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EDITORIAL

New Evidence Demonstrates That Self-Monitoring of Blood Glucose Does Not Improve Outcomes in Type 2 Diabetes—When This Practice Is Not Applied Properly

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Two new studies were reported in the *British Medical Journal* (BMJ) online first on April 17, 2008[1,2] which concluded that self-monitoring of blood glucose (SMBG) is unlikely to be cost-effective if added to standard usual care. Furthermore, these studies also concluded that SMBG reduces the quality of life in type 2 diabetes.

The first of these two studies was an economic analysis of SMBG in type 2 diabetes[1] conducted by the same team that reported the Diabetes Glycaemic Education and Monitoring (DiGEM) results in 2007.[3] This analysis was based on unreleased economic data from that study. The DiGEM study had found no clinical benefit from SMBG in type 2 diabetes.

The economic analysis of the DiGEM study concluded that self-monitoring of blood glucose with or without additional training in incorporating the results into self-care was associated with higher costs and lower quality of life in patients with noninsulin-treated type 2 diabetes. Given the original DiGEM study's conclusion of no benefit from SMBG in type 2 diabetes, it was not surprising that the follow-up economic study demonstrated SMBG to not be cost-effective. When a cost is associated with a practice that offers no benefit, then an economic analysis will always demonstrate an absence of cost-effectiveness. Therefore, the negative conclusion of the economic portion of this trial was a foregone conclusion from when the original study was published. The shortcomings of the DiGEM study have been well described in previous correspondence in BMJ.

The second of these two studies was the Efficacy of Self Monitoring of Blood Glucose (ESMON) study of patient satisfaction among newly diagnosed patients with type 2 diabetes.[2] The objective of this study was to assess the effect of SMBG on glycemic control and psychological indices. In this prospective randomized controlled trial, newly diagnosed noninsulin-treated subjects with type 2 diabetes were randomized to receive or not receive SMBG. The investigators found that SMBG had no effect on glycemic control. However, this practice was associated with a 6% higher score on a depression subscale of a satisfaction questionnaire. The conclusions of the ESMON study are themselves questionable, as explained later.

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Abbreviations: (BMJ) *British Medical Journal*, (DiGEM) Diabetes Glycaemic Education and Monitoring, (ESMON) Efficacy of Self Monitoring of Blood Glucose, (RCT) randomized controlled trial, (SMBG) self-monitoring of blood glucose

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Headlines in the Press

After these two studies were released, the popular press announced the results of these studies with alarm, decrying the use of SMBG in type 2 diabetes. Among the headlines describing this research were "Home diabetes kits waste £100m a year, says research,[4]" "Blood glucose self checks waste of money,[5]" "Studies Question £100 Million/year Spent On Diabetes Self-monitoring,[6]" "Self-Testing Blood Sugar Levels Lowers Quality Of Life In Diabetes?,[7]" and "Self-testing sugar levels harm diabetics.[8]"

Literature on SMBG in Treating Type 2 Diabetes

Considering that SMBG is a widely practiced behavior in type 2 diabetes and that three recent meta-analysis studies of this practice concluded that SMBG confers a benefit of lowering the Hemoglobin A1c by approximately 0.4%,[9–11] it is noteworthy that the recent DiGEM and ESMON studies came to opposite conclusions about the benefit of SMBG in this population. Might these recently reported studies help clinicians understand whether or not to use SMBG in type 2 diabetes?

The DiGEM Study

The DiGEM study had a flawed protocol with respect to answering whether SMBG confers benefit in type 2 diabetes. Glycemic control was compared after 1 year in three cohorts of subjects with type 2 diabetes: nontesters, less intensive testers, and more intensive testers. The more intensive testers were given training to use the glucose values to enhance motivation and maintain adherence to therapy.[3]

Four significant problems weakened the conclusions of the DiGEM study. First, the subjects in both the less intensive testing cohort and the more intensive testing cohort had Hemoglobin A1c levels in the range of 7.5%, which obviated a need to modify therapy. This is particularly relevant in the United Kingdom where the study (and ESMON) was conducted, as pay for performance metrics in the United Kingdom only incentivize physicians to obtain a Hemoglobin A1c of <7.5%. Second, no specific plan for modification of treatment was utilized in the study, although in both groups, clinical suggestions were made based on Hemoglobin A1c. SMBG data may or may not have been shared with the physicians responsible for making therapeutic changes. Third, the unstructured intervention appears to have been ineffective in altering behavior or therapy because by completion of the study: (a) there was no difference in weight loss between more intensive users and nonusers of SMBG; (b) the less intensive testers had a higher rate of compliance with testing (defined as the percentage of subjects testing themselves at least twice weekly for the entire 12-month intervention) than the more intensive testers; and (c) the more intensive SMBG users did not alter medication therapy more frequently than the control group. Fourth, the study appears to have been underpowered because the investigators powered the study assuming a 10% dropout rate; in fact, in each of the two testing cohorts, approximately 10% dropped out and an additional approximately 40% did not persist in monitoring, resulting in a loss of approximately 50% of study subject intervention data. The investigators intended to detect a decrease in Hemoglobin A1c of 0.5 %, even though the benefit of a comparable intervention in the three largest meta-analysis articles on the topic has been a decrease in Hemoglobin A1c of 0.39–0.42%.[9–11] If the originally planned sample size of intervention subjects had been studied (rather than cohorts with a 50% intervention dropout rate), then the investigators might have reached different conclusions with the very same effect size they described.[12] Negative results from an underpowered study do not contribute to furthering knowledge of an intervention and may even adversely affect the field because the study will be cited as negative evidence against the intervention, despite its lack of statistical power.[13,14]

