Self-Monitoring of Blood Glucose in Diabetic Patients Not Taking Insulin: Does It Affect Hypoglycemia?

Brian J. Neil, MD, Alisha Baines, MS, Barbara Clothier, MS, MA,
David B. Nelson, PhD, and Hanna E. Bloomfield, MD, MPH

With controversy surrounding the use of self-monitoring of blood glucose in this patient population, these VA investigators set out to determine whether the practice has any effect on the occurrence of severe hypoglycemia.

Self-monitoring of blood glucose (SMBG), using disposable test strips and a portable glucose meter, can help diabetic patients understand how food, exercise, and medication affect their blood glucose levels. This understanding, in turn, allows them to adjust their habits accordingly. SMBG has become increasingly common since it was devised in the 1970s, and it is now an accepted component of routine care for patients with diabetes who are taking insulin.[1]

For patients who are not taking insulin, the method has been prescribed as a way of improving glycemic control, preventing hypoglycemic events, and improving patients' quality of life and satisfaction. Yet, in recent years, the actual efficacy of SMBG to improve glycemic control in this patient population has been hotly debated.[2–4] While a 2005 meta-analysis conducted by the Cochrane Collaboration found SMBG to be associated with a statistically significant 0.39% mean reduction of hemoglobin A_{1c} (HbA_{1c}) levels,[2] this finding has been disputed.[3]

Almost absent from this debate is the question of whether or not routine SMBG affects the risk of hypoglycemic events in patients who are not taking insulin. Due to insufficient data, the meta-analysis authors were unable to comment on the effects of SMBG on hypoglycemia. Only one trial within the analysis included hypoglycemia as an outcome, and that trial monitored fewer than 700 patients for less than six months.[5]

Given the relative sparsity of data about SMBG's relationship to hypoglycemia prevention in patients with type 2 diabetes who are not taking insulin, we designed and undertook a study to investigate this issue further in a large patient sample. Specifically, we sought to determine whether there was an association between the use or nonuse of SMBG and the occurrence of hypoglycemic events in this population.

STUDY DESIGN AND METHODS

Our sample was drawn from patients enrolled at five facilities—all within the VA Midwest Health Care Network. The participating facilities were: the Iowa City VA Medical Center, Iowa City, IO; the Omaha Division of the VA Nebraska Western Iowa Health Care System (VA NWIHCS), Omaha, NE; the Lincoln Division of the VA NWIHCS, Lincoln, NE; the Minneapolis VA Medical Center (MVAMC), Minneapolis, MN; and the St. Cloud VA Medical Center, St. Cloud, MN. All of the facilities' institutional review boards approved the study.

Using administrative databases, we identified 11,529 patients who had type 2 diabetes and were prescribed sulfonylureas, but not insulin, between October 1, 2004 and March 30, 2005. We then sent each of the patients a survey about their use of SMBG and diabetes medications and their experiences with hypoglycemia. (Our decision to collect patient data this way, rather than through a review of databases, was based on the survey's potential to provide information about hypoglycemic events that were treated in patients' homes or in medical facilities where we did not have access to data.) Finally, we analyzed the survey results to identify any associations between SMBG and hypoglycemia.

Sample size

The size of the patient sample that received the mailed survey was based on the power required for assessing equivalence between the rates of

Dr. Neil is a staff physician, **Ms. Baines** is a programmer and database manager, **Ms. Clothier** is a codirector of data analysis, **Dr. Nelson** is the senior statistician, and **Dr. Bloomfield** is the director, all with the Center for Chronic Disease Outcomes Research at the Minneapolis VA Medical Center, Minneapolis, MN. In addition, Drs. Neil and Nelson are assistant professors and Dr. Bloomfield is a professor, all in the department of medicine at the University of Minnesota, Minneapolis.

severe hypoglycemic events among users and nonusers of SMBG, assuming event rates ranging from 4% to 12% among SMBG users. For event rates up to 8% among users, equivalency was defined as no more than a 2% difference between users and nonusers. For event rates between 8% and 12% among users, equivalency was defined as no more than a 3% difference between users and nonusers. Assuming nonparticipation rates up to 30% of our sample, a targeted sample size of approximately 11,000 provided 90% power for assessing equivalence of event rates among SMBG users and nonusers.

