Intensified Blood Glucose Monitoring Improves Glycemic Control in Stable, Insulin-Treated Veterans With Type 2 Diabetes

The Diabetes Outcomes in Veterans Study (DOVES)

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Objective — To examine the effect of intensified self-monitored blood glucose (SMBG) testing on glycemic control.

Research Design and Methods — Subjects with stable, insulin-treated type 2 diabetes performed SMBG using an electronic blood glucose meter before all meals and at bedtime for 8 weeks. Baseline data were collected on demographics, clinical characteristics, diet, and exercise. HbA1c was measured at baseline, at 4 weeks, and at 8 weeks. After the intensified monitoring period, subjects resumed their usual monitoring. HbA1c was then measured at 24, 37, and 52 weeks. Multivariate linear regression was used to determine the effect of monitoring on glycemic control.

Results — A total of 201 subjects completed the monitoring period. The baseline HbA1c (8.10 ± 1.67%) decreased during the monitoring period by 0.30 ± 0.68% (P < 0.001) at 4 weeks and by 0.36 ± 0.88% (P < 0.001) at 8 weeks. Although entry HbA1c and compliance independently predicted the week 8 HbA1c (r = 0.862, P < 0.001), standardized regression analysis found that compliance with the SMBG protocol influenced the week 8 HbA1c more than age, sex, BMI, exercise level, carbohydrate consumption, or treatment intensity at baseline. However, SMBG benefited only subjects whose testing compliance exceeded 75% or with an entry HbA1c >8.0%. Decreases in HbA1c (~0.31 ± 1.17%, P = 0.001) persisted in the 159 subjects followed for 52 weeks.

Conclusions — Intensified blood glucose monitoring improved glycemic control in a large cohort of stable, insulin-treated veterans with type 2 diabetes. SMBG provided a strong stimulus for improved self-care resulting in clinically important and sustained reductions in HbA1c.

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Intensified SMBG improves glycemic control

Table 1—Effect of SMBG on week 8 HbA1c, stratified by baseline HbA1c and testing compliance

<table>
<thead>
<tr>
<th>HbA1c Level</th>
<th>Subjects</th>
<th>Change (from baseline)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤7.0%</td>
<td>54</td>
<td>−0.10 ± 0.58%</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;7.0% and ≤8.0%</td>
<td>56</td>
<td>−0.10 ± 0.83%</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;8.0%</td>
<td>91</td>
<td>−0.67 ± 0.97%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Compliance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60%</td>
<td>33</td>
<td>−0.33 ± 0.98%</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;60% and ≤75%</td>
<td>40</td>
<td>−0.22 ± 1.21%</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;75% and ≤90%</td>
<td>58</td>
<td>−0.56 ± 0.66%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;90%</td>
<td>70</td>
<td>−0.29 ± 0.77%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are n or means ± SD.

if they had a history of alcoholism or substance abuse, if they suffered from chronic liver disease, pancreatic insufficiency, a chronic infectious disease, or an endocrinopathy associated with abnormal glucose homeostasis, if they had a most recent creatinine level >266 μmol/dl; if they received glucocorticoids or immunosuppressive drugs; or if they were being treated with an insulin pump.

Eligible subjects were followed until their diabetes had been stable for at least 2 months. Subjects were considered stable if their daily insulin dose was increased by no more than 10 units or 15% of the baseline dose, whichever was smaller, if no new oral medications were prescribed, and if the dose of established oral medications was not increased.

At entry into the study, subjects completed a questionnaire regarding their disease complications, disabilities, treatment regimes, and dietary habits. Subjects were also given the 108-item Fred Hutchinson Cancer Research Center Food Frequency Questionnaire to complete at home with the assistance of household members (23). We quantified physical activity by analyzing all routine activities according to frequency, duration, and intensity. Average metabolic-hours per week were calculated using the Compendium of Physical Activities (24).

Subjects were then instructed to measure their blood sugars before breakfast, before lunch, before dinner, and at bedtime for the next 8 weeks. The intensified monitoring protocol was designed to characterize the incidence and risks for hypoglycemic episodes. Levels were recorded using a blood glucose meter (Accu-Chek Complete, Roche Diagnostics, Montclair, NJ) with the capacity for storing 1,000 readings with the dates and times of testing. Subjects visited the research coordinators at 4 and 8 weeks to download data from the blood glucose meters and for measurement of HbA1c. Although the intensified monitoring ended at 8 weeks, subjects remained in the longitudinal DOVES study and HbA1c was remeasured at 24, 37, and 52 weeks. During the entire study, investigators never made any recommendations to subjects regarding medications, weight control, diet, or exercise. All treatment decisions and consultations were deferred to the subject’s primary care provider.