The ESMON Study

The ESMON study compared Hemoglobin A1c levels at 1 year in two cohorts of recently diagnosed subjects with type 2 diabetes: a non-SMBG group and an SMBG group that tested eight times per week. The intervention subjects received advice on the need for dietary review or exercise in response to high readings. Both groups were treated according to an algorithm for prescribing oral hypoglycemic agents based only on Hemoglobin A1c levels. After 12 months, mean Hemoglobin A1c levels fell from 8.8 to 6.9% in the intervention cohort and from 8.6 to 6.9% in the control cohort. At each 3-month time point up to 12 months, the net improvement in Hemoglobin A1c was greater among intervention subjects than nonintervention subjects, but these differences were never statistically significant.[2]

The ESMON study protocol was flawed with respect to answering whether SMBG affects control or mood.

In this study, the recommended intervention was described, but the actual actions taken in response to this intervention were not reported. Compliance was defined in terms of the frequency of performing SMBG and not with the frequency of performing a treatment modification in response to an out-of-range glucose reading and the specific treatment modifications were not reported. The treatment algorithm utilized by the caregivers at 3-month intervals was structured to include modification of medication dosages in both groups based only on Hemoglobin A1c levels. If the subjects who practiced SMBG had used such a more structured treatment algorithm, then the results for this cohort might have been better than they were. This group was, in effect, held back by not being allowed to modify medication dosages in response to glucose readings. Because therapies in both arms were adjusted by the caregivers based only on Hemoglobin A1c levels, it is not surprising that the final Hemoglobin A1c values were similar in both cohorts. Finally, the study was powered to detect a 1% difference in Hemoglobin A1c levels between the two groups, which left the study underpowered to detect a Hemoglobin A1c difference in the range of 0.4%, which is the figure in the literature for adding SMBG to basic care in subjects with type 2 diabetes.[9–11] It should be noted that the investigators did not compare the fall in Hemoglobin A1c of the SMBG and non-SMBG users, but instead compared the absolute Hemoglobin A1c between the groups at each 3-month interval. Because the SMBG users started at a higher level, the identical Hemoglobin A1c levels attained by both cohorts at the final time point represented a greater decrease for the SMBG users than the nonusers. At 12 months, based on the maximum confidence intervals of the mean difference between Hemoglobin A1c levels in SMBG users and nonusers, an effect of SMBG as high as 0.38% in Hemoglobin A1c could not be excluded by this study.[15] Such an improvement in Hemoglobin A1c with SMBG is comparable to the mean Hemoglobin A1c improvements that have been actually reported in the three most recent meta-analyses of this practice.

The ESMON study tested for seven psychological indices as primary outcomes and reported that one of them, depression, was present significantly more frequently in SMBG testers than in nontesters. The other six indices were not present in statistically greater frequencies in either cohort. The practice of testing multiple independent hypotheses from a single pair of comparators (such as SMBG testers and nontesters in this case) may yield misleading results.[16] What is the likelihood that none of seven independent hypotheses based on comparing two cohorts of subjects would cross the threshold of significance of 0.05 by chance alone? This probability is calculated by multiplying the probability of the test of the first hypothesis not crossing the 0.05 threshold by chance alone (which is 0.95) by the probability that the test of the second hypothesis would also not cross the 0.05 threshold by chance alone and so on seven times. This calculation requires 0.95 to be raised to the seventh power to calculate the probability that all seven tests would not cross the threshold of significance of 0.05 by chance alone. The product of 0.95 to the seventh power is 0.70. Therefore, when seven independent hypotheses are tested, the probability that at least one result is statistically insignificant is approximately 1 in 3 and not 1 in 20, which is the probability of the null hypothesis being incorrectly rejected for a single measurement. In order to maintain the overall boundary for statistical significance at 0.05, it is necessary to divide the threshold p value by the number of independent measures, which in this case means dividing the threshold p value by seven, so that each of the seven tests uses a boundary value of $p = 0.007$. The null hypothesis, that none of the characteristics differed significantly between the two observed groups, would be rejected only if one of the differences was significant at $p < 0.007$. None of the seven psychological indices measured by ESMON differed between SMBG testers and nontesters by $p < 0.007$. If the authors had initially specified a single psychological primary outcome (instead of multiple psychological outcomes) or if they had derived a global test statistic to incorporate all seven measures of psychological distress into a single measure, then they could have avoided their problem with multiple hypothesis testing.