Survey

The surveys were sent, along with a stamped return envelope and a cover letter explaining the study, through a single mailing in July 2005. No patient identifiers were included on the survey, although each one had a unique form identification number that was linked to the patient's facility.

The three-page survey (available at http://www.hsrd.minneapolis.med.va.gov/PDF/Diabetes_Health_Survey.pdf) was calibrated to a sixth grade reading level and contained 14 multiple choice questions. Its SMBG-related questions asked whether patients currently used glucose test strips and, if so, how often; whether they had used the strips six months ago and, if so, how often; whether they used strips that came from the VA, strips obtained outside the VA, or both; and how often they had performed SMBG during the two weeks before their worst hypoglycemic event of the past six months. Several questions dealt with hypoglycemic events over the past six months, asking whether such events had occurred; caused patients to seek treatment at a VA facility or other medical facility; led to an overnight hospital stay; or prompted assistance from a family member, friend, bystander, paramedic, physician, nurse, or other person. In addition, the survey provided a list of eight diabetes medications and asked patients to check all that they had used over the past six months.

Analysis

In interpreting patients' responses, we defined a severe hypoglycemic event as one that required the assistance of another person to treat—a definition similar to that used in the Diabetes Control and Complications Trial.[6] If the severe event rates were equal, then the upper 95% CI for the difference in rates would not exceed the aforementioned amounts with the probability of 90% with the aforementioned assumptions. The Pearson chi-square test was used to assess independence between two categorical variables. We were interested in the relationship, if any, between the occurrence of a severe hypoglycemic event and two variables: prior SMBG and frequency of prior SMBG. The Cochran-Armitage test for trend was used to assess trends in the proportion of those respondents who experienced a severe hypoglycemic event across an ordinal variable, such as frequency of SMBG. Severe event status was regressed on either testing status or SMBG frequency six months prior, controlling for site by using logistic models that initially included the in-

Table 1. Medication use and frequency of testing among survey respondents

Survey question	% of respondents
Medications used (n = 6,070)	
Sulfonylureas	
Glyburide	52%
Glipizide	44%
Glimepiride	1%
Tolazamide	< 1%
Metformin	51%
Glitazones	
Rosiglitazone	14%
Pioglitazone	3%
No. of medications (n = 6,070)	
0	1%
1	43%
2	46%
3	10%
4	< 1%
5	< 1%
Current testing frequency (n = 5,709)	
Less than once per week	8%
Once or twice per week	42%
Once per day	32%
Twice per day	13%
More than twice per day	5%

teraction between site and the independent variable.

OUR FINDINGS

Of the 11,529 surveys mailed, 6,471 (56%) were returned. Response rates for the five facilities ranged from 54% to 60%. Of the returned surveys, 369 reported insulin use, 19 were missing one or more pages, 10 were blank, and three indicated that the patient was deceased. These 401 surveys were excluded from further analysis, leaving 6,070 (53% of the mailed surveys) for the final sample.

SMBG use and frequency

Of the patients included in our final sample, 5,709 (94%) reported themselves to be current users of SMBG, with the majority (42%) reporting a testing frequency of one to two times per week (Table 1). In addition, 5,540 respondents (91%) reported that they had been using SMBG six months prior to the survey. In response to our question about where they received test strips, 3,241 respondents (57% of the respondents who reported current SMBG use) reported receiving them from the VA only, 1,879 (33%) reported receiving them from non-VA sources, and 573 (10%) reported receiving them from both VA and non-VA sources.

Hypoglycemic event rate

Of the 5,965 respondents who provided information regarding hypoglycemic events, almost half (47%; 95% CI, 46% to 48%) reported experiencing an event within the past six months. Of these, 538—9% of the total respondents—identified one or more of the events as severe (according to our definition).

