Journal of Diabetes Science and Technology
Volume 1, Issue 6, November 2007

COMMENTARY

Noninvasive Glucose Monitoring Systems: Will We Ever Have Such Sensors for Practical Use?

Lutz Heinemann, Ph.D.

Abstract

It is still the dream of patients with diabetes and diabetologists to be able to monitor glucose changes in the human body over prolonged periods of time without hurting the patients, i.e. without having the need to break the skin barrier. This commentary tries to highlight why we should invest more brain power and money in this area of research while also raising the following critical question: Can we be sure that a reliable system for noninvasive glucose monitoring will ever be possible? Finally, I propose establishing an international working group for glucose monitoring. Such an independent group of researchers (which would not focus on noninvasive approaches only) might be very instrumental in bringing a critical and constructive approach in this area of research forward.

J Diabetes Sci Technol 2007;1(6):936-939

A Lot of Money Has Been Spent—For What?

Billions of dollars have been spent on the development of noninvasive (NI) glucose monitoring systems, and (as a consequence of this investment) numerous original manuscripts/reviews have been published on this topic in the past decades. However, no reliable NI system for glucose monitoring is on the market (has Food and Drug Administration approval) and it is not clear when and if ever such a system will become a reality! This is in contrast to the fact that it has been shown in the past over and over again that it is, in principle, possible to monitor glucose changes in the human body by NI systems. However, this was possible only under highly controlled clinical–experimental conditions. When it comes to daily life conditions, none of the attempts (some of them have been under development for more than a decade now!) have been shown to work with a sufficient reliability and precision to be clinically useful.

This is in sharp contrast to the many very optimistic announcements (mainly in the daily press, in the lay press, or on the home page of the respective companies) that all problems have been solved and that the "revolution" in NI glucose monitoring is here! At the end, all such breakthrough news turned out to be unreliable. One has

Author Affiliation: Institute for Metabolic Research, Neuss, Germany

Abbreviations: (NI) noninvasive, (SMBG) self-monitoring blood glucose

Keywords: cost considerations, evidence-based medicine, glucose monitoring, noninvasive

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*

to acknowledge that the many attempts to develop a NI system were not scientific approaches or were at least not communicated in such a manner. Therefore, many diabetologists (and financial analysts) nowadays are very skeptical about NI approaches in general. In other words, they stopped believing that a reliable NI system will ever come to the market, and the willingness of venture capitalists to invest in such approaches seems to be minimal. Too often they have believed the promises made by small companies to invest *x* million dollars and have a product on the market within 5 years. However, I assume this is the typical statement such people hear from anyone seeking funding from them. The big diagnostic companies active in blood glucose self-monitoring are also reluctant to invest in such developments at the present time; all of them have had different NI technologies under development for a while. Yet even with the financial resources and know how with respect to development and regulatory aspects of such companies, none of these attempts have been successful; none of these companies have a NI system in their portfolio. Another reason for the reluctance of big companies to invest heavily in the development of continuous glucose monitoring is that minimally invasive systems have not appeared to be big business until now. When you have a good business running (=test strips), one can assume that it is not easy to convince your management to invest large amounts of money in product developments with an unclear return on investment. For many people interested in glucose monitoring, NI research appears to be a graveyard with many tombstones! This has led to severe "depression" in many people that were hopeful at one point.

At the 2007 American Diabetes Association meeting held in Chicago, during which many presentations were about continuous glucose monitoring, the number of oral presentations, posters, and so on regarding NI systems was fairly small. In the single oral presentation given, it was fairly obvious that the interface of the optical NI sensors studied with patients with diabetes resulted in an insufficient measurement quality in daily life. So, are we more or less at the end of the NI story and should we focus on minimally invasive glucose monitoring systems and see how we can improve them from a technical point of view and also try to optimize their clinical use?

