Journal of Diabetes Science and Technology
Volume 2, Issue 4, July 2008
© Diabetes Technology Society

MEETING PROCEEDINGS

Measuring Glucose Concentrations: Daily Practice, Current and Future Developments

Lutz Heinemann, Ph.D.

Abstract

Self-monitoring of blood glucose (SMBG) by means of modern glucose meters is of relevance for all patients with diabetes. It not only provides important information about the effect of therapeutic interventions on metabolic control, but about the effect of exercise and meals as well. Therefore, it is an essential part of diabetes therapy. However, it has received little interest from academia in the last 10 years. This is in sharp contrast to the massive increase in SMBG use in the last decades and its economic impact on health care systems. Many physicians and patients believe that SMBG and the measurement technologies behind it are a no-brainer nowadays, i.e., that the measurement provides reliable results in practically all cases. In reality, it appears as if patients have only mediocre knowledge about the appropriate handling of the procedure and subsequent therapeutic action. Also, evaluation of the measurement quality of blood glucose meters is not studied adequately in many cases. Such studies should also take into account handling by the patients themselves under daily life conditions. Unfortunately, most of such studies are initiated and sponsored by the manufacturers of blood glucose meters/test strips, and not by an independent institution. In view of the costs and risks combined with SMBG, we should consider that all patients participate in a course that ends with a little examination and provides them with a "driver's license" for this diagnostic measure.

J Diabetes Sci Technol 2008;2(4):710-717

Self-monitoring of Blood Glucose: Cornerstone of Diabetes Therapy

Patients with diabetes—especially those on insulin therapy—have to measure their current blood glucose (BG) level several times per day to be able to adjust their insulin dose and/or to avoid acute metabolic deteriorations. In addition, self-monitoring of blood glucose (SMBG) by means of easy to use and reliable glucose meters provides patients with important information about the effects of exercise, meals, and therapeutic interventions on their metabolic control. In that sense, SMBG is of relevance also for patients not treated with antidiabetic drugs. For them, SMBG can act as a compass showing them the effect of meals and lifestyle interventions on their acute metabolic status.

Author Affiliation: Profil Institute for Metabolic Research, Neuss, Germany

Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitoring, (RCT) randomized controlled trial, (SMBG) self-monitoring of blood glucose

Keywords: self-monitoring of blood glucose, insulin therapy

Corresponding Author: Prof. Dr. rer. nat. Lutz Heinemann, Profil Institut für Stoffwechselforschung, GmbH, Hellersbergstr. 9, D-41460 Neuss, Germany; email address *lutz.heinemann@profil-research.de*

History of SMBG

We have come a long way from BG measurement in the lab—originally requiring huge amounts of blood, time, and expensive materials—toward modern technologies for SMBG. SMBG by means of test strips was introduced in the 1960s. In these early years, test strips were mainly used for screening purposes or by health care professionals for rapid BG measurements (point of care). It was not before the 1970s that it was more often used in clinical practice and also by the patients themselves for taking immediate action, e.g., adapting the preprandial insulin dosage. Many diabetologists were very critical at this time about the use of a laboratory/diagnostic measurement by the patients themselves! At the same time, the first BG meter came to the market. The first devices were bulky, cumbersome to handle, and not very precise. In these early years, many papers were published about the technical aspects, measurement quality, etc., of the different BG meters.

Blood Glucose Meters

Since the 1970s, multiple generations of BG meters have been developed, and nowadays we have high-tech products available that require minute amounts of blood, provide results in seconds, and store hundreds of values. There are a plethora of glucose meters available, with new ones showing up every other month. The exact number is difficult to evaluate as it varies from market to market. In the 2008 issue of the Diabetes Forecast Resource Guide, which has a clear focus on the US market, 34 different BG meters from 14 different companies are listed.[1] According to this source, 14 new BG meters have come into the market (no clear definition of "new" was provided—most probably refers to the last year). Also, glucose monitors are now on the market that combine BG measurement with blood pressure measurement. In addition, 64 different lancing devices (discussed later) are listed.

