Impact of Real-Time Continuous Glucose Monitoring on Children and Their Families

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Introduction

Real-time continuous glucose monitoring (CGM) devices have great potential to improve glycemic management in children and adolescents with diabetes and other disorders of glucose regulation. These devices can be used as either adjuncts or replacements for traditional meters because they have additional features such as blood sugar alarms and glucose-trend information. These features allow for dynamic adjustments in therapy and, hopefully, will be key components to closed-loop insulin infusion devices.

The DirectNet research group, which was created to study the use of new diabetes management technologies in pediatric and adolescent patient populations, is currently looking for the best methods to translate continuous glucose data into meaningful adjustments in therapy. This presentation examines possible ways to use CGM devices to their maximize benefits. Of note, not all of the devices discussed are Food and Drug Administration (FDA) approved (i.e., some are investigational) and those sensors that are FDA approved are not labeled for use in children.

Challenges to Measuring Impact of CGM

The first challenge in assessing the clinical use of a new technology is determining what aspects should be measured, how it should be measured, and what the actual goals should be. In this case, it is helpful to divide the issues into two basic areas: improvements in diabetes management and improvements in lifestyle.

Diabetes Management

A1c and Glycemic Variability

Two key variables in diabetes management are A1c and glucose variability. Although A1c has long been used as an indicator of glycemic control, a growing body of evidence now points to the importance of glucose variability independent of A1c levels. A re-examination of data from the Diabetes Control and Complications Trial (DCCT) strongly suggests that glycemic variability may be as important as A1c in the development of microvascular complications.[1]

In pediatric patients where hypoglycemia is a greater worry, the challenge is to establish realistic glycemic goals so that incremental gains in lowering A1c levels are not overshadowed by increased risk of hypoglycemia. In our efforts to avoid hypoglycemia through use of CGM, we must consider the accuracy of these devices, particularly in the lower range.
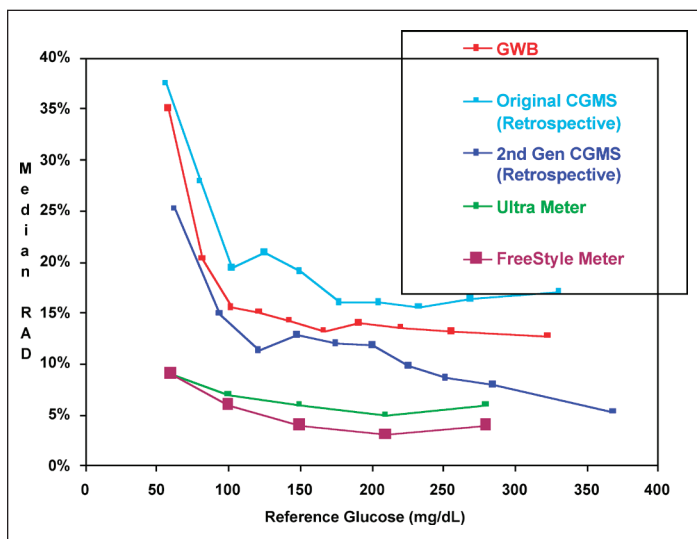

Figure 1 shows the accuracy of various CGM devices and traditional blood glucose meters as compared to a reference glucose reading.[2]

Using median absolute relative difference as the metric for accuracy, the graph clearly shows that the CGM devices (Glucowatch [GWB], original CGMS, 2nd generation CGMS) are significantly less accurate than the Abbott FreeStyle and LifeScan One Touch Ultra blood glucose meters at glucose concentrations less than 100 mg/dL.

Hypoglycemia Detection

An important factor in the design and assessment of CGM technologies is the monitoring device's algorithm for detecting hypoglycemia. Should the goal be to detect all values below a given level, or should we be focusing only on the major hypoglycemic events that may lead to convulsions, coma or death?

Many clinicians are now looking at hypoglycemia in both degree and duration of low glucose; there is an impression that it takes a relatively low glucose level over a fairly long time to cause a serious problem. Given this, it may be advantageous to design CGM algorithms that alert patients only when they are at risk for a major hypoglycemic event because their glucose has been low for a long time. This would decrease the rate of false positives.

Study Design

Study design is another issue that must be addressed when assessing the value and clinical utility of CGM technology. It is important that we conduct studies in both controlled clinical settings as well as free-range clinical settings. Only then can we study in detail how to best use these devices and how they can be designed to work better.

"Free-Range" vs Controlled. Glucose sensor studies take one of two main approaches. One is a laissez-faire or "free-range" approach where participants are given a CGM device without any instruction or even guidance as to how to interpret and act upon the data. The other approach attempts to develop algorithms to help participants (or families) use the data to make therapeutic changes. How information from a study should be interpreted will depend on which of these approaches was followed .

Randomized and Controlled. With the exception of pilot studies, CGM studies should be randomized and controlled. Although it is impossible to mask subjects, it is important that a concurrent control group is used and that subjects in the control group and active group receive similar treatment. Numerous studies have shown that there is a study effect that can independently influence outcomes. In other words, once patients are in a controlled study where clinicians are actually paying attention to them, their control almost always improves.

Study Duration. It is also important that studies have a reasonable duration. There is often a short-term effect from new devices that eventually wears off when people become less interested in "playing" with them; CGM devices are no exception.

Subject Interaction. There is also a need to document patient interaction with the device being studied. Are study participants actually wearing their sensors? Are they interacting with the devices in a meaningful way? If not, it becomes impossible to accurately measure the impact of the device on glycemic control or patient lifestyle. It has been suggested that device companies incorporate some type of memory capability into their systems to track the interaction between patient and device.

Collection of Data-Driven Adverse Events. As different algorithms and approaches to CGM are developed, it will become very important to understand and address how patients respond to to the glucose data and the alarms. Are they over-responding, under-responding, or making appropriate decisions?

Reasonable Expectations. It is important that both patients and researchers have reasonable expectations for the devices being studied. CGM is still in its infancy; it has not yet been perfected. Yet despite its limitations, it is already better than what most patients are currently using. We should not allow perfection to become the enemy of meaningful progress.

Point of Diminishing Returns. One key issue is understanding when using the technology has reached the point of diminishing returns. Numerous studies that looked at A1c improvement have demonstrated that each incremental reduction becomes increasingly more difficult. In other words, it takes significantly less effort and resources to move from 14% to 9% than to move from 7% to 6%.

Cumulative Impact. Another issue that must be considered is the difficulty of parsing out the contributions of individual technologies from the cumulative impact of therapeutic intervention. Bulsara and colleagues showed that a significant rise in the rate of hypoglycemia during the past decade has been accompanied by an equally significant reduction in mean A1c levels. There is no one answer to the question of what caused the reduction in A1c, only a series of possibilities including: improved glucose meters, better use of glucose meters, availability of insulin analogs, better patient training/education, availability of insulin pumps, and more effective dietary approaches, among others.

These numerous possibilities illustrate the difficulty of designing clinical studies to measure the impact of a single intervention. For example, if we assume that 20 factors have resulted in the drop of A1c by 2% and we want to determine whether our device (the 21st factor) can lower A1c by an additional 0.5%, a randomized controlled trial would require approximately 2,000 subjects in order to measure the anticipated 0.5% change. In fact, achieving such a substantial improvement would be extremely difficult due to the effect of diminishing returns, as discussed earlier. Therefore, designing studies that measure frequency of hypoglycemia or duration of euglycