Blood Glucose Monitoring is Associated with Better Glycemic Control in Type 2 Diabetes: A Database Study

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BACKGROUND: The value of self-monitoring blood glucose (SMBG) in type 2 diabetes is controversial.

OBJECTIVE: To determine if SMBG testing rates are positively associated with glycemic control in veterans on oral hypoglycemic agents (OHA).

DESIGN: Observational database study.

SUBJECTS: Southwestern Healthcare Network veterans taking OHA in 2002 and followed through the end of 2004.

MEASUREMENTS: OHA and glucose test strip (GTS) prescriptions were derived from pharmacy files. Subjects were categorized into five groups according to their end-of-study treatment status: group 1 (no medication changes), group 2 (increased doses of initial OHA), group 3 (started new OHA), group 4 (both OHA interventions), and group 5 (initiated insulin). We then used multiple linear regression analyses to examine the relationship between the SMBG testing rate and hemoglobin A1c (HbA1c) within each group.

RESULTS: We evaluated 5,862 patients with a mean follow-up duration of 798±94 days. Overall, 44.2% received GTS. Ultimately, 47% of subjects ended up in group 1, 21% in group 2, 9% in group 3, 8% in group 4, and 16% in group 5. A univariate analysis showed no association between the SMBG testing rate and HbA1c. However, after stratifying by group and adjusting for initial OHA dose, we found that more frequent testing was associated with a significantly lower HbA1c in groups 1, 4, and 5. The effect ranged from -0.22% to -0.94% for every ten GTS/week.

CONCLUSIONS: Higher SMBG testing rates were associated with lower HbA1c, but only when stratifying the analyses to control for treatment intensification.

KEY WORDS: diabetes mellitus; type 2; hemoglobin A; glycosylated; hypoglycemic agents; blood glucose self-monitoring.

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INTRODUCTION

The American Diabetes Association recommends routine self-monitoring of blood glucose (SMBG) for patients with type 2 diabetes.¹ Despite this recommendation, the benefits of monitoring on glycemic control have not been clearly established for patients on oral hypoglycemic agents (OHA) alone.²⁻⁵ Few randomized controlled trials have found that SMBG is associated with a statistically significant decrease in HbA1c compared with control groups.^{4,5} Considering the substantial cost and inconvenience of SMBG,^{6,7} recommendations for routine monitoring should be justified by clinical evidence for effectiveness.

Although randomized clinical trials are considered the gold standard for evaluating SMBG, they have important limitations.^{6,8} SMBG trials cannot be blinded, monitoring alone is not sufficient to improve glycemic control, and subjects are vulnerable to a Hawthorne effect. These trials also tend to enroll highly selected patients, are of short duration, and use resources that are not easily replicated in routine practice. Observational studies of SMBG can evaluate subjects receiving routine care and are the most feasible designs for detecting small effects or showing long-term benefits.

However, observational studies cannot evaluate SMBG as an experimental factor. Additionally, assembling and characterizing an inception cohort are challenging, SMBG testing cannot be standardized, and endpoints will not necessarily be measured at the optimal time. The greatest challenge in analyzing observational data is removing the effect of confounders, particularly treatment intensity and other factors associated with glycemic control. There are many risk factors that affect glycemic control, such as insulin resistance, B-cell dysfunction, poor dietary habits, physical inactivity, and medication non-adherence. If poor glycemic control prompts more intensive therapy—and concomitant increased use of SMBG—then the benefit of SMBG on glycemic control will be obscured.

We used a computerized database of all diabetic patients receiving care at 3 main Southwestern VA medical centers and 26 affiliated community-based clinics. We established a cohort

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of patients using only oral hypoglycemic agents (OHA) and examined the effect of SMBG on hemoglobin A1c (HbA1c) after 2 years. The different facilities had markedly different policies regarding the use of glucose test strips over this time frame. One facility restricted SMBG use to patients receiving insulin. In order to adjust SMBG use for covariates related to glycemic control, we stratified the analysis by treatment intensification. We then used multiple linear regression analyses to test the relationship between the SMBG rate and final HbA1c within each stratum. This strategy allowed us to control for the confounders that could obscure the potential benefit of SMBG testing on glycemic control.

METHODS

We conducted a longitudinal observational study that used electronic databases to assess the association between SMBG testing and glycemic control stratified by treatment intensification and adjusted for baseline OHA use.

