per unit of time and thus normalize for variable lengths of the monitoring period, and they can be directly compared with SMBG numbers. The only imprecision introduced by using means rather than AUC is that in AUC, the first and last point weigh half as much as all other points, a trivial consideration in curves that contain >40 points.

The defined time periods and the corresponding SMBG tests with which the values were correlated are shown in Table 1.

**RESULTS**

Of the patients, 18 performed a total of 211 monitoring periods, of which 99 were rejected for technical reasons, by the criteria enumerated in **RESEARCH DESIGN AND METHODS**. Therefore, a total of 112 monitoring periods were analyzed. Results are shown in Table 1.

As expected, strong correlations were found between the SMBG at breakfast and CGMS mean for the 8 h before breakfast ($r = 0.7514, P < 0.000013$), and the SMBG at dinner and CGMS mean for lunch to dinner ($r = 0.7538, P < 0.00003$). Somewhat unexpectedly, we also found a strong correlation between SMBG bedtime and the CGMS for dinner-to-bedtime ($r = 0.8145, P < 0.0005$). The remaining pre-SMBG correlation, SMBG lunch, and CGMS for breakfast to lunch was poor ($r = 0.2138$) and not statistically significant ($P = 0.32$). All of the defined post-SMBG correlations had
the only practical daily monitoring method for most patients with diabetes. Our findings also allow more meaningful use of SMBG results in the adjustment of insulin dose and other diabetes-management parameters aimed at improving IGBL during specific time periods in the patient’s day.

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References