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What Are the Next Steps in Continuous Glucose Monitoring?

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Abstract

The development of glucose sensors for continuous glucose monitoring (CGM) is likely still in its early days. A number of novel approaches—along with many attempts to improve current CGM systems—are in development. The next generation of glucose sensors (NGGS) will also enable, for example, reliable glucose measurement in the low glycemic range. NGGS systems represent an important step forward for closed-loop systems. This commentary discusses a number of aspects that are relevant in this context.

Keywords

Glucose sensors, continuous glucose monitoring, diabetes therapy, artificial pancreas, quality of life, hypoglycemia

Continuous glucose monitoring (CGM) as a novel diagnostic technology is still in its infancy. Current CGM systems are still not optimal from a number of perspectives: duration of usability, measurement performance in all clinically relevant glucose ranges, handling, and making full usage of the information provided. A number of new CGM technologies are in development and will certainly play a major role in the market introduction of next generation glucose sensors (NGGS) in the next years. The aim of this commentary is to discuss emerging trends in CGM, with a focus on the usage of NGGS.

Usage of CGM in the Future

CGM does not work as a stand alone system. The amount, that is, the amount of information about the glucose profile that this approach provides clearly requires the subsequent step of combining it in a smart way with insulin administration. There is a range of approaches as to how such a combination could look. In its most simple version, the CGM data are shown only on the display of a handheld device or another medical product device (smartphone, insulin pump, blood glucose meter). One step up from this sees the CGM system and the insulin pump more closely connected. In case the pump receives the CGM data directly it can interpret the CGM data and, for example, stops basal insulin infusions if glucose values decline below a certain threshold (low glucose suspend [LGS] systems). In this case, a predictive model analyzes the glucose profile and reacts when the prediction indicates that low glucose values can be expected within a determined amount of time (eg, 20 minutes) and stops insulin infusions before they take place. To close the loop for this smart system, CGM recordings are interpreted by an algorithm and changes to insulin infusion rates are (also an increase in case of evelated blood glucose values) initiated automatically by the system. In principle, this type of technical approach would mean that glycemia would remain within the euglycemic range under all daily life conditions—which would be the next best thing to the cure of diabetes. It remains to be seen if a fully automated artificial pancreas would also require a glucagon infusion to counteract insulin action. Nevertheless, it might very well be that not all patients can or will use an artificial pancreas (eg, for cost reasons). Therefore, the large group of patients treated with multiple daily injections (MDI) of insulin cannot simply be ignored. The number of clinical trials evaluating the benefit of CGM in this patient group is quite small; In most cases the patients included in clinical trials with CGM use an insulin pump. Even if the insulin therapy with MDI is not as flexible as with an insulin pump, such patients might also benefit from having more detailed information about their glucose profile. In the future, CGM usage will be embedded into the entire diabetes management process including routine diabetes education, analyzing and interpretation of data, as well as personalizing treatment goals in diabetes. Such a system may

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consist of a CGM, an "intelligent" insulin pen and a bolus calculator.

Next Generations of CGM Systems

The progress made in the past decade with the more or less constant development of the glucose sensors has led to CGM systems that are clearly outperforming the first generations. Thus, results obtained in clinical trials with the actual CGM systems are difficult to compare with the older studies in which the first generations were used. Nevertheless, a new generation of so-called next generation glucose sensors is in development and will become available within the next years.[1,2] All manufacturers of CGM systems are working on such sensors. Also, Roche Diagnostics has announced the development of such a NGGS. The question is which level of performance NGGS should fulfill. One definition is that they should have a median absolute relative deviation (MARD) ≤ 10% and a precision absolute relative difference (PARD) of 7%; in the error grid analysis 99% of all data pairs should be in zones A (85%) and B (14%).[3] PARD is a method to compare the results obtained with 2 sensors used simultaneously by the same patient to assess the accuracy of these sensors.

Improvement of the interaction of the sensor itself with the subcutaneous tissue by using appropriate coatings can be a big help when it comes to the duration of successful usage of an individual glucose sensor and good measurement quality.[1] With most current CGM systems the so-called biofouling is associated with a profound reduction in sensor sensitivity toward glucose over time of usage and acts as the major source of unreliability of given CGM systems.