Subjects. Veterans receiving primary care at the New Mexico VA Health Care System (NMVAHCS), the Southern Arizona VA Health Care System (SAVAHCS), and the Carl T. Hayden VA Medical Center were eligible for this study if they were: (1) on an OHA (acarbose, glipizide, glyburide, metformin, pioglitazone, rosiglitazone, and/or tolazamide) but not insulin in the first, second, or third quarter of FY 2002; (2) not given an insulin prescription for the subsequent two quarters; (3) still receiving diabetic medications during the last quarter of FY 2004; (4) had a hemoglobin A1c measured within 90 days of the end-of-study date (31 December 2004). The criteria assured that all subjects were followed for at least 2 years. We excluded patients receiving chlorpropamide, glimiperide, miglitol, nateglinide, repaglinide, or tolbutamide at entry. These medications represent <0.5% of all prescriptions, and including patients taking these medications would have made the regression models too cumbersome. We also excluded patients receiving a qualifying OHA at a dose above the recommended range—as defined by MicroMedex, the standard on-line drug reference for the Department of Veterans Affairs.

Data Collection. This study utilized region-wide clinical data compiled through the Data Warehousing Initiative of Veterans Integrated Service Network 18. No patient identifiers were available to the investigators in this study. Accordingly, the three hospital institutional review boards approved this protocol as an exempted study.

We assessed hypoglycemic medication by searching pharmacy files in the regional database for patients receiving eligible OHA medications during the first, second, or third quarters of FY 2002. We excluded patients receiving any insulin preparation during the next two quarters or who did not receive any prescriptions for OHA or insulin during the fourth quarter of FY 2004. A search for root syllables for each OHA in the regional database did not reveal any entries in other VA drug classes. The study entry date was the date of the first OHA prescription in the first three quarters of FY 2002, while the follow-up date was defined as the date of the last OHA or insulin prescription in the subsequent 24+ months. Duration of follow-up was defined as the difference between

these two dates expressed in days. We calculated the mean daily dose for each OHA at entry and at follow-up by using the following formula: tablet strength $\times$ quantity dispensed/number of days supplied.

For each subject, we searched the regional database to retrieve all prescriptions for glucose test strips (GTS) dispensed between the entry and follow-up dates from VA drug class DX900. A search for the terms “glucose” and “strip” in all other item descriptions captured the GTS prescriptions that were recorded in other VA drug classes.

We used all prescriptions for glucose test strips (GTS) during the study period to estimate the SMBG testing rate. The total number of strips dispensed was calculated for the time period in question. The rate of monitoring (per week) was given by the following: $7 \times$ total number of GTS/follow-up period (days).

We assessed the outcome of glycemic control by retrieving HbA1c values from the regional database by searching all items under the VA root laboratory name “glycohemoglobin.” A preliminary search for the root syllables “hemo,” “alc,” and “glyc” did not reveal any entries under other root terms. For analyses, we used the HbA1c value obtained nearest to the end of the study period (31 December 2004).

Data Analysis. We used univariate and multivariate linear regression analyses to evaluate the association between SMBG testing and glycemic control. We stratified the multivariate analyses by creating five outcome groups, based upon a patient’s treatment status in the last quarter of FY 2004 compared to the first quarter of FY 2002:

- Group 1: Stable - the patient did not end up with a change in his or her initial medications.
- Group 2: OHA dose(s) increased - the patient had a net increase in dose(s) of initial medications. Doses for the seven OHA classes on follow-up were compared to doses at entry. A “net increase” occurred if the number of medications for which doses were increased exceeded the number of medications for which doses were reduced.
- Group 3: New OHA started - the patient was being treated with an OHA on follow-up that had not been prescribed at entry.
- Group 4: Both interventions - the patient had doses of initial medications increased and a new OHA started.
- Group 5: Initiation of insulin - the patient received a prescription for insulin more than two quarters after entry.

The stage of diabetes is usually defined by the type of treatment that the patient receives (e.g., “insulin-treated”). We adjusted the analyses for the initial doses of glyburide and metformin (the most commonly prescribed OHA at the study sites) and the total number of OHA prescriptions to account for the fact that patients were at different stages of disease at entry.

Plots of residuals versus estimates were used to test the assumptions of linearity and homoscedasticity. Semi-probability plots were used to test normality of residuals. Outliers were identified by their studentized residuals. Group differences were tested by the Kruskal-Wallis one-way analysis of variance by ranks because the distributions of most dependent variables were highly skewed. P-values <0.05 were considered significant.

