SEE DAVIDSON (P. 1531)

Point: Self-Monitoring of Blood Glucose in Type 2 Diabetic Patients not Receiving Insulin

The sanguine approach

Self-monitoring of blood glucose (SMBG), one of the important technical advances in the management of diabetes in the last few decades (1,2), has provided patients and providers remarkable insights into day-to-day excursions in blood glucose concentrations obtained in natural settings. The best evidence for its acceptance by both patients and providers is the multi–billion dollar industry that has arisen to provide devices and strips that are continually improving in both sophistication and simplicity of use. Despite a documented increase in use of SMBG (3) in response to expert opinion and exhortations of the American Diabetes Association (4), no appreciable corresponding cost reduction in supplies has occurred, leading to an expanding economic burden on health care systems worldwide. Therefore, it is not surprising that the need for routine SMBG in diabetes management is increasingly being questioned (5–8).

Although SMBG as a tool for achieving glycemic targets is considered to be effective in type 1 diabetes (9,10) and type 2 patients on insulin (11,12), questions have been raised about the need for its use (5–8) in the majority of potential users, non–insulin-treated type 2 diabetic (NIT-DM) patients. Those challenging the use of SMBG in NIT-DM patients generally cite two major problems in support of their position: the enormous cost of supplies and the lack of evidence for effectiveness in this group. In many well-run health care systems, this combination is usually sufficient to put an end to a medical practice. In this commentary we will address these two claims and point out why providing SMBG in NIT-DM patients is still necessary.

The cost of SMBG is unarguably a major expense in health care delivery (8). In the U.S. alone, SMBG leads to an annual expense of hundreds of millions of dollars in NIT-DM patients. The expense can only be justified if current use of SMBG will provide cost savings in the future. Numerous estimates indicate that sustained improvement in diabetes control is an incontrovertible cost saver by its effect to prevent or delay the development of diabetes complications (13,14). If SMBG assists in glycemic control in NIT-DM patients, as well as insulin-treated patients, then this large financial outlay can be justified. Thus the second issue, the evidence for its usefulness in this group of patients, comes into critical focus.

A new review and meta-analysis in this issue of *Diabetes Care* helps us to apply this focus. Welschen et al. (15) summarized the literature and evaluated the use of SMBG in NIT-DM patients. The authors arrive at some important conclusions. The first is that few studies meet optimal standards for data-driven evidence (8,11,16–21), using a modified Maastricht-Amsterdam score list for evaluation of randomized clinical trials. They highlight six randomized clinical trials using this methodology, of which only two had statistically significant results. Meta-analysis of five of the studies in which comparisons with appropriate control groups were included demonstrated a statistically significant greater reduction in A1C of 0.39% in NIT-DM patients who used SMBG. Unfortunately, their enthusiasm for the positive results in the meta-analysis for the effects of SMBG was tempered by their assessment that many of the studies were of relatively poor quality. Thus, a closer look at the data is warranted.

At the outset, it is difficult not to ask the question: How do we find ourselves, almost 3 decades after the introduction of SMBG, with insufficient evidence for a clear recommendation that affects the largest group of patients with diabetes? Space precludes discussion of this query in any depth, so we will rephrase the question for the sake of simplicity: If SMBG is useful in patients with NIT-DM, why is that so difficult to demonstrate? The answers reside primarily in two considerations: *1*) SMBG alone provides documentation, not necessarily change, and 2) the effect of SMBG is variable and apparently relatively small (compared with the effect of medications to improve A1C). A third possibility is that SMBG is ineffective, but as we shall show, the data to date are insufficient to support that hypothesis. We will now look at the six randomized clinical trials studies identified by Welschen et al. in light of the first two considerations, illustrate why the third is likely not viable, and evaluate the data for possible effect on policy.

SMBG alone provides documentation, not necessarily change

SMBG has value as an arm in a feedback loop: if SMBG is simply an exercise in collecting blood glucose information, it cannot reliably alter A1C levels. Meaningful responses are necessary to generate a feedback effect. This requires that either the patient and/or a provider evaluate SMBG values and act on data to achieve a desired change in homeostasis. If a patient is the respondent, education is necessary and, if combined with empowerment to make change, may be sufficient to enable appropriate alteration of diet, exercise, or medication. This logic requires providers to be active participants in examining SMBG records and providing feedback in the form of pharmacotherapy or lifestyle recommendations (4). In our experience, an optimal method to provide consistent and continuing feedback is diabetes case management, where provider-patient interactions are based on the principle of data-driven feedback (22). Thus, when clear guidelines for modifying caloric intake and activity level were given to

NIT-DM patients based on data from daily SMBG, lower A1C values were achieved (17,20). However, if feedback is important, why did some studies that used it not show effectiveness in significantly lowering A1C? The answer lies in the magnitude and variability of the effect.