Ideally NGGS would be calibrated directly during the manufacturing process thereby significantly reducing the needs for calibration and recalibration measurements. This would not only ease the handling procedure, it would eliminate 1 important source of user error. However, other sources of error will be introduced and patients have no measure to check whether the measurements of the CGM system are correct or not. It has to be seen in clinical trials how reliable such an approach might work.

All CGM systems require a so called run-in time. Immediately after insertion of the needle the measurement is not reliable. It would be advantageous if this time (which might differ from insertion site to insertion site) could be reduced well below 6 hours. With NGGS the run-in phase can hopefully be reduced to the limit given by the tissue interaction, for example to 2 hours. At this time also the first calibration should be performed.

NGGS should also show no—or significantly reduced—large inaccuracies from sensor to sensor and a massively reduced batch-to-batch variability combined with a comparable day-to-day sensitivity.

Other future benefits of NGGS will be identified through the clinical usage. It may be hypothesized that NGGS will increase the safety, well-being, and quality of life of the patients. They will enable both patients and diabetes teams to make better treatment decisions and may increase the frequency of reaching target levels of glucose control. In light of the clear tendency to personalize treatment goals in diabetes, this may be specifically advantageous for those whose daily life is characterized by frequent changes in food intake and physical activity.

Interferences

The risk of interferences by other electrochemically active substances should be minimized in NGGS. Many patients use substances or products (such as Tylenol in the United States) containing acetaminophen (paracetamol), but thankfully falsely elevated glucose readings have not widely been noted with respect to these substances. Nonetheless, it is of utmost importance that a list of potential interfering drugs be derived, with concentrations listed within, as well as above, the normal range. It is essential that manufacturers test their CGM systems accordingly. This could, in turn, lead to a CGM system without relevant deviations of the measurement results from the true glucose levels caused by interfering substances.

Replacement Claim

The current CGM systems have a market approval as adjunctive devices to self-monitoring of blood glucose (SMBG). Thus each time patients make a therapeutic decision, they need to confirm the glucose value shown by the CGM system with a capillary blood glucose measurement. If NGGS become available, this might allow applying for an approval by the regulatory authorities with a replacement claim. So, the CGM measurements must not be confirmed in all cases by conventional capillary blood glucose measurements before a therapeutic decision can be made by the patients. However, this basically requires that the NGGS provide reliable glucose measurements under all conditions at all times. It remains to be studied if this can become a possible reality. This claim is not only driven by technology per se, the question is to which extent physiology allows it. If a blood vessel is damaged during insertion of the needle of the sensor, local bleeding might induce a local trauma that impairs glucose monitoring performance. Adequately designed clinical trials focused on such aspects are needed.

Performance of Clinical Trials

When NGGS systems will come to the market in the future, will it be necessary for all clinical trials that have been performed thus far with previous generations of CGM systems to be repeated? If NGGS offer significant advantages above existing systems, one would be in favor of repeating the trials because comparing NGGS systems with the old CGM systems would be like comparing apples and oranges. However,

what exactly counts as "significant"? Clinical trials are expensive and time-consuming, and it is important to remember that not every single new feature or improvement, for example, improving MARD by 2%, can justify a new clinical trial. The scientific community (which, in our opinion, includes the manufacturer, sick funds, and regulatory authorities) should discuss the progress made with CGM systems regularly and try to agree on at what point in time new studies are needed or not.

Practical Usage of NGGS

Successful usage of NGGS in clinical usage also requires high-quality teaching and training programs. In other words, an improvement in technology per se does not solve all issues. As with many devices and technologies, the success of CGM usage has to be continuously monitored over time to make sure that this investment has been made wisely.

The patient himself has only little influence on the metabolic effect of administered insulin or antidiabetic drugs. The metabolic effect induced determines the success of the therapy. By contrast—as with any diagnostic intervention—it is the patient who has to react to a given glucose value or alarm triggered by a diagnostic system. So if optimization of diabetes management is the goal (= defined as an acceptable HbA1c value and/or low rate of hypoglycemic events), a patient who is acting adequately depending on the information provided is the most important factor in fulfilling this aim. This also explains why the usability and practicability of technical features, like alarms, are of such importance in attaining the benefit of using CGM systems. All these features must be assessed carefully when focusing on the patient's perspective. This might sound obvious; however, it is sometimes the case that when working with complex medical devices, the patient's perspective is put aside while working toward fulfilling regulatory and liability goals.

