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

The Diabetes Outcomes in Veterans Study (DOVES)

GLEN H. MURATA, MD[1]
JAYENDRA H. SHAH, MD[2,3]
RICHARD M. HOFFMAN, MD[1]
CHRISTOPHER S. WENDEL, MS[2]
KAREN D. ADAM, RN[1]
PATRICIA A. SOLVAS, RN[2]
SYED U. BOKHARI, MD[4]
WILLIAM C. DUCKWORTH, MD[3,4]

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. HbA_{1c} was measured at baseline, at 4 weeks, and at 8 weeks. After the intensified monitoring period, subjects resumed their usual monitoring. HbA_{1c} 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 HbA_{1c} (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 HbA_{1c} and compliance independently predicted the week 8 HbA_{1c} ($r = 0.862$, $P < 0.001$), standardized regression analysis found that compliance with the SMBG protocol influenced the week 8 HbA_{1c} 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 HbA_{1c} >8.0%. Decreases in HbA_{1c} (−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 HbA_{1c}.

Diabetes Care **26:1759–1763, 2003**

From [1]Department of Medicine, New Mexico VA Health Care System, Albuquerque, New Mexico; the [2]Southern Arizona VA Health Care System, Tucson, Arizona; the [3]Departments of Medicine and Radiology, University of Arizona College of Medicine; and the [4]Department of Medicine, Carl T. Hayden VA Medical Center, Phoenix, Arizona.

Address correspondence and reprint requests to Richard M. Hoffman, MD, Albuquerque VA Medical Center 111GIM, 1501 San Pedro Dr. SE, Albuquerque, NM 87108. E-mail: rhoffman@unm.edu.

Received for publication 13 December 2002 and accepted in revised form 24 February 2003.

W.C.D. is a paid consultant for and receives research support from Roche Diagnostics.

Abbreviations: DOVES, Diabetes Outcomes in Veterans Study; SMBG, self-monitored blood glucose.

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

The value of self-monitored blood glucose (SMBG) testing in type 2 diabetes is controversial (1–3). Results from observational studies of SMBG have been inconsistent (4–13). Randomized trials of SMBG have also led to different conclusions. Two studies suggested that monitoring is valuable when coupled with a structured plan for treating glucose elevations (14,15). However, most trials comparing SMBG with urine testing or no monitoring have not demonstrated beneficial effects (16–21). To our knowledge, few investigations have evaluated the effect of intensified SMBG on insulin-treated patients. The purpose of this study was to examine the effect of four-times daily blood glucose testing on glycemic control in subjects with stable insulin-treated type 2 diabetes.

RESEARCH DESIGN AND METHODS

— The Diabetes Outcomes in Veterans Study (DOVES) was a prospective, observational study of risk factor control in stable, insulin-treated veterans with type 2 diabetes. The primary DOVES objective was to identify correctable problems in implementing methodologies shown to improve outcomes in patients with type 2 diabetes. The study methodology has been described elsewhere (22). Briefly, potential subjects were identified from computer pharmacy records at the New Mexico VA Health Care System, the Carl T. Hayden VA Medical Center, and the Southern Arizona VA Health Care System. Candidates were randomly drawn from this sample frame by computer-generated random numbers. Patients were eligible for this study if diabetes developed after age 35 years, if they had no history of diabetic ketoacidosis, if they took at least one injection of a long-acting insulin preparation daily, and if they did not self-titrate their insulin doses. We excluded patients

Table 1—*Effect of SMBG on week 8 HbA_{1c} stratified by baseline HbA_{1c} and testing compliance*

	Subjects	Change	*P* value
By entry HbA_{1c}			
≤7.0%	54	−0.10 ± 0.58%	NS
>7.0% and ≤8.0%	56	−0.10 ± 0.83%	NS
>8.0%	91	−0.67 ± 0.97%	<0.001
By compliance			
≤60%	33	−0.33 ± 0.98%	NS
>60% and ≤75%	40	−0.22 ± 1.21%	NS
>75% and ≤90%	58	−0.56 ± 0.66%	<0.001
>90%	70	−0.29 ± 0.77%	0.003

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 regimens, 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 HbA_{1c}. Although the intensified monitoring ended at 8 weeks, subjects remained in the longitudinal DOVES study and HbA_{1c} 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 χ^2 analysis and unpaired Student's *t* test, respectively. We tested within-subject changes in HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} was 8.10 ± 1.67%. The mean BMI was 31.9 ± 5.7 kg/m^2, 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