It is quite difficult to develop an overview of the different meters and the differences between them. The 34 meters listed in the Resource Guide had an average test time (time from applying the blood drop and showing the measurement result) of 9.8 s (range 4–45 s). With 18 meters, the statement was that they were "without" coding (discussed later). All except two provided a control solution, however, only four provided a high/low solution. The required blood volume, weight, and size of the different meters was not very different. No statement could be made about the ease of handling and how much training was required for adequate handling. Quite interestingly, practically no statements were made about the quality of measurement! However, the marketing activities of the manufacturers of these diagnostic devices try to make a lot of noise about relatively small differences in certain parameters of the meters or their design ("feature war"). Unfortunately, the number of respective studies proving the relevance of such differences for the treatment of patients is small (to phrase it carefully). In view of all the marketing efforts of the manufacturers, mainly suggesting in their advertisement that everything is easy with their individual meter and no issues do exist, one wonders about the costs for such efforts (e.g., spots on TV!) in relation to the number of scientific activities, including publications.

Publications about SMBG

The number of publications per year listed in PubMed in the 20 years since 1998 shows an increase in the last years (**Figure 1**). It might very well be that respective articles published in journals are not indexed in PubMed or that not all respective journals were covered by PubMed in the 1980s. However, with an average number of 10.8 studies published per year between 1998 and 2008, the number of published studies appears to be relatively small. Clearly, the other question that cannot be answered by such an analysis is that of the scientific quality of these publications.

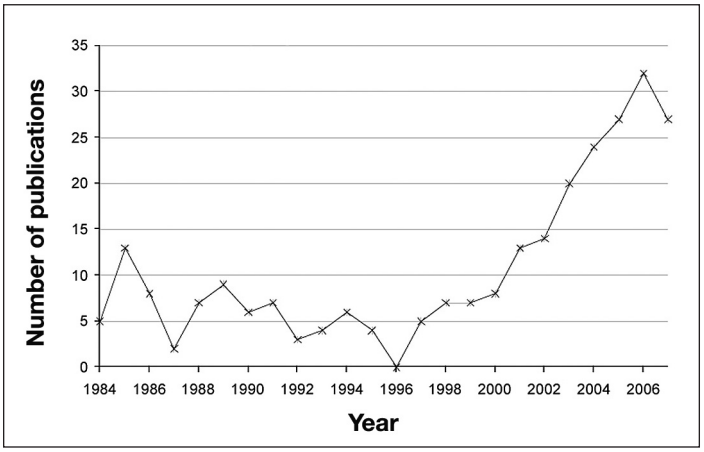

Figure 1. Number of publications per year listed in PubMed (search limits: "SMBG" and different years (1998–2008)).

There are practically no sessions at international or national diabetes meetings devoted to SMBG, except when it comes to the costs. This very limited interest in SMBG is also highlighted by the fact that at the 2nd European Diabetes Technology and Transplantation Meeting meeting in 2008 not a single poster or oral

presentation (except this lecture) was devoted to SMBG! Another proof of the limited interest in this topic is the fact that, for example, in Germany there is no academic site that has a clear focus or in-depth knowledge on SMBG. Studies are predominately performed or initiated by manufacturers of BG meters. Morever, the focus of such studies is on the analytical performance of their devices and not on all the other aspects of SMBG (discussed later). Nevertheless, a group of academic experts recently formed the International SMBG Working Group.[2] This group of diabetologists and scientists will work to together to improve the quality of clinical trials in this area of research. In other words, the main focus is more on the clinical aspects and cost issues of SMBG than on the technical aspects.

SMBG: Market in General

In contrast to the relatively small number of publications and studies about SMBG, the SMBG market is very large with a worldwide turnover of about 6.5 billion dollars in 2006. In addition, the market growth per year is high (in comparison to many other markets) with a rate of 6.5% in 2006. However, it was as high as 10–20% during a number of preceding years. Clearly, this market is by far driven by the massive increase in the number of patients with type 2 diabetes. The four biggest players, having >90% of the market, are Roche Diagnostics, Johnson & Johnson (LifeScan, Inc.), Bayer Diagnostics, and Abbott Diabetes Care. There is a fierce battle for market share in the different countries, driven by new meters, marketing campaigns, and so on. Each and every journal for diabetes has many advertisements for BG meters. In addition, manufacturers are addressing the end users (i.e., patients) directly with intensive marketing campaigns. The promise conveyed in the advertisements for patients is: no worries; everything is easy. It is tempting to speculate what the costs for such marketing efforts are in relation to the costs for scientific studies about SMBG.

SMBG: Current Beliefs

- Today, SMBG is a diagnostic method well performed by the patients.
- Performance of the measurement is relatively simple and the measurement results are highly reliable.
- SMBG is a commodity!
- Continuous glucose monitoring (CGM) systems will take over the SMBG market within the next few years anyway.