There was no association between the number of diabetes medications used and the frequency of severe events: 8.3% of the respondents using one medication and 9.5% of those using two or more reported such events ($P = .11$). Most severe events were treated in patients' homes or communities by family members, friends, or bystanders; only 59 respondents (less than 1% of the total respondents) reported hospitalization for treatment of hypoglycemia.

The incidence of severe hypoglycemia was 5.2% among respondents who had not been testing six months prior to the survey date, compared with 9.4% for those who had been testing ($P < .01$). The difference in event rates, therefore, was 4.2% (95% CI, 2% to 6.3%). Among the 5,473 respondents who reported using SMBG six months prior to the survey and provided information on both the frequency of testing and the occurrence of severe events, the proportion of severe hypoglycemic events rose in a monotonic fashion across the levels of testing frequency. The rate of severe events was 4% among those who tested least frequently, compared with 21% among those who tested most frequently ($P < .0001$) (Figure).

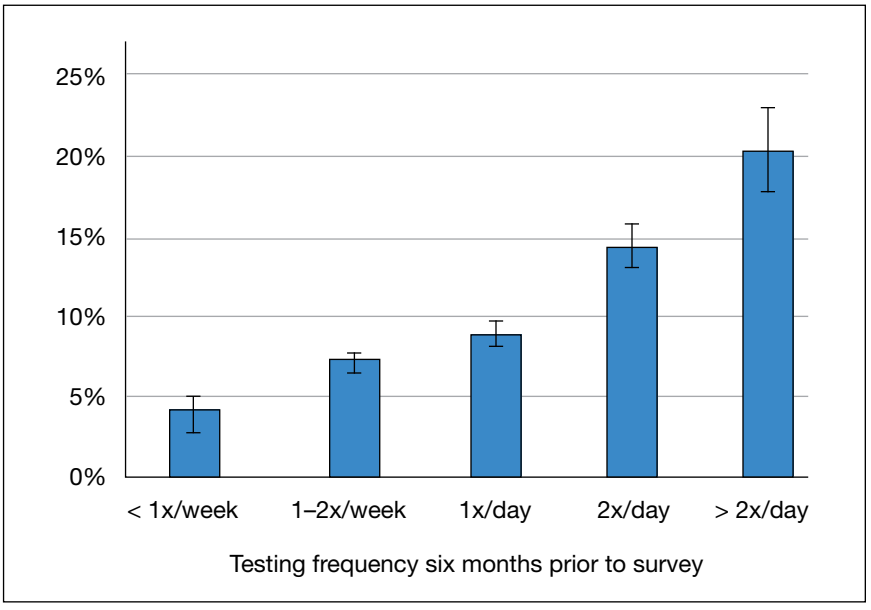

Figure. Proportion of respondents with at least one severe hypoglycemic event over a six-month period, by testing frequency (n = 5,473).

Relationships between variables

After controlling for facility site, we found both testing status and frequency of testing to be significant predictors of severe event status ($P < .01$ and $P < .0001$, respectively). The odds of experiencing a severe event as a function of testing frequency in the prior six months were 1.8 (95% CI, 1.1 to 3.1) for those who tested one to two times per week and 6.3 (95% CI, 3.5 to 11.2) for those who tested more than two times per day (Table 2). There were no significant interactions between site and either testing status or testing frequency, indicating that the results did not vary across the five facilities.

Change in SMBG frequency

Finally, we examined whether a severe event led to a change in testing frequency. Among those with a severe event, 70% reported they had not

changed their testing frequency after that event, while 13% said they had increased the frequency and 17% said they had decreased the frequency ($P < .0001$). Thus, 87% of participants did not increase the frequency of testing after a hypoglycemic event.

SMBG A NECESSITY?

Even among clinicians who agree that the medical literature does not unequivocally support the use of routine SMBG for improving glycemic control in diabetic patients not taking insulin, some still believe that SMBG should be recommended to prevent hypoglycemia.[2–4] Yet, our study results show that 9% of the population sampled experienced a severe hypoglycemic event in a six-month period—and that SMBG was not associated with a lower risk of such events. To the contrary, testing was associated with a higher risk of a severe hypoglycemic event (9% in testers versus 5% in nontesters, $P < .007$). Furthermore, we found a significant dose-response relationship by which those who performed SMBG most often were most likely to have a hypoglycemic event.