Need for Noninvasive Glucose Monitoring

Let us take a different view on continuous glucose monitoring in general and then rethink our need for NI systems. Currently, there are a number of minimally invasive systems on the market (others will come in the near future) that allow us to monitor glucose profiles in patients with diabetes for a number of days with a certain measurement quality. I won't discuss issues such as calibration, lag times (=alternate site testing-like phenomenon), and side effects, which all have an impact on the reliability of continuous glucose monitoring, but I would like to focus on the costs of this innovative diagnostic measure. In view of attempts to cut down on the costs of capillary blood glucose measurements by patients with diabetes in many countries (the costs for the necessary test strips can be up to some dollars per day), one wonders how many patients are willing and able to pay for minimally invasive glucose monitoring systems on their own. Will patients pay a certain amount per day out of their pockets to have a more or less reliable monitoring system that "prevents" acute metabolic deteriorations and helps them optimize metabolic control?

In many countries (especially in Europe), patients are used to the fact that health care costs are covered by government/health management funds. Are these agencies willing to pay for minimally invasive glucose monitoring systems? In reality, they ask (have to!) for a good medical/economic reason why they should do so! Here is where evidence-based medicine comes into play. If it can be demonstrated in appropriately designed and performed studies (=randomized controlled trials) that the use of minimally invasive systems helps cover medical needs and reduces costs for the treatment of diabetes-related late complications by improving metabolic control, they might be willing to do so! Unfortunately, one has to acknowledge that the studies performed so far have not been convincing, to say the least! To my understanding, it is critical to teach the patients appropriately to make optimal use of the information provided by the glucose monitoring systems, which is by far more than the amount of information provided by capillary self-testing (=snapshot vs movie). In addition, patients appear to use the systems in a manner that is optimal for them under daily life conditions. This in turn does not necessarily result in an improvement in metabolic control!

Cost of Glucose Monitoring

Having this in mind, let us assume that good and convincing studies will demonstrate such an advantage to the payers so that they will have to accept that continuous glucose monitoring is of relevance and that it is helpful for patients with diabetes. Now the next issue pops up: the number of patients with diabetes is already very high and will most probably increase very rapidly in the next years. Recent estimates of the World Health

Organization show that there will be >300 million patients with diabetes worldwide in the not too distant future. Let us assume that because of medical reasons that, for only 1% (!) of these patients, it makes sense to monitor glucose changes by means of a minimally invasive system and let us also assume that price per day will be $1 (which is well below the current prices of test strips used per day by patients in many countries!). Three million dollars per day multiplied by 365 days means more than $1 billion per year for continuous glucose monitoring in a minority of the patients. This is a simple calculation made by all companies active in this field. This is also the number with which small companies searching for venture capital use to convince the financial analysts to invest in their development. However, are the health care providers willing (and able!) to reimburse these systems with another billion dollars? Until now, most of them have been very skeptical (see earlier discussion). Some progress has been made in the United States lately, indicating that certain medical coverage programs are willing to pay for these systems. However, will they still be willing to reimburse the costs if the number of patients interested in using such a system increases to 10% because it makes diabetes therapy easier and safer? Suddenly we are talking about more than $10 billion per year!

With the currently available minimally invasive sensors, patients (at least officially) have to measure capillary blood glucose each time they want to adjust insulin therapy. Thus, they have to perform blood glucose monitoring and continuous glucose monitoring in parallel! The effect of this is that the costs for continuous glucose monitoring will add to those of self-monitoring blood glucose (SMBG). Also, the pain of capillary measurements is not reduced. In addition, even if the needles of the minimally invasive systems are thin, the insertion of needles for minimally invasive glucose monitoring is painful, with a certain risk of side effects, such as infections. Also, an additional device has to be carried around. A simple shower can be a costly issue if you use such a system and have to withdraw it prior to this event and to replace it with a new one. It might be possible to avoid showering for 2 or 3 days, but definitively not for 7 days!

So, if we believe in continuous glucose monitoring and that it will be of real help for many patients (30%), do we have a chance of offering this to so many patients using minimally invasive systems? I personally do not believe this is possible due to economical reasons. If we, however, had a device that showed actual glucose levels with a sufficient precision and reliability for 365 days per year (=abolishing the need for SMBG!) with a NI measurement, probably at the same costs that SMBG generates right now or considerably lower (50% reduction?), this would help us drastically increase the number of patients that could use such a system without increasing the total costs. In the long run, the costs for glucose monitoring could potentially be reduced to 10% of current costs by such a NI approach. These price reductions have been seen quite often in the last years with computers, mobile phones, and so on. This in turn would allow us to increase the number of patients who could use an NI system day by day without increasing total costs for the health care system!