The author of this article strongly disagrees with these beliefs! What follows is a discussion of these aspects.

Reality of SMBG

A patient-orientated survey performed in Germany showed that, in reality, patients have mediocre knowledge about the appropriate use and performance of SMBG, and its postanalytical applications.[3] For this survey, 2000 people with diabetes were randomly chosen as a representative sample of patients performing SMBG. The questionnaire was sent out in the middle of 2006 and approximately 1000 people responded. The survey was performed by the Marktforschungsinstitut Ipsos, Hamburg, and sponsored by Roche Diagnostics, Mannheim, Germany. The number of males and females (462 (48%) vs 504 (52%), respectively) was comparable, the age distribution was typical for patients with diabetes (<40 years = 89 (9%), 41–60 years = 290 (30%), >60 years = 587 (61%)), and approximately one third of the patients had type 1 diabetes (345 (36%)) and two thirds had type 2 (621 (64%)).

As the site for the collection of a capillary blood sample, 51% used the lateral fingertip, 31% the center of the fingertip, 12% any one site of the finger, and 5% other parts of the body. Only 10% used the lancet intended for finger pricking once; 19% used it 2–4 times, 22% 5–7 times, 25% 8–10 times, and 21% 11 times or more. An impressive number, 52% of the patients, stated that they did not perform SMBG from time to time for different reasons (**Table 1**). Also, a number of patients were uncertain about the outcome of the SMBG (**Table 2**).

Table 1.
Reasons for Not Performing SMBG

Forgot	50%
Too complicated when abroad	41%
Awkward in public	37%
Utensils forgotten	36%
Location not appropriate	35%
Did not feel like it	35%
Preparation too time-consuming	13%
Not enough time	11%
Unpleasant	10%

Approximately two thirds of the patients had participated in a diabetes training session. This was more than 2 years ago in 44% of the cases. In 43%, it was between 0.5 and 2 years. When it comes to the interesting question how many

of the patients drew consequences from the analysis of the measured BG values, the responses were disappointing:

Yes, I analyze my blood glucose profile on a regular basis myself 38%

Yes, my treating physician analyzes my blood glucose profile regularly 67%

No, I just document the glucose values without closer notice 11%

The subsequent question about which consequences are drawn highlighted that in many cases no action was undertaken by the patients or the treating physician:

Yes, documentation of the values inspired me to a more active/healthy lifestyle 52%

Yes, my treating physician uses the data for optimization of my therapy 43%

No, neither my physician nor myself draw consequences from the data analysis 2%

From this (limited) look into the reality of SMBG use, the following conclusions can be made: In contrast to the beliefs stated earlier, evaluation of SMBG use documents the limited knowledge of and the many errors made by diabetes patients. This is an aspect that is widely ignored. Counteracting such information deficits requires additional efforts in the training of people with diabetes (discussed later). Such training sessions would probably improve metabolic control to a greater extent than any improvement in technology could. From my point of view, we need more of such studies describing the reality of SMBG usage; some of the shortcomings of this survey can be avoided in subsequent surveys.

Table 2.
Reasons for Uncertainty with SMBG

Sometimes I feel uncertain because I'm not sure…	
About the precision of the values measured	30%
If I measured at the appropriate time	15%
If enough blood was on the test strip	14%
If I did everything right during the measurement	7%
What to do with the measured value, i.e., what are the consequences	6%
If the test strips are still good/valid	5%
If external effects, like scratches on the test strip, have an impact on the measurement result	5%
If I store my test strips adequately	4%

Ignorance When It Comes to Lancing

It is finger pricking that makes SMBG an annoying procedure; the relative pain is greater than that of the insulin injection. Beside costs, this is the major reason why patients tend not to measure their BG frequently enough. The very small number of publications about lancets and modern lancing devices is fascinating. Again, this appears to be an aspect of SMBG that is highly relevant for patients but is ignored by academic research. One of the reasons is that the market for lancets is relatively small and has low margins for manufacturers. However, inside these respective companies, considerable knowledge has been accumulated regarding significant factors that reduce the pain of finger pricking:

- Optimal shape of the needle tip
- Polish of the needle
- Depths of the insertion
- Guidance of the needle while penetrating the skin to avoid swings of the needle

Novel devices are coming into the market (www.pelikantechnologies.com) that appear to reduce the pain using innovative technology. The hope is that such innovations will have an impact on our attitude toward lancing in general.