Do We Make Optimal Usage of the Continuous Information Provided by CGM Systems?

Clearly each CGM system shows the current glucose concentration, the trend and also glucose profile over time. However, up to now, pattern recognition has not been implemented in CGM systems. Usage of this information will be of help to improve CGM systems performance further. A precise estimation of the rate of change of glucose concentration over time can be used to improve the glucose signal provided by CGM systems. However, this requires a low-noise glucose measurement with a high reliability and a small number of missing values ("dropouts"). In summary, smart usage of all information provided by CGM systems can provide medical benefit. One manufacturer has recently announced a version of his most recent CGM system (DexCom G4AP) that makes use of such a "Smart Sensor Concept."[4] Clearly the algorithms implemented in this CGM system are complex and there is no larger clinical study showing the benefit of approaches offer in CGM usage. Therefore, a clinical study with sufficient study duration (at least 12 months) should be performed in which the same CGM system is used by a considerable number of subjects, in 1 group with and 1 group without the additional information.

Receiver Operated Characteristics

As it is not possible to completely avoid false positive and false negative alarms but at the same time, one has to find a good balance between the 2 risks. Receiver operating characteristic (ROC) curves provide an excellent tool for evaluating the diagnostic sensitivity and specificity of a given CGM system design. The true positive rate on one axis is plotted against the false positive rate on the other axis. For each CGM system, there is a fixed and specific relationship (functional slope) between these 2 parameters. This relationship is fundamentally dictated by the analytical performance of the glucose sensor of the CGM system. The developers of CGM systems have to fine-tune this relationship. They have to define the relationship of true positive to false positive results taking the function as a given. Having defined the rate of true positive results (eg, 80%), the rate of false positive results is given (eg, 40%). Increasing the true positive rate, also will lead to an increase in the false positive rate. On the other hand, decreasing the false positive rate will lead to a decreased true positive rate.

As this functional relationship is a characteristic of the specific CGM system, again the quality with which this CGM system measures glucose is of paramount importance when a good analytical performance is aimed for: CGM systems with a poor performance in the glycemic range <100 mg/dl will induce many more false alarms than systems with a high performance in the low glucose range. There is a need to perform head-to-head comparison studies with a focus on this range and analyze the rates of true and false alarms at the same time. Thus, evaluate the alarm rates when 2 or 3 different CGM systems are applied at the same time in the same subject. Then glucose concentration declines into low values, likely also at different rates of change. It might be worth discussing whether the requirements for avoiding alarms have to be identical under all circumstances; for example, false positives are much more disturbing at night than during the day. It would be helpful, if the manufacturer will publish the NGGS specific ROC curves.

Advantage of a NGGS for Insulin Application

It is of interest to speculate that if the glucose measurement is precise and the prediction of glucose values is reliable, the

system might react overly punctually and induce alarms rapidly—before glucose values actually drop low. This in turn would mean that a LGS system is not needed at all as (if the patient is awake and responsive) the NGGS combined with an insulin pump and the respective algorithms would reduce insulin application (not only the basal infusion but also the bolus application) in due time to avoid a drop in glucose concentration into the critically low range.

It also goes without saying that all versions of closed-loop systems that currently are in development critically depend on the quality of the CGM measurement. One of the major reasons for this is the small therapeutic window of insulin. The dosing has to be precise to prevent hypoglycemia and hyperglycemia. Once insulin is applied the metabolic effect induced by this hormone can't be stopped itself, only administration of glucagon can counteract a decline in glycemia by releasing glucose from the storage compartments. As the patient is not going to double-check each glucose measurement result and changes in insulin administration driven by the closed-loop system, the reliability of the CGM measurement result (especially in the low glycemic range) is crucial for a successful closed-loop system. Stability of measurement in this aspect is also crucial and should be optimized with NGGS, preventing changes in measurement quality over the days of usage.