Another problem in the ESMON study's data presentation was the method for determining the 6% increase in depression (at the end of the study compared to baseline) in the SMBG cohort. The baseline and post-study levels of depression in the non-SMBG cohort were not reported. The article did not specify whether, during the study, the non-SMBG users experienced a similar increase in depression as the SMBG users did. The investigators also did not report whether the baseline levels or final levels of depression in the SMBG users and non-users were similar, and they did not report the absolute levels of depression at the completion of the study, which would have permitted an analysis as to whether the SMBG users started out with more depression than the non-users of SMBG.

Purposes of SMBG

The purpose of SMBG is to monitor the clinical situation and to take appropriate action. Any test in medicine should only be done if the information can lead to action. This includes SMBG testing, which is recommended to allow patients to understand current levels of glycemia and ongoing patterns of glycemia and to modify their diet, activity, and medication dosages in response to glycemic levels that are out of a target range.

Self-monitoring of blood glucose is performed for four reasons. SMBG provides a patient with (1) data for detecting high or low blood glucose levels, which can facilitate self-adjustment of medication dosages and behavior factors that are affecting glycemia; (2) protection by allowing immediate confirmation of acute hypoglycemia or hyperglycemia; (3) education and motivation about the disease to stimulate greater self-care responsibilities; and (4) information to the health care provider to assess and modify the treatment regimen.[17]

Randomized Controlled Trials of SMBG in Type 2 Diabetes

In a recent literature review of whether SMBG improved patient control, McAndrew and colleagues noted among nine randomized controlled trials (RCTs) and one time series analysis of SMBG in subjects with type 2 diabetes not receiving insulin[18] that SMBG was associated with lower levels of Hemoglobin A1c in six RCT studies[19–24] and the one time series analysis.[25] SMBG was not associated with worse control in any study; however, in three studies[26–28] of SMBG, improvements in Hemoglobin A1c were not statistically greater for intervention subjects than for controls. They concluded that SMBG may be effective in controlling blood glucose for patients with type 2 diabetes not receiving insulin. Because of major inconsistencies in the literature in the types of treatment protocols used for trials of SMBG, they also recommended that studies be conducted to implement comprehensive treatment algorithms for the self-regulation of glycemia to assess whether patient use of SMBG improves Hemoglobin A1c levels. Evidence shows that algorithms for responding to SMBG data, which utilize insulin dosage adjustments in type 2 diabetes[29] and gestational diabetes,[30] improve control. Such studies are needed for type 2 diabetes patients who are using oral agent therapy.

Responsibilities of Patients and Physicians or Caregivers

In order for SMBG to be effective, both the patient and the physician or other caregiver must take responsibility for appropriately performing, interpreting, and acting upon SMBG information.[31] The literature of clinical trials of SMBG in type 2 diabetes contains no systematic detailed description of exactly what these responsibilities were in each trial and whether they were carried out by the patients and caregivers. It is therefore very difficult to be certain exactly which interventions in response to SMBG have been tested and how faithfully they have been carried out. This deficiency applies to the recent two trials reported in BMJ, which are commented upon in this article, and it also applies to every randomized controlled trial of SMBG in type 2 diabetes that I have read. In order to assess the benefit or lack of benefit of SMBG, such activities that are part of each intervention must be clearly stated and subject compliance with these actions must be determined. **Table 1** lists a set of responsibilities of the patient in order to appropriately perform, interpret, and act upon SMBG information. **Table 2** lists a set of responsibilities of the physician or other caregiver in order to appropriately interpret and act upon SMBG information. I propose that these types of lists be utilized in the design of future trials of SMBG.