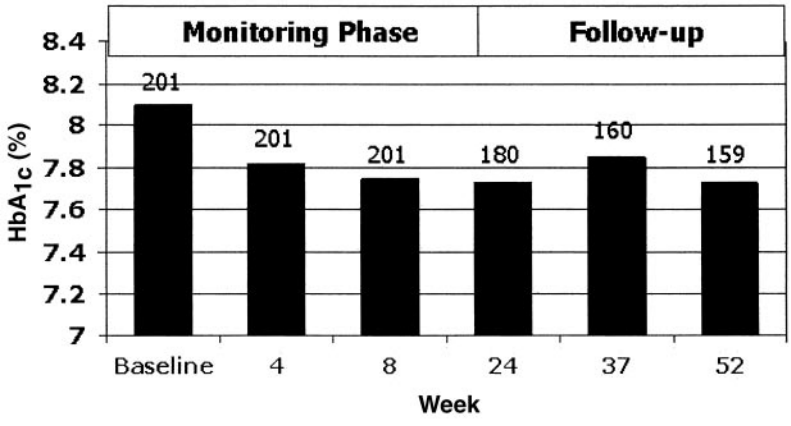

Figure 1—*HbA_{1c} levels during intensified monitoring and follow-up. Numbers above the bars represent the number of subjects followed to that time.*

Table 2—*Multivariate models for predicting week 8 HbA_{1c}*

Variable	Coefficient	Standard deviation	Standard coefficient	*P* value
Model A				
Constant	3.05	0.40	0.000	<0.001
Baseline HbA_{1c} (%)	0.692	0.033	0.800	<0.001
Compliance (%)	−1.17	0.29	−0.155	<0.001
Model B				
Constant	10.97	1.04	0.000	<0.001
Compliance (%)	−2.80	0.49	−0.38	<0.001
Age (years)	−0.013	0.010	−0.090	NS
Sex*	0.252	0.403	0.040	NS
BMI (kg/m^2)	−0.037	0.019	−0.144	0.06
Exercise (metabolic-hours per week)	0.001	0.001	0.066	NS
Carbohydrate intake (gm per day)	0.002	0.001	0.184	0.005
Insulin units per day	0.006	0.002	0.182	0.015
Use of oral agents†	0.173	0.134	0.090	NS

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

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. Compliance ranged from 3 to 100% (mean 78.4 ± 19.3). We found a significant and sustained decrease in HbA_{1c} 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 HbA_{1c} >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 HbA_{1c} level and compliance were strong predictors of HbA_{1c} at 8 weeks ($r = 0.862$, $P < 0.001$) (Table 2, Model A). Compliance was the most influential self-care determinant of week 8 HbA_{1c} ($P < 0.001$), 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 HbA_{1c}, whereas higher carbohydrate consumption and higher insulin doses were associated with higher HbA_{1c}. 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}, compliance with the intensified monitoring protocol was a strong predictor of the week 8 HbA_{1c}. Compliance was more influential on HbA_{1c} 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 HbA_{1c} 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

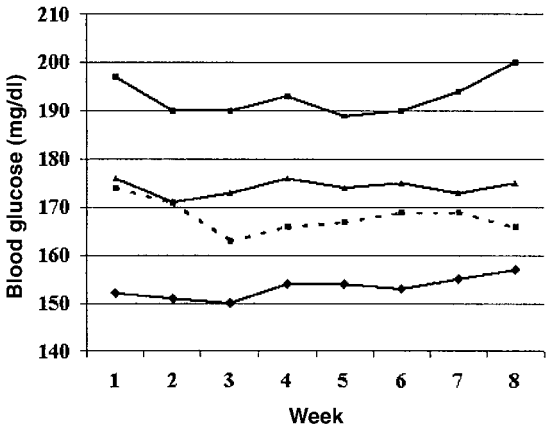

Figure 2—*Diurnal changes in mean glucose levels during intensified monitoring. —■—, bedtime, —▲—, predinner; - - ■ - -, prelunch; —◆—, prebreakfast.*

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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 in other populations. Although we found that significant decreases in HbA_{1c} 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 HbA_{1c}. 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 HbA_{1c} 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.

Acknowledgments— This study was supported by Grant VCR 99–007 from the Health Services Research & Development Service and Veterans Integrated Service Network 18, Department of Veterans Affairs.