Statistical analysis
Compliance was defined as the number of readings obtained by each subject divided by the number specified by the protocol (224 per subject). Daily readings were used to identify the subject’s customary times for breakfast, lunch, dinner, and bedtime. Weekly average glucose values for each mealtime and bedtime were calculated for each subject. Group differences in nominal variables and continuous variables were analyzed using χ² analysis and unpaired Student’s t test, respectively. We tested within-subject changes in HbA1c and blood glucose by paired Student’s t test and repeated-measures ANOVA. Multiple linear regression was used to examine the association between the week 8 HbA1c and a variety of clinical variables. Specified models were fitted to the data to control for self-care behaviors and treatment intensity. Outliers were identified by Cook’s distances and studentized residuals (25). Plots of residuals versus estimates were used to evaluate the assumptions of linearity and homoscedasticity. Semiprobability plots and the Kolmogorov-Smirnoff one-sample test using a theoretical normal distribution were used to test the normality of residuals (26). All P values <0.05 were considered significant.

RESULTS — A total of 247 patients were invited to participate in the study; 218 (88%) were enrolled, but we excluded eight subjects who did not perform SMBG and another nine who did not obtain a week 8 HbA1c level. The remaining 201 patients (81% of the eligible patients) form the basis for this report. The mean (± SD) age of this group was 65.0 ± 10.0 years, 94% were men, and 30% were members of a minority group. The mean baseline HbA1c was 8.10 ± 1.67%. The mean BMI was 31.9 ± 5.7 kg/m²; the average amount of exercise was 62.1 ± 63.9 metabolic-hours per week, the entry insulin dose was 66.1 ± 45.1 units per day, 35% were taking oral hypoglycemic agents, and the average

Figure 1—HbA1c levels during intensified monitoring and follow-up. Numbers above the bars represent the number of subjects followed to that time.
carbohydrate consumption was 162 ± 111 g daily. Only 10.5% of subjects took insulin once daily, whereas 72.6% took insulin twice daily.

The subjects obtained 35,499 (79%) of the SMBG readings specified by the protocol. SMBG readings ranged from 3 to 100% (mean 78.4 ± 19.3). We found a significant and sustained decrease in HbA1c beginning at 4 weeks (−0.30 ± 0.68%; P < 0.001) and becoming maximal at 8 weeks (−0.36 ± 0.88%; P < 0.001). Subset analysis showed that these improvements occurred only in subjects with entry HbA1c >8.0% or SMBG compliance >75% (Table 1). The change was sustained in the 159 patients followed for 52 weeks (−0.32 ± 1.17%; P = 0.001; Fig. 1).

Multiple linear regression analysis showed that the entry HbA1c level and compliance were strong predictors of HbA1c at 8 weeks (r = 0.862, P < 0.001) (Table 2, Model A). Compliance was the most influential self-care determinant of week 8 HbA1c (P < 0.001), followed by carbohydrate intake (P = 0.005), and daily insulin dose (P = 0.015) (Table 2, Model B). Compliance was inversely associated with the week 8 HbA1c, whereas higher carbohydrate consumption and higher insulin doses were associated with higher HbA1c. We found no effect for age, sex, BMI, level of exercise, or use of oral agents. Regression diagnostics showed that both multiple linear models provided an appropriate description of the data.

Diurnal changes in mean blood glucose level were analyzed in 150 subjects with regular mealtimes and bedtimes. Significant week 4 decreases were found in the prelunch (−0.61 ± 2.63 mmol/dl, P = 0.006) and predinner blood glucose concentrations (−0.41 ± 2.38 mmol/dl, P = 0.047) (Fig. 2). However, by the end of the 8-week intensified monitoring period, only the prelunch value was significantly lower than at entry (−0.48 ± 2.81 mmol/dl, P = 0.041). No changes were found in the prebreakfast or predinner values.

CONCLUSIONS — The value of SMBG in insulin-treated patients with type 2 diabetes is unknown. Most observational studies and randomized trials have focused on patients treated with oral agents and have led to conflicting results (4–15). Despite the absence of consistent data, the American Diabetes Association recommends SMBG for “all insulin-treated patients with diabetes” (27). We conducted one of the few longitudinal studies that prospectively measured HbA1c at different times after starting an intensified protocol, precisely ascertained compliance, and controlled for the effect of other variables affecting glycemic control. Our results support the American Diabetes Association monitoring recommendation because we found that intensified blood glucose monitoring resulted in significant and sustained reductions in HbA1c in stable, insulin-treated subjects. This change was remarkable because study investigators did not provide subjects with any self-care recommendations, referrals, or treatment modifications. In fact, parallel changes were detected in prelunch and bedtime blood glucose readings even before subjects returned to download data from their blood glucose meters and first received summary time-of-day readings and interpretations.