Measurement Quality: Requirements and Reality

In most countries, glucose meters should fulfill the requirements stated in the ISO NORM 15197, 2004(E). Thus, they should have an accuracy of ±20% in comparison to the reference method in the euglycemic and hyperglycemic range in 95% of the cases. This means that the measurement results can differ from the true value of 100 mg/dl, in the range from 80 to 120 mg/dl. For values in the hypoglycemic range (defined as <75 mg/dl) the accuracy should be <±15 mg/dl.

In reality, not all BG meters fulfill these requirements! At least in Europe, some meters are available that have a CE mark but do not comply with the ISO NORM. Thus, the quality of the measurement is questionable, especially when it comes to some "cheap" BG meters. The same holds true for test strips produced by some companies and sold at a significantly lower price, for use with common BG meters without any authorization by the original manufacturer of the meter. This can result in unexpected and clinically relevant SMBG errors.

Evaluation of the Measurement Quality

The usual procedure for the evaluation of the measurement performance of a given BG meter is to collect capillary blood samples from a given number of patients with diabetes and to measure the glucose concentration in these samples by the meter and at the same time with a so-called reference method. One important disadvantage of this approach is that the majority of the measurement results will fall in the BG range between 80 to 200 mg/dl. The number of paired values in the hypo- and the hyperglycemic range most often is relatively small. Due to the fact that an accurate measurement, especially in the hypoglycemic range, is of pivotal importance for patients and their therapeutic decisions, this is difficult to accept. In other words, for most of the BG meters on the market, we have only limited knowledge about their measurement quality outside the normal range.[4]

By means of the glucose clamp technique, it is possible to keep the blood glucose level of different patients constant at different levels—covering the whole therapeutically relevant range—over longer periods of time. Only the use of such an approach allows a true evaluation of the accuracy and of the precision (!) of measurement at different BG levels.

Another question is which statistical approach is best in describing the quality of the measurement. Unfortunately, we have no standardized approach here as of yet. In principle, for such a method comparison, a graphical presentation like the Bland-Altman plot is ideal. However, many people prefer the Error Grid Analysis due to the fact that this is simply used most often and provides "a number" to describe the measurement quality. Nevertheless, there are also new mathematical approaches available for this purpose.

Clinical Measurement Quality of SMBG in the Patient's Hands

The evaluation of the technical/analytical measurement quality of BG meters is most often performed by highly trained technicians. This provides no information about the measurement quality in the patient's hands in daily life. Only a limited number of studies evaluate this question. The interface between patient and the respective glucose meter is not well-studied. In reality, the in-the-hands-of-patients error limits for SMBG might exceed ±20% by far. Also, we have no agreed standard procedures for such evaluation studies. Companies do not regard it as their responsibility to invest in such studies.

SMBG: Much More than Just the BG Measurement

Blood glucose measurement is a complex procedure with many different components. Quite often the focus is too much on the analytical measurement procedure only, ignoring more or less all the other steps involved. However, these can have such a profound effect on the final measurement results in the hands of patients, so it is necessary to look at all the components:

- Storage/shelf life of the test strips/BG meters
- Cleaning of the hands/disinfection (avoidance of contamination)
- Size of blood drop
- Measurement site (fingertip vs alternative measurement sites)
- Lancing device, depth of finger prick

The quality of the BG measurement is also influenced by many technical factors, e.g., the measurement technique of the meter, the batch of test strips, calibration (blood/plasma), maintenance of the meter, and measurement conditions (temperature, humidity, and altitude). Additionally, blood-related factors that can have an impact on the reliability of the measurement results are the hematocrit of the patients, the measurement conditions, and interference by other blood constituents such as aspirin, vitamin C, and other drugs. Again, one has to acknowledge that there are a limited number of related publications with the current generation of SMBG meters investigating the impact of all these factors!

Longterm Measurement Quality

BG meters and test strips must demonstrate defined measurement quality at the point of sale, i.e., immediately after manufacturing only. A critical question is as follows: What is the quality of the measurements during the lifetime of a BG meter, e.g., what is the measurement quality after 6 or 12 months of daily use? We have to keep in mind that meters and test strips in reality are exposed to a challenging environment (to phrase it carefully). So, the clinical quality of SMBG measurements in the hands of patients over longer periods of time is questionable. However, one has to state again that this is a question that is very seldom addressed in appropriately designed clinical studies.