There are several possible explanations for these apparently counterintuitive findings. One is that being prone to hypoglycemia might cause patients to develop a particularly strong concern with their glucose levels and, thus, to practice SMBG more often than other patients. We do not believe this is the most likely explanation, however, since the majority (87%) of patients in our study did not increase the frequency of testing after they experienced a hypoglycemic event. Another possible explanation is that patients who use SMBG are more likely than nonusers to ascribe nonspecific symptoms to hypoglycemia. We also find this scenario unlikely, however, since our survey very explicitly defined what constituted a severe event. Finally, it is possible that more frequent testing leads to hypoglycemia by virtue of more frequent and intense self-adjustment of medication, diet, and exercise in testers in response to high glucose readings—a possibility that has been suggested by others.[7]

Table 2. Odds of experiencing a severe hypoglycemic event based on frequency of self-monitoring of blood glucose (SMBG) in the six months prior to the survey

Frequency of SMBG	Odds ratio	95% CI
Less than once per week	Reference	–
Once or twice per week	1.8	1.1–3.1
Once per day	2.4	1.4–4.0
Twice per day	4.2	2.4–7.1
More than twice per day	6.3	3.5–11.2

OTHER SUPPORTING STUDIES

Although data on the association between SMBG and hypoglycemia in patients with type 2 diabetes who do not take insulin are scarce, two studies that did address this question corroborate our findings that SMBG may increase hypoglycemia risk in this population.[5,8]

In the first study, 988 patients with type 2 diabetes who were not taking insulin were randomly assigned to a usual care group or a routine SMBG group. During six months of follow-up, patients in the routine SMBG group had a 10.4% reported incidence of hypoglycemia, compared with 5.2% in the usual care group ($P = .003$). The authors reported "no serious episode of hypoglycemia" in the study patients, but they did not include a description of how hypoglycemia was defined or detected. Furthermore, they did not include information on a possible dose-response relationship between testing frequency and hypoglycemia risk.[5]

In a much more recent study, 453 patients with non–insulin-treated type 2 diabetes were divided into an intensive SMBG group (in which patients used a blood glucose meter and were trained and supported in interpreting their blood glucose results to maintain adherence to diet, exercise, and medication regimens), a less intensive SMBG group (in which patients used a blood glucose meter but deferred to their physicians for interpretation of results), and a control group (in which patients received usual care and did not use a blood glucose meter). Although the main outcome measure was HbA_{1c} levels, the authors reported that mild symptoms of hypoglycemia (those that did not require third party intervention) occurred in 28% of 151 patients in the intensive group, 22% of 150 patients in the less intensive group, and 9% of 152 patients in the control group. One patient in the control group had a hypoglycemic event that required third party intervention. The authors pointed out that the increased occurrence of hypoglycemia in the SMBG groups may have been a result of the increased awareness of low blood glucose levels, arising from blood glucose meter use, rather than

Continued on page 33

Continued from page 30

from a true difference between the groups.[8]

A third study that may suggest a link between SMBG and hypoglycemia examined glycemic control and SMBG frequency. Although this study did not measure hypoglycemic event rates, it showed that SMBG was related to higher rates of hospitalization and emergency department visits—which could indicate higher rates of severe hypoglycemia—in patients with non–insulin-treated diabetes.[9]

STUDY STRENGTHS AND LIMITATIONS

The primary strengths of our study are, first, that it was conducted in a general clinical population in which patients were being treated routinely by their primary care providers in a large health care system and, second, that we ascertained the occurrence of hypoglycemic events by direct patient self-report. Most of the other studies examined this question either in highly selected research populations or through administrative data in which it was not possible to detect hypoglycemic events that did not result in a clinical encounter.

Our study also has important limitations. First, the fact that the vast majority of our respondents (94%) identified themselves as SMBG users contrasts with unpublished MVAMC, VA Midwest Health Care Network, and national VA data, as well as data from medical literature—all of which suggest that only about 30% to 60% of patients with non–insulin-treated diabetes perform routine SMBG.[9–11] This discrepancy suggests that patients who did not use SMBG were less likely to respond to our survey. Whether those nontesters who did respond are representative of the group as a whole is not known.