With a precise glucose measurement other combinations of CGM systems and insulin pumps can also be envisaged, for example, autonomous activation of the insulin pump if glycemia starts to increase into the hyperglycemic range, and so on. Another option for NGGS includes intelligent diabetes management algorithms, for example, smart algorithms that act as bolus calculators that automatically suggest an insulin dose (or repeat the dose / prolong infusion in case of still elevated blood glucose values) for subjects using conventional insulin therapy. Such a system might also provide detailed instructions for the user instead of just showing a glucose concentration (actionable results). By using all the information provided in a continuously recorded glucose profile, the rate of change in glycemia can be calculated and displayed, and pattern recognition over several days or even weeks is possible.

CGM Systems for the Intensive Care Unit (ICU)

Already more than 10 years ago Gret Van den Berghe[5] from Belgium published a study in which drastic benefits were described when in patients who underwent surgery were subject to an aggressive insulin therapeutic scheme to reduce hyperglycemia. The ICU is a world of its own when it comes to the requirements an ideal CGM system should fulfill as very special physiologic conditions and unusual pharmaceuticals can show up, elevating the sensor requirements. These differ from the requirements of patients with diabetes who use a CGM system in daily life, for example, when it comes to the size and handling properties such a system should have. Development of CGM systems for this special application would reduce the workload for nurses who currently monitor glucose levels frequently with conventional capillary or venous measurements. However, the NGGS glucose sensor itself might be the same for both worlds. It would be a major step forward if a reliable glucose sensor became available that enabled CGM of patients under hospital conditions as well as patients with diabetes.

Professional Versus Personal CGM System

It is interesting to speculate on the idea of 1 single CGM system developed for different usages. It might appear that the systems look quite identical from the outside, but there is a software switch that allows for toggling between personal and professional usage. Until now, systems intended for professional use (= usage by physicians and trained medical personal) that were used in retrospective data analysis for, for example, diagnostics purposes by a physician have usually been blinded (= no online data display for the patient). The data recorded are calibrated retrospectively.

A CGM system that is used under professional conditions has to fulfill additional requirements when it comes to cleaning and disinfecting reusable parts versus a system that is used by a single patient only. If a given component of a CGM system is used in different patients, the risk of cross-contamination must be avoided.

Single Port

One important disadvantage of using a CGM system and an insulin pump in parallel is the need to puncture the skin for each of the 2 devices. The insulin infusion catheter should be changed in 2-/3-day intervals (this is the minimum recommendation by the manufacturers); whereas the sensor of the current CGM systems can stay in place 5 to 7 days (again according to the recommendations of the manufacturers).

If it were possible to combine the glucose measurement and the insulin infusion within 1 catheter, this would drastically ease the practical application of AP systems (and similar systems). It has been shown that this approach is feasible in principle;[6-8] however, no product is on the market yet. Nevertheless a number of companies and researchers are working on such systems. The major limitation still being struggled with today is the fact that the duration of wear of the insulin infusion catheter cannot be prolonged significantly due to physiological reasons (interaction between the issue and both, the insulin and the excipients).

Reimbursement if an Additional Medical Benefit Could Be Shown

One of the issues when talking about CGM is that the high dynamic in this area of research and development is ignored

to a given extent. As stated above, more recent CGM systems differ from the first generations in terms of performance just as the first generations of blood glucose (BG) meters differ from the recent ones. In other words, it might very well be that the relatively small improvements seen with the first clinical studies on CGM systems when it comes to metabolic control/frequency of hypoglycemia is at least—in part—due to the relatively poor performance of those first generations of systems. If one would repeat such studies it would be entirely likely that such benefits would be significantly larger with more recent CGM systems. However, reimbursement decisions are made based on an analysis taking all CGM studies into account (see above). According to this way of thinking only recent studies should form the basis of any meta-analysis performed. In turn this also has the consequence that the number of respective studies that can be analyzed is relatively small. Nevertheless, the actual medical benefit of NGGS should be the base for defining the reimbursement level and not the historically based reimbursement for CGM systems of the first generations.