Magnitude of effect of SMBG

Expectations for potential effectiveness of an intervention and the inherent variability in the outcome measure determine the number of subjects that should be studied in a clinical trial and therefore are critical design elements. Study size, provided by power analysis, determines the sensitivity, i.e., the statistical power to detect an intervention effect of a specified magnitude. Of the six selected studies (8,16–20), four provided a power analysis; among these, only two (19,20) had sufficient subjects to detect a 0.75% SMBG effect on A1C with >80% power and also obtained outcome variability within their projections. Importantly, these two studies were the only reports to show a positive and clinically significant effect of SMBG (19,20). Another study was designed with sufficient subjects to detect a similar SMBG effect with 90% power (16), but subject outcome heterogeneity was greater than projected and this study actually had <60% power. The fourth powered study compared SMBG with a use of a urine test only (18). The two studies that lacked reported power analyses were the smallest and had <60% power to detect 0.75% SMBG effects, based on the heterogeneity of their populations. As a result, one of the smaller studies (17) showed the largest mean A1C reduction of this group of randomized clinical trials (0.69%) but did not achieve significance. Another consequence of an insufficiently powered study is lack of precision, and thus confidence for concluding that an intervention is ineffective. The sixth study illustrates this point (8). Estimated SMBG effect was between 0.6% (deleterious effect) and −1.1% (beneficial) and thus did not show lack of effect but rather a 95% certainty that the SMBG effect does not exceed a reduction of 1.1% in A1C.

Variability in response to SMBG

In evaluating the role of SMBG, it is particularly important at the design stage to specify the characteristics of the target population and the degree of outcome heterogeneity that might be expected in the groups chosen for study. Multiple factors impact upon an outcome such as A1C. As an example, baseline A1C values may reflect important clinical situations that impact design, particularly when disproportionately high or low. Patients with A1C close to normal may not show much change with either SMBG or usual care, and inclusion of a large number of such patients in studies may minimize differences between groups (23). Very poor glycemic control may also be associated with little benefit of SMBG (18). In type 2 diabetic patients with high A1C on maximal dose and number of oral agents, insulin therapy may be the only solution to improve glycemic control and SMBG would be unlikely to influence the outcome. The number of oral agents per patient was not clearly described in many of the six studies, or if reported, subjects on such a regimen were not always equally divided between intervention and control groups. Finally, the actual number of SMBG measurements performed in the course of the study or their relationship to meals is not always reported; understanding effectiveness requires that compliance with SMBG frequency and timing also be documented and reported.

Where do we go from here?

Thus, we agree with Welschen et al. that a large-scale, definitive study or studies be performed to bring closure to the debate on this very important issue. This should take the form of randomized clinical trial design and such studies should include a consensus on *1*) precisely what "SMBG intervention" entails (this was drastically different among the six studies and could require several arms in a new randomized clinical trial), *2*) inclusion/exclusion criteria such as baseline A1C and oral agent use, and *3*) the minimal magnitude of intervention improvement in A1C that would warrant a policy recommending its use. Consider that a 0.5% A1C reduction is associated with an estimated 21% decrease in microvascular complications (24). Regardless of decisions on these three design issues, study size is critical. As pointed out above, of the randomized clinical trials, only two that were adequately powered demonstrated a clinically and statistically significant effect of SMBG (19,20). To determine study size, four of the studies discussed in Welschen et al. (8,16,19,20) provide useful information on subject heterogeneity. In these studies, initial mean A1C values ranged from 8.2 to 9.0% and SDs of A1C changes in intention-to-treat analyses ranged from 1.3 to 2.1%. Based on these studies, a randomized clinical trial with 80% power to detect an intervention effect of 0.5% in mean A1C change would require 110–280 subjects per intervention group, depending on the degree of heterogeneity of the population chosen. This is clearly larger than almost all the studies performed thus far.

The discussion afforded by this forum is an invaluable opportunity to provoke practical responses to resolve the issues raised. Most importantly, the hope is that the discussion will accelerate the development of studies that could provide a degree of finality to this issue that has so many financial and patient care consequences. But the format of this discussion (point-counterpoint) should not imply that these issues are unidimensional in nature, with an all-or-none response to the question of SMBG in NIT-DM patients. A fund or don't fund approach can mislead us in the adoption of solutions. Studies should address factors that influence cost, including the possibility that subgroups of patients may not need routine SMBG, the optimal frequency of measurements for different clinical situations, and optimal timing of SMBG measurements in the course of a day.

Our focus on the randomized clinical trials chosen by Welschen et al. reveals that study size can explain why only a minority of reports demonstrates a significant effect of SMBG in NIT-DM patients and also why more negative studies are reported. Overall, their meta-analysis shows a positive effect (15), supporting the view that SMBG is likely to be helpful in NIT-DM patients. We and they acknowledge the need for more studies so as to provide a stronger basis to support or refute their current findings. At any rate, the result of their meta-analysis suggests that it is certainly premature to draw conclusions that drive the debate toward limiting third-party payments for SMBG supplies. Limiting access by requiring patients to pay for strips has been shown to diminish use of SMBG and lead to poor glucose control in patients with NIT-DM (10). Thus, the point is that large as well as carefully designed studies need to be done so that there is unequivocal evidence that will help decide the role of SMBG in NIT-DM patients either way.

The recent trend in publicly sponsored, industry-funded, multicenter (possibly multinational) trials that accomplish large-scale studies of diverse patient populations, designed and performed by a group of experts who compete to participate in such a trial, may be the optimal way to get the job done.

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