Another limitation of our study was the relatively low overall response rate to the survey (56%), which raises the concern of response bias. Because our reported rate of severe hypoglycemic events is comparable to that seen in other studies,[5,9] though, we feel reasonably confident that our sample was representative of the target population.

Finally, this study was not designed to evaluate glycemic control, so we were unable to explore the associations between glycemic control and frequency of hypoglycemia in the SMBG user and nonuser groups.

TIME FOR CLOSER SCRUTINY

We conclude that routine SMBG for patients with type 2 diabetes who are not taking insulin is of unproven benefit and may be associated with excess symptomatic hypoglycemia. Important to note is that SMBG is a very costly modality—estimated at billions of dollars in the United States annually.[3,9,12] Given these high costs, along with the testing method's unproven benefits and possibility of clinical harm, we believe that it is time to heed calls for a well designed, randomized, controlled trial to determine definitively the appropriate role of SMBG in this large and growing population.

Acknowledgements

This work was supported by the VA Midwest Healthcare Network and the Health Services Research and Development Office of the VA Office of Research and Development, Washington, DC. We would like to acknowledge the technical assistance of Diane Smith, Michelle Haas, Gita Karasov, Nadav Karasov, Jenny Katz, Jonathan Rubins, and Maya Sztainer.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

The opinions expressed herein are those of the authors and do not necessarily reflect those of Federal Practitioner, *Quadrant HealthCom Inc., the U.S. government, or any of its agencies. This article may discuss unlabeled or investigational use of certain drugs. Please review complete prescribing information for specific drugs or drug combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.*

REFERENCES

1. American Diabetes Association. Standards of medical care in diabetes—2006. *Diabetes Care*. 2006;29(suppl 1):S4–S42.
2. Welschen LM, Bloemendal E, Nijpels G, et al. Self-monitoring of blood glucose in patients with type 2 diabetes who are not using insulin: A systematic review. *Diabetes Care*. 2005;28(6):1510–1517.
3. Davidson MB. Counterpoint: Self-monitoring of blood glucose in type 2 diabetic patients not receiving insulin: A waste of money. *Diabetes Care*. 2005;28(6):1531–1533.
4. Saudek CD, Derr RL, Kalyani RR. Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. *JAMA*. 2006;295(14):1688–1697.
5. Guerci B, Grange V, Bougneres P, et al., for the ASIA group. Self-monitoring of blood glucose significantly improves metabolic control in patients with type 2 diabetes mellitus: The Auto-Surveillance Intervention Active (ASIA) study. *Diabetes Metab*. 2003;29(6):587–594.
6. DCCT Research Group. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. *Am J Med*. 1991;90(4):450–459.
7. 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*. 1997;20(9):1482–1486.
8. Farmer A, Wade A, Goyder E, et al. Impact of self monitoring of blood glucose in the management of patients with non-insulin treated diabetes: Open parallel group randomized trial. *Br Med J*. http://www.bmj.com/cgi/content/full/bmj.39247.447431.BEv1. Epub June 25, 2007. Accessed July 16, 2007.
9. Karter AJ, Ackerson LM, Darbinian JA, et al. Self-monitoring of blood glucose levels and glycemic control: The Northern California Kaiser Permanente Diabetes registry. *Am J Med*. 2001;111(1):1–9.
10. Harris MI; National Health and Nutrition Examination Survey (NHANES III). Frequency of blood glucose monitoring in relation to glycemic control in patients with type 2 diabetes. *Diabetes Care*. 2001;24(6):979–982.
11. Soumerai SB, Mah C, Zhang F, et al. Effects of health maintenance organization coverage of self-monitoring devices on diabetes self-care and glycemic control. *Arch Intern Med*. 2004;164(6):645–652.
12. Kennedy L. Self-monitoring of blood glucose in type 2 diabetes. *Diabetes Care*. 2001;24(6):977–978.