RESULTS

During the first, second, and third quarters of FY 2002, there were 5,862 patients on an OHA alone who then continuously received primary care through the end of FY 2004 and had an HbA1c within 90 days of the study conclusion. The mean ($\pm$ SD) duration of follow-up was 798 ± 94 days. During this time, only 2,572 (44%) subjects received GTS. Among those who monitored, the median rate was 2.8 times per week (inter-quartile range 1.3 to 4.5). By the end of the observation period, 2,739 (47%) had no changes in their initial medications; 1,214 (21%) were on increased doses of their initial medications; 519 (9%) had started a new OHA; 466 (8%) received both OHA interventions; 924 (16%) had initiated insulin. For the latter group, the time to treatment failure was 729 ± 140 days. Ninety-five percent of subjects had an HbA1c measurement during the observation period. The final mean value was $7.45 \pm 1.43\%$ and was measured 793 ± 215 days from entry.

Table 1 shows that patients with more intensified treatment were more likely to monitor and had higher SMBG weekly testing rates. Simple linear regression on the pooled sample showed no relationship between the SMBG testing rate and final HbA1c. However, stratifying the analysis by treatment intensification and adjusting for initial glyburide dose, initial metformin dose, and number of OHA at entry revealed highly significant negative correlations between the weekly SMBG testing rates and HbA1c for three groups (Table 2). The estimated effect on HbA1c was -0.22% to -0.94% for every ten GTS used per week. The improvement in glycemic control associated with SMBG was more pronounced in subjects who required the highest level of treatment intensification or who started insulin. Regression diagnostics showed that multiple linear models were appropriate for the latter groups. Specifically, the linearity assumption was verified, suggesting that there was a graded response between the SMBG weekly testing rates and reduction in HbA1c.

DISCUSSION

When we stratified patients according to their 2-year treatment status (stable medical management, intensification of oral agents, initiating insulin), we found that SMBG testing was inversely associated with glycemic control both for stable patients and those who required treatment intensification.

Table 1. Self-Monitored Blood Glucose Testing Practices Across Outcome Groups

Group	Proportion monitoring	Median weekly testing rate (IQ range)*
#1 OHA dose(s) unchanged	36.3%	2.5 [1.2 to 4.0]
#2 OHA dose(s) increased	38.0%	2.6 [1.2 to 4.1]
#3 New OHA added	39.7%	2.8 [0.9 to 4.1]
#4 OHA dose(s) increased and new OHA added	41.8%	2.7 [1.1 to 3.9]
#5 Insulin added	77.6%	3.7 [1.7 to 7.2]

*Among patients monitoring

Abbreviations: IQ = interquartile range, OHA = oral hypoglycemic agent

Table 2. Effect of Self-Monitored Blood Glucose Weekly Testing Rate on HbA1c Stratified by Treatment Intensification

Treatment strata	Coefficient (standard error)	R ² *	P-value
OHA dose(s) unchanged	-0.2 (0.01)	0.08	0.04
OHA dose(s) increased	-0.09 (0.02)	0.02	0.63
New OHA added	-0.4 (0.03)	0.05	0.21
OHA dose(s) increased and new OHA added	-0.9 (0.03)	0.04	0.002
Insulin added	-0.5 (0.01)	0.03	<0.001
All subjects	-0.06 (0.01)	0.04	0.38

*Coefficients represent change in A1c for every ten glucose test strips used each week. Coefficients and R² were derived for each outcome stratum using separate multivariate linear regression models adjusting for initial doses of glyburide and metformin and the number of oral hypoglycemic agents at entry

Abbreviations: OHA = oral hypoglycemic agent

The improvements in glycemic control associated with SMBG were clinically important, ranging from -0.22% to -0.94% for every ten GTS used/week. The effect was more pronounced in subjects who received more intensified treatment. The estimated effects on HbA1c were comparable to the effects of pharmacotherapy.^{9,10}

Numerous observational studies of SMBG have failed to find any clinical benefits for monitoring.¹¹⁻²³ However, our study suggests that SMBG benefits will be missed if analyses fail to appropriately adjust for treatment intensification — which is a marker for risk factors leading to poor glycemic control. While multivariate approaches are necessary, these analyses are not sufficient to adjust for unmeasured confounders of glycemic control. Observational studies test the hypothesis that more frequent SMBG decreases HbA1c. Patients with poorly controlled diabetes may have both treatment and monitoring intensified so that the true association between monitoring and HbA1c can be obscured. We addressed this problem by following a cohort to a clinical endpoint. We assumed that each patient had a set of risk factors that strongly influenced the rate of disease progression and ultimately treatment intensification. While some of these risk factors can be controlled with treatment and monitoring, others cannot, including physiologic abnormalities, knowledge, attitudes, and unhealthy behaviors. We stratified the entire cohort into five clinical groups based on treatment patterns, with each group characterized by treatment intensification. By evaluating SMBG testing within the different groups — thus removing the bias arising from more frequent use of SMBG testing in patients requiring more intensified treatment — we were able to demonstrate a beneficial effect for monitoring on the biochemical outcome of HbA1c.

Even when accounting for disease-progression risk factors, observational studies are susceptible to bias because cohorts are often comprised of patients at different stages of disease. Diabetes treatment often mirrors the stage of disease because medications target specific physiologic defects. For example, metformin has been used in pre-diabetes because the predominant defect is insulin-resistance. A secretagogue is used when insulin secretion becomes inadequate, and insulin is required for beta-cell failure. These disease states may also be linked with different SMBG testing strategies, particularly for insulin-

dependent patients, which can obscure the link between monitoring and glycemic control. By requiring that all subjects were initially treated with only an OHA and adjusting for initial doses and drug classes, we were able to assemble an inception cohort at relatively the same stage of disease.

We also used an electronic pharmacy database for GTS orders and refills to minimize the potential problems caused by inaccurate self-reporting. Although the most accurate method for determining monitoring rates is direct observation (e.g., downloading glucometers), this is not feasible for an observational database study. However, measuring the number of glucose test strips (GTS) issued over a prolonged period in the VA system is reasonably accurate because these supplies are dispensed only when the patient requests refills or a primary care provider places an order. Test strips are not automatically refilled. Using the electronic pharmacy database also allowed us to accurately measure treatment intensity, an important determinant of glycemic control. By pooling data across three health-care systems, including one hospital that restricted SMBG testing for patients on oral agents alone, we were able to model substantial practice variation, allowing us to further dissociate testing practices from treatment intensification.

A recently published observational study conducted in the Northern California Kaiser Permanente Medical Care Program also found beneficial effects for SMBG.²⁴ Similar to our study, investigators followed a cohort of more than 31,000 patients, the majority of whom had type 2 diabetes, for 4 years. Investigators used electronic databases to identify patients with diabetes and to capture pharmacy data on glucometer strip and medication fills as well as laboratory data on HbA1c. Kaiser Permanente guidelines support SMBG, but do not specify monitoring protocols so that providers had flexibility in recommending monitoring use. To avoid the confounding effect of treatment intensity on SMBG and glycemic control, investigators excluded subjects who modified their treatment regimen during follow-up. Multivariate adjusted analyses found a dose-response benefit regardless of pharmacologic treatment type (oral hypoglycemic agent or insulin) with an even greater benefit for patients who newly initiated SMBG during the study period.^{8,24}

We realize that observational studies cannot prove that SMBG improves glycemic control or definitively determine the mechanisms by which SMBG exerts its effect. Our database study also had some limitations. We had region-wide data only on diabetes testing, treatment, and glycemic control and could not adjust our analyses for demographic or other clinical data. Additionally, data on other potential important confounders, including health behaviors and forms of self-management, are not routinely available even in the local clinical databases. These data limitations could lead to residual confounding. Prospective studies designed to better measure potential confounders would provide more definitive information about the value of SMBG testing. Nonetheless, by using a large clinical database we were able to include every OHA-treated subject in the region who met our study inclusion criteria — giving us the statistical power to detect an overall clinically important inverse correlation between glucose monitoring and glycemic control. We also studied a population of veterans with type 2 diabetes largely comprised of older males who had substantial co-morbidity and a relatively low socioeconomic status. Our results may not be applicable to non-veterans, younger patients, women, or patients with type 1 diabetes.

Finally, we excluded subjects who did not have an HbA1c measured during follow up, though this represented less than 5% of the cohort.

In summary, our observational study was able to suggest potential benefits for SMBG because we assembled a large inception cohort, used an electronic database to accurately capture SMBG and medication prescriptions and HbA1c values, and followed the cohort for 2 years. The results from our and other observational studies^{24,25} and meta-analyses of randomized trials^{4,5} point out the continued need for a large, well-designed, long-term randomized controlled trial to evaluate the cost effectiveness of SMBG testing. Such studies will need to ensure that subjects are able to appropriately monitor and then modify behaviors in response to SMBG readings. Appropriate subjects would be selected based on their knowledge and attitudes about diabetes self-management, physical and psychological health, and socioeconomic status, including social support and access to health care. In the meantime, observational studies that do not adequately adjust for potential confounding variables may underestimate the benefits of SMBG. Policy changes surrounding SMBG testing based on such studies — particularly restricting use — should be applied cautiously.²⁶

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