Reliable Clinical Evaluation

In summary, this is why I believe that we have to continue with our efforts to develop a NI glucose monitoring system. I clearly acknowledge the risk that currently we are not absolutely sure that a practical, usable NI system is physically/technically possible at all. If somebody convinces me that because of limits set up by Mother Nature that it is not possible to develop a NI system for daily life use, I will cease my interest in this area of research. However, I'm not yet at this point. In contrast, I am impressed with all the ingenious ideas that come up every year. So, for the time being, it appears that there is no shortage of good ideas, but I see a huge dilemma with the following two aspects.

1. The quality of the clinical evaluation of new developments is very poor! Each (small) company having a new NI sensor (also those with minimally invasive sensors) shows glucose profiles of a "typical" patient that look beautiful. They will surely present an error grid analysis that indicates that the measurement quality is good or excellent and so on. However, there is no standardized procedure that allows an unbiased evaluation of the performance of such systems. Most probably we need an independent (!) group of academic people (clinicians, scientists, patients) that would set up/design such an evaluation procedure. Let me therefore propose the establishment of an international working group for glucose monitoring. Clearly such a group would not focus on NI systems alone but would cover the whole range of continuous glucose monitoring. Also clear is that such a group needs funding for their activities, which at the same time should have no impact on their work. If one takes the DirecNet group as an example, governmental agencies such as the National Institutes of Health or independent organizations such as the Juvenile Diabetes Research Foundation may be

willing to support such a group or be at least willing to provide some help to start! I also see the need for cooperation of such a group with the industries active in this area. The academic group cannot work with one or a certain group of companies as this would eliminate their position. If the companies would organize such a group that could act as a partner for the academic world, certain restrictions would have to be taken into account to avoid complaints about an "industry trust." The regulations in this direction (for good reasons) are very strict. However, if lawyers or other independent people were members of such a group as well, this should help. If the academic group and the industry group would agree on the need of an independent research institute that evaluates the performance of continuous glucose monitoring systems while sticking to professional standards, this would be of great help in communicating with the health care providers! I find it fascinating that there is no independent academic institute worldwide that is focused on the basics of (continuous) glucose monitoring. I have difficulties in understanding this in view of the economical relevance of diabetes worldwide (see the recent statement of the United Nations about diabetes: http://www.unitefordiabetes.org/assets/files/UN_Resolution.pdf). I do not believe that basic scientific and clinical research (and this is needed for many aspects in this area of research) is something that companies should take care of!

Basic Research Needed

2. I (=we) cannot force venture capitalists to invest heavily into NI research! However, as outlined previously, I see a clear need to have NI sensors practically available. Much of the research necessary to develop such systems is more basic research. One wonders why the number of academic sites doing in-depth basic research in diabetes technology/glucose monitoring is so small. This is in sharp contrast to the economic burden of this disease for our communities. Investment in such a type of research by the government or nonprofit organizations (as done in other areas of diabetes research) would promote technological progress. Another advantage of such a source of funding is that the results would become available for everyone. When companies invest in this type of research, they tend to withhold publication in order to achieve a competitive advantage. Interestingly, much of the basic research is done in "worlds" that diabetologists have practically no communication with, for example, in biophysics and optical research. Unfortunately, the "cross talk" between worlds is suboptimal.

Dear colleagues, the aim of this appeal is to open a critical and public scientific and political discussion about the position of NI research and about the consequences of such thoughts. I strongly believe that a reliable and affordable NI system is needed for our patients in the long run. The following question may help initiate a good discussion: Why is there no NI system available?

- Not enough money was invested (in general or into a specific company)
- "Mistakes" in development (not enough brain power invested and/or not enough progress in technical development)
- Principal physical limitations (and/or physiological limits)

Whatever the true reason turns out to be eventually, we owe it to our patients to continue our efforts.

Funding /Acknowledgment / Disclosures:

This commentary reflects many thoughts and aspects that I have presented in numerous presentations about glucose monitoring over the years. Many of these aspects have also been discussed during scientific advisory board meetings with different companies that I have attended in the last years. For such meetings and oral presentations I have received honoraria. The company Profil Institute for Metabolic Research, of which I am one of two CEOs and part-owner, has performed a number of clinical trials with numerous companies in this area of research over the last 9 years.