After adjusting for baseline HbA1c, compliance with the intensified monitoring protocol was a strong predictor of the week 8 HbA1c. Compliance was more influential on HbA1c than demographic factors, carbohydrate consumption, amount of exercise, BMI, insulin dosage, or use of oral agents at entry. Although this study was not a randomized trial, the strong dose-response between SMBG compliance and HbA1c suggests that SMBG is an important determinant of glycemic control.

We found that intensified SMBG seemed to be a powerful stimulus for changing subjects’ behaviors. Unfortunately, we do not know which behaviors led to improving glycemic control. The possibilities include better adherence to

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard deviation</th>
<th>Standard coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>3.05</td>
<td>0.40</td>
<td>0.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>0.692</td>
<td>0.033</td>
<td>0.800</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Compliance (%)</td>
<td>−1.17</td>
<td>0.29</td>
<td>−0.155</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Model B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant</td>
<td>10.97</td>
<td>1.04</td>
<td>0.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Compliance (%)</td>
<td>−2.80</td>
<td>0.49</td>
<td>−0.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>−0.013</td>
<td>0.010</td>
<td>−0.090</td>
<td>NS</td>
</tr>
<tr>
<td>Sex*</td>
<td>0.252</td>
<td>0.403</td>
<td>0.040</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>−0.037</td>
<td>0.019</td>
<td>−0.144</td>
<td>0.06</td>
</tr>
<tr>
<td>Exercise (metabolic-hours per week)</td>
<td>0.001</td>
<td>0.001</td>
<td>0.066</td>
<td>NS</td>
</tr>
<tr>
<td>Carbohydrate intake (gm per day)</td>
<td>0.002</td>
<td>0.001</td>
<td>0.184</td>
<td>0.005</td>
</tr>
<tr>
<td>Insulin units per day</td>
<td>0.006</td>
<td>0.002</td>
<td>0.182</td>
<td>0.015</td>
</tr>
<tr>
<td>Use of oral agents†</td>
<td>0.173</td>
<td>0.134</td>
<td>0.090</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Sex is coded male = 1 and female = 0; †use of oral agents is coded yes = 1 and no = 0

![Figure 2](https://example.com/figure2.png)
diet, increasing exercise, improving medication compliance, consulting with a health care provider, or self-titrating medications. The latter possibility, however, is unlikely because we excluded subjects who were self-titrating their insulin doses. Analysis of blood glucose data showed that improvements occurred only in the postprandial periods after breakfast and dinner. Therefore, it is unlikely that the reduction in HbA1c resulted from intensified use of long-acting insulins, a global reduction in caloric intake, or a generalized increase in physical activity.

Our study provides some insight into the difficulties previous investigators have had in showing that SMBG is beneficial in type 2 diabetes. SMBG can lead to a variety of self-care improvements, including weight control, dietary compliance, exercise, adherence to medication regimens, or increased interactions with providers. Each of these behaviors is, in turn, affected by the patient's knowledge, motivation, physical disabilities, and opportunities for change. Our finding that the variation in HbA1c response was much larger than its mean may reflect these complex relationships between testing and glycemic control. By using a large cohort and a pre/post design, we may have more effectively controlled for covariates than smaller randomized trials, enabling us to detect a significant effect for monitoring. In addition, we found improvements in HbA1c only when subjects monitored blood glucose three or more times daily, a higher level than used in most previous studies. We also found that changes were confined to those with poorer glycemic control, suggesting that the effects of monitoring are detectable only in those with suboptimal self-care.

Our study had some potential limitations. The subjects were generally older men; our results may be less applicable to other populations. Although we found that significant decreases in HbA1c persisted at 52 weeks, selection bias may have affected our results. Nearly 25% of the subjects did not return for the last visit. These missing subjects were similar in age and glycemic control to those completing the study, although they had been significantly less compliant (66 vs. 81%, P < 0.001) with the intensified monitoring protocol. They likely would have had poorer glycemic control at the end of the study period, which would have diminished the overall improvement in HbA1c.

However, we would still expect SMBG compliance to be strongly correlated with glycemic control.

In summary, intensified SMBG had a clinically important and sustained effect on HbA1c in stable, insulin-treated veterans with type 2 diabetes. Compliance with monitoring was more influential than other self-care behaviors and treatment factors affecting glycemic control. Intensified SMBG was most effective in subjects with poorer baseline glycemic control. Future studies should be undertaken to replicate these findings and to identify the self-care behaviors that were improved by SMBG.

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References
20. Estey AL, Tan MH, Mann K. Follow-up