Many manufacturers provide a "control solution" as a quality check. However, most often only one solution

at a normal glucose level is provided and not two or three covering the therapeutically relevant range. The other question is if the quality of the measurement is poor, how do the patients react (if they react at all)? Bad measurement quality can be the result of a "failure" of the BG meter or the test strips used. It is also not clear how many patients use this form of quality check. Why are the patients not forced by their meter to run such an evaluation after every twentieth measurement?

Risks Involved if Quality of Measurement is Not Sufficient

It is worth recognizing what the impact of measurement errors is: false, too high results lead to injection of too high insulin doses. This induces an increase in the risk of hypoglycemic events with potentially dangerous immediate consequences. In contrast, false, too low results lead to injection of too low insulin doses. The consequence of this is insufficient metabolic control with its longterm deleterious effects.

Measurement Quality: Need for an Unbiased View

In summary, the belief that modern BG meters are relatively simple to use and offer highly reliable measurement results is questionable, especially with regard to measurement quality in the patient's hands. From my point of view, it is not sufficient to simply state this; some action should also be taken.

An idea would be to establish a new institution that takes care of all aspects of SMBG, with a focus on BG meters.[5] If such an institute employed a systematic, standardized, and critical approach to all aspects of SMBG, including technical aspects and practical aspects, it could be quite helpful for all interested in SMBG. At first glance, many people will deny the need for such an institution saying "This will be a new costly and bureaucratic monster!" However, on second thought, they will realize that this could bring very many benefits. Clearly, such an institution should have an independent position (i.e., not be a clinical research organization!), and should be financed by performance-of-evaluation contracts. Full transparency of all financial aspects would be necessary, including clear descriptions of all procedures (standard operating procedures). There are activities already underway in some European countries (Norway (http://www.uib.no/isf/noklus/english.htm), Sweden, and the Netherlands). However, it would be clearly advantageous to have an EU wide initiative.[6]

Postanalytical Requirements: Consequences of SMBG Measurements

One has to acknowledge that BG measurement is not the end of the story! SMBG *per se* is a diagnostic procedure that by itself does not change metabolic control; it is not a therapeutic intervention! Just looking at the data and drawing no immediate and adequate therapeutic consequences is of no help. This does not necessarily mean that adaptations in medication have to take place; it can also mean lifestyle changes. In essence, responsible use of SMBG, which is a costly undertaking, requires that it is an essential part of a treatment package. Just to provide test strips and a BG meter to patients is simply not sufficient and most probably will not be accepted anymore in the future by health care payers!

This might sound trivial, however, a recent analysis of all SMBG-related randomized controlled trials (RCTs) performed in patients with type 2 diabetes showed that one of the major reasons why these studies probably do not provide a reliable answer is that these RCTs did not simply compare the same treatment protocol plus/minus SMBG but compared intervention strategies![7] Information on this crucial point is quite condensed in most reports. Only 7 of the 18 study protocols included an algorithm or some guideline teaching patients how to respond to elevated SMBG readings, fasting or postprandial. Thus, most RCTs of SMBG in type 2 diabetes do not provide a sufficiently detailed description of the SMBG-guided disease management strategy used, although it is this intervention strategy that is analyzed in the trial. Clearly, this hampers combination of the different trials in a meta-analysis.

Also, the results of the survey, reported earlier, show the same pattern: only 757 of the 966 patients document their BG values. Of these, 649 of 757 patients analyzed their BG profiles and only 636 patients (two-thirds!) drew therapeutic consequences.[3] One of the major reasons is probably a lack of training.

Driver's License for SMBG

In view of all the aspects mentioned earlier, it becomes clear that patients with diabetes need more training in SMBG and the consequences they should draw. One attempt to overcome this insufficient situation would be that each patient has to participate in a training course similar to "driving school" with an examination at the end. In the practical part, the patient should be taught

in the technique of the BG meter and the appropriate handling. In the theoretical part, the patient should learn about the necessary treatment consequences. Thereby, the patients would not only learn the rules and signs, but in the practical lessons they would also learn how to control the steering wheel and use the pedals to keep their metabolic control on track.[7] If reimbursement of SMBG will only be covered if the patient has such a driver's license, this will most probably increase meaningful usage of SMBG. In turn, this can also mean that a patient then has the right to get SMBG reimbursed by health care payers!

Most probably, a single training session (especially in elderly patients) will not be sufficient in the long run. Patients should participate in a retraining session every other year to make optimal use of SMBG. Clearly, there are many open questions associated with such a license: Who will train? Who will pay? Is this too high an obstacle? However, in view of the costs and potential risks combined with SMBG, a driver's license for SMBG should be a serious consideration!