Table 1.
Responsibilities of the Patient in Order to Appropriately Perform, Interpret, and Act upon SMBG Information

1. Accurately perform SMBG according to a prescribed regimen
2. Recognize confounding factors that can degrade monitor performance
3. Understand appropriate timing and testing sites for monitoring
4. Interpret SMBG results relative to predetermined target levels
5. See a connection between out-of-range results and lifestyle (e.g., eating, exercise, stress) or medication dosing
6. Possess the knowledge to make adjustments in therapy
7. Act consistently upon an action plan for responding to deviant glucose levels
8. Accurately record SMBG test results on paper or electronically
9. For electronic recording, accurately program the date, time, and events into the monitor
10. Rely more on SMBG readings than subjective sensations of well-being

Table 2.
Responsibilities of the Physician or Other Caregiver in Order to Appropriately Interpret and Act upon SMBG Information

1. Interpret SMBG results relative to appropriate target levels
2. Possess the knowledge to make adjustments in therapy
3. Evaluate SMBG readings in a nonjudgmental manner
4. Respond to SMBG readings by adjusting ongoing lifestyle and medication regimens and responding to deviant glucose levels
5. Create a simple action plan for the patient
6. Address both fasting and postprandial glucose levels
7. Act to prevent hypoglycemia
8. Select appropriate end points for determining control of diabetes

Design of Future Clinical Trials of SMBG in Type 2 Diabetes

Several serious flaws in the protocol and statistical analyses have degraded the significance of the DiGem[1,3] and ESMON[2] studies. To enhance the quality of future clinical trials of SMBG in type 2 diabetes and avoid the flaws of these recently reported studies, it will be important to conduct well designed studies which apply SMBG properly as well as to measure outcomes using proper statistics. I propose that in trials of this intervention, the following five elements of the protocol and statistical analysis should be included (**Table 3**). First, information from SMBG must be translated into specific actions and therapy including modifications of diet, exercise, stress exposure, and medication dosages. Second, subject compliance with the protocol must be ascertained and reported. Third, if all intervention subjects (consisting of study completers and dropouts) undergo an Intention To Treat analysis, then a Per Protocol analysis must also be presented of just the intervention study completers. Fourth, if multiple primary or secondary endpoints are being observed to test multiple hypotheses, then the investigators must establish appropriate probability thresholds. Fifth, if differences in outcomes between intervention and control cohorts at the end of a study are reported, then baseline measurements for each group must also be reported. Moreover, any future literature review of SMBG in type 2 diabetes must account for the quality of the protocol methods and statistical presentations to avoid assigning undue significance to poorly designed studies. Such a literature review, classified according to the quality of evidence, is currently needed to better understand the role of SMBG in type 2 diabetes. Without proper protocol design and statistical methods, it is easy to "cherry pick" studies from the literature and select only the most self-serving conclusions or evidence, which is what many of the stakeholders in this technology are now doing.

Table 3.
Recommendations for Required Protocol and Statistical Elements of Future Clinical Trials of SMBG in Type 2 Diabetes

1. SMBG information must be translated into specific therapeutic modifications of diet, exercise, stress exposure and medication dosages
2. Subject compliance must be ascertained and reported
3. Intention To Treat analyses must be accompanied by Per Protocol analyses
4. Multiple hypothesis testing must utilize appropriate probability thresholds
5. Differences in outcomes between cohorts must be accompanied by baseline data

Conclusions

Based on the aforementioned two recently published articles in last month's BMJ, one could conclude that self-monitoring of blood glucose does not improve outcomes in type 2 diabetes—when this practice is not applied properly. It appears that SMBG does not improve control in type 2 diabetes if this activity is carried out with inadequate frequency, inadequate training, and insufficiently clear directions for responding to data in the form of specific recommended actions for modifying food intake, exercise performance, and stress exposure, as well as medication dosages. Glucose goals—not just Hemoglobin A1c goals—need to be established for patients with type 2 diabetes,[32] and glucose data obtained by these patients need to be shared and discussed with their treating physicians. It is now time to investigate whether this practice is beneficial when applied properly with appropriate and effective utilization of SMBG. The results of future clinical trials of efficacy and economic benefit may well turn out to be very different than those from recently reported studies.

Based on meta-analysis studies of the practice of SMBG to date, the majority of RCTs of this practice in type 2 diabetes have demonstrated a small benefit. Some trials have not demonstrated a benefit. In order to make sense of the literature that contains multiple types of protocols, statistical analyses, and interventions for SMBG in type 2 diabetes, it would be very advantageous if agreement could be reached as to what constitutes an appropriate clinical trial of this intervention. Well-designed randomized controlled trials

are now needed to evaluate the effect of SMBG in type 2 diabetes. Now is the time for experts in clinical diabetes, statistics, and clinical trial design to come together to determine and define appropriate end points that should be measured in these types of studies. It is also time to reach a consensus as to what features of appropriate protocols are needed for testing the outcomes of SMBG in type 2 diabetes. These recommendations can be developed through a consensus process that will identify and endorse appropriate metrics and treatment algorithms, followed by a set of clinical trials to properly test the merits of SMBG in type 2 diabetes. Such experimentally derived performance information will be useful for allocating resources toward care of this patient population.

Disclosure:

Dr. Klonoff is a consultant for C8 MediSensors, InsuLine Medical, and Medingo.

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