Requirements to a NGGS based CGM system

A reduction in the number of false alarms and an improved measurement quality (as evaluated by the patients themselves by means of capillary BG measurements) might be key to improving patient usage of CGM systems. It is impressive to see that many of the relatively small number of patients using CGM systems do not use them each and every day. The reasons for this "patient inertia" toward CGM usage can be seen in economic aspects (missing reimbursement in many countries), but also in psychological barriers. The usability of CGM systems has improved considerably in recent years (also supported by the Human Factor Initiative of the FDA). Clearly the better a given CGM system works and the more practical, usable features it offers, the more patients will use it in daily life.

It is practical aspects that are of high importance and relevance to patients in daily life such as ease of insertion/low level of pain of when inserting the sensor, frequency of (re) calibration, type of alarms (possibility to switch them off), readability of the remote control display, and so on. If benefits of CGM systems are not clear in daily life, patients do not feel motivated to use them. We should not forget that using a CGM system requires carrying around yet another technical system 24/7. Despite the many benefits of CGM this is clearly 1 of the major disadvantages. It has to be noted that quality of life aspects have not been intensively studied in most of the clinical trials performed to date.

Patients who download their CGM data (which they do not do regularly in daily life) can process and asses these data with the proper software. If they do this together with their treating physician/diabetes team this is the basis for individualized diabetes therapy.

Optimization of the diabetes therapy is done by most patients using CGM all the time, that is, they use the continuously available glucose information in an immediate feedback manner because optimal immediate metabolic control is their aim. This should be clearly separated from the interest of the treating physician/diabetes team; their focus is more on the long-term optimization of metabolic control. Availability of NGGS also allows detects the shortcomings of the current insulin therapy in the sense that any "mistake" becomes visible, for example in the basal rate selected by the patients on an insulin pump.

Clinical Trials Demonstrating the Benefits of NGGS Systems

If the assumption holds true that the benefits of NGGS systems are of clinical relevance, adequately designed clinical studies should be able to demonstrate them. There is a pressing need to perform such studies. What are adequate endpoints for such studies? When it comes to hypoglycemic events, the sample size and study duration might have to be high and long to be able to detect a significant difference between low- and high-quality CGM systems. This will especially hold true if a difference in the occurrence of severe hypoglycemic events is to be demonstrated, as these occur on a relatively seldom basis. It would be much easier to demonstrate this in comparison to conventional insulin therapy; however, it has to be discussed if patients treated with MDI (or insulin pumps) are the right control group. A recent study performed in Australia showed that with a LGS system the number of severe hypoglycemic events could be reduced to zero.[9]

It will be a matter of debate whether such studies should be performed with highly experienced study sites only (which introduces some kind of artificial situation) or with sites that have a certain interest and experience, that are treating the majority of patients with CGM. In view of the larger group of patients treated with MDI (at least in most countries), the medical benefit of next generation CGM systems should be studied in such patients as well.

Summary

In summary, the development of NGGS will provide a number of advantages compared to current CGM systems. These advantages will also increase the clinical acceptance of CGM in daily diabetes management. NGGS may also support preventive strategies for reducing both hypoglycemia and glycemic variability. With exactly which technical approach such NGGS will become available is not clear yet; however, the need for these is obvious. LGS systems as well as closed-loop systems that work reliably under daily life conditions have a desperate need for NGGS. The higher costs that will most likely be associated with the better performance can be justified if an additional medical benefit can be

demonstrated. The current prices for CGM systems are based on old CGM systems that did not provide an additional and proven benefit of this technology in comparison to SMBG. Sufficient reimbursement is needed to allow companies to continue with the development of NGGS and maximize CGM usage within diabetes management—not only in patients with type 1 diabetes but also to some extent in patients with type 2 diabetes. The hope is that we will have a better understanding of the indication for usage of CGM in the future and also that reimbursement will be available without endless discussions for patients with these indications in general and not on a case to case basis. Clear guidelines by the academic associations will be of help in this respect.

Abbreviations

BG, blood glucose; CGM, continuous glucose monitoring; ICU, intensive care unit; LGS, low glucose suspend; MARD, median absolute relative deviation; MDI, multiple daily injections; NGGS, next generation glucose sensors; PARD, precision absolute relative difference;SMBG, self-monitoring of blood glucose.

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