New Developments and Clinical Research Related to SMBG

If you look into the crystal ball, what do you envision with respect to further developments in SMBG? Most probably, BG meters will not become much smaller, otherwise patients will not be able to handle them anymore. However, clearly integrated systems are the future. That means we will have systems that you have to apply to the skin; the pricking, collection of blood, and the subsequent measurement will be performed automatically. Also, more meters will be able to communicate directly with an insulin pump.

In general, the already-existing diversification of the market will become even more prominent, i.e., cheaper systems will allow an acceptable measurement quality, and more expensive systems will provide better measurement quality and other features. The already huge SMBG market will attract more companies with new meters to come into the market. In view of the costs associated with SMBG, there is a considerable pressure by health care payers toward cheaper meters and strips. However, if the measurements are not reliable, the price is not the whole story.

Continuous Glucose Monitoring: When Will This Technology Take Over the SMBG Market?

A small number of systems for CGM are already on the market, and new ones will come on the market in the near future. Until now, the market share of these systems has been very small. The recent versions of these CGM systems allow relatively reliable glucose monitoring over a number of days. However, all these minimally invasive systems have a number of practical limitations that hamper their usage. This is combined with relatively high costs (several dollars per day). Nevertheless, the prices for electrodes have gone down considerably over the last years and might be in the range of test strips/electrodes for glucose monitoring in the near future.

Reimbursement is still an issue for CGM. Unfortunately, up until 2008 there has been no good evidence that the use of CGM improves metabolic control and/or other parameters (e.g., hypoglycemic events or quality of life) in appropriately designed randomized clinical trials. As long as such studies do not prove unanimously that the use of CGM systems is worth the effort, health care payers will remain skeptical. We should also keep in mind that, at least for the current generation of CGM systems, the patients have to perform SMBG at least once per day to calibrate the measurement of the CGM system. Even if the technique of the CGM system allows longer intervals between recalibrations, they appear to be necessary for safety reasons. In addition, it might very well be that not all patients are keen on carrying around a system attached to their body all the time. Such additional psychological aspects have to be acknowledged.

If a noninvasive CGM system can be developed that allows reliable CGM over prolonged periods of time with low costs, some of the arguments raised against it might become obsolete. Nevertheless, SMBG will most probably remain an attractive market for a number of years to come. It might also very well be that CGM will never take over the whole SMBG market.

Summary and Conclusions

SMBG will most probably remain in its position as an integral part of diabetes therapy, especially for intensified insulin therapy, for a number of years before novel approaches gain greater acceptance. The technology involved has improved a lot in the last decades. However, there is a clear need for a more systematic evaluation of the performance of both the BG meter and the SMBG

procedures in general. A number of open questions exist in this respect. It appears to be absolutely mandatory to train the patients more adequately in the use of SMBG, and most probably also the diabetes team!

In summary, SMBG should gain more attention as a scientific topic in the future. In this respect, the diabetes technology community has the obligation to become active.

Disclosure:

Lutz Heinemann is the chief executive officer of Profil in Neuss, Germany, which performs clinical-experimental and clinical studies for a variety of pharmaceutical companies in Europe and the United States such as Novo Nordisk, Eli Lilly, sanofi aventis, Merck, Roche, Bayer, LifeScan. He is not a shareholder of any of these companies.

References:

1. Diabetes Forecast 2008 Resource Guide.
2. International SMBG Working Group. Self-monitoring of blood glucose in type 2 diabetes: steps toward consensus. Diabetes Care. 2007;30(10):e105.
3. Koschinsky T. Blood glucose self-monitoring report 2006 reveals deficits in knowledge and action. Diabetes Stoffwechsel und Herz. 2007;16(3):185-192.
4. Mahoney JJ, Ellison JM. Assessing glucose monitor performance—a standardized approach. Diabetes Technol Ther. 2007;9(6):545-52.
5. Heinemann L. Measurement quality of blood glucose meters: is there a need for an institution with an unbiased view? J Diabetes Sci Technol. 2007;1(2):178-80.
6. Kristensen GBB, Nerhus K, Thue G, Sandberg S. Standardized evaluation of instruments for self-monitoring of blood glucose by patients and a technologist. Clin Chem. 2004;50(6):1068-71.
7. Kempf K, Neukirchen W, Martin S, Kolb H. Self-monitoring of blood glucose in type 2 diabetes: a new look at published trials. Diabetologia. 2008;51(4):686-8.