References

1. Faas A, Schellevis FG, Van Eijk JT: The efficacy of self-monitoring of blood glucose in NIDDM subjects: a criteria-based literature review. *Diabetes Care* 20:1482–1486, 1997
2. Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R: Self-monitoring in type 2 diabetes mellitus: a meta-analysis. *Diabet Med* 17:755–761, 2000
3. Kennedy L: Self-monitoring of blood glucose in type 2 diabetes: time for evidence of efficacy. *Diabetes Care* 24:977–978, 2001
4. Franciosi M, Pellegrini F, De Berardis G, Belfiglio M, Cavaliere D, Di Nardo B, Greenfield S, Kaplan SH, Sacco M, Tognoni G, Valentini M, Nicolucci A: The impact of blood glucose self-monitoring on metabolic control and quality of life in type 2 diabetic patients: an urgent need for better educational strategies. *Diabetes Care* 24:1870–1877, 2001
5. Karter AJ, Ackerson LM, Darbinian JA, D'Agostino RB Jr, Ferrara A, Liu J, Selby JV: Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes registry. *Am J Med* 111:1–9, 2001
6. Schiel R, Muller UA, Rauchfub J, Sprott H, Muller R: Blood-glucose self-monitoring in insulin treated type 2 diabetes mellitus a cross-sectional study with an intervention group. *Diabetes Metab* 25:334–340, 1999
7. Harris MI: Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. *Diabetes Care* 24:979–982, 2001
8. Evans JM, Newton RW, Ruta DA, MacDonald TM, Stevenson RJ, Morris AD: Frequency of blood glucose monitoring in relation to glycaemic control: observational study with diabetes database. *BMJ* 319:83–86, 1999
9. Rindone JP, Austin M, Luchesi J: Effect of home blood glucose monitoring on the management of patients with non-insulin dependent diabetes mellitus in the primary care setting. *Am J Managed Care* 3:1335–1338, 1997
10. Oki JC, Flora DL, Isley WL: Frequency and impact of SMBG on glycemic control in patients with NIDDM in an urban teaching hospital clinic. *Diabetes Educ* 23: 419–424, 1997
11. Klein CE, Oboler SK, Prochazka A, Oboler S, Frank M, Glugla M, Winters S: Home blood glucose monitoring: effectiveness in a general population of patients who have non-insulin-dependent diabetes mellitus. *J Gen Intern Med* 8:597–601, 1993
12. Patrick AW, Gill GV, MacFarlane IA, Cullen A, Power E, Wallymahmed M: Home glucose monitoring in type 2 diabetes: is it a waste of time? *Diabet Med* 11:62–65, 1994
13. Newman WP, Laqua D, Engelbrecht D: Impact of glucose self-monitoring on glycohemoglobin values in a veteran population. *Arch Intern Med* 150:107–110, 1990
14. Rutten G, van Eijk J, de Nobel E, Beek M, van der Velden H: Feasibility and effects of a diabetes type II protocol with blood glucose self-monitoring in general practice. *Fam Pract* 7:273–278, 1990
15. Muchmore DB, Springer J, Miller M: Self-monitoring of blood glucose in overweight type 2 diabetic patients. *Acta Diabetol* 31:215–219, 1994
16. Gallichan MJ: Self-monitoring by patients receiving oral hypoglycaemic agents: a survey and a comparative trial. *Practical Diabetes* 11:28–30, 1994
17. Miles P, Everett J, Murphy J, Kerr D: Comparison of blood or urine testing by patients with newly diagnosed non-insulin dependent diabetes: patient survey after randomised crossover trial. *BMJ* 315: 348–349, 1997
18. Allen BT, DeLong ER, Feussner JR: Impact of glucose self-monitoring on non-insulin-treated patients with type II diabetes mellitus: randomized controlled trial comparing blood and urine testing. *Diabetes Care* 13:1044–1050, 1990
19. Fontbonne A, Billault B, Acosta M, Percheron C, Varenne P, Besse A, Eschwege E, Monnier L, Slama G, Passa P: Is glucose self-monitoring beneficial in non-insulin-treated diabetic patients? Results of a randomized comparative trial. *Diabetes Metab* 15:255–260, 1989
20. Estey AL, Tan MH, Mann K: Follow-up

intervention: its effect on compliance behavior to a diabetes regimen. *Diabetes Educ* 16:291–295, 1990
21. Wing RR, Epstein LH, Nowalk MP, Scott N, Koeske R, Hagg S: Does self-monitoring of blood glucose levels improve dietary compliance for obese patients with type II diabetes? *Am J Med* 81:830–836, 1986
22. Murata GH, Shah JH, Wendel CS, Hoffman RM, Adam KD, Bokhari SU, Solvas PA, Duckworth WC: Risk factor management in stable, insulin-treated patients with type 2 diabetes: the Diabetes Outcomes in Veterans Study. *J Diabetes Complications*. In press
23. Kristal AR, Abrams BF, Thornquist MD, Disogra L, Croyle RT, Shattuck AL, Henry HJ: Development and validation of a food use checklist for evaluation of community nutrition interventions. *Am J Public Health* 80:1318–1322, 1990
24. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr: Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 25:71–80, 1993
25. Systat: *The System for Statistics: Nonparametric Statistics*. Evanston, IL, Systat, 1990
26. Glantz SA, Slinker BK: *Primer of Applied Regression and Analysis of Variance*. New York, McGraw-Hill, 1990
27. American Diabetes Association: Tests of glycemia in diabetes. *Diabetes Care* 23 (Suppl. 1):S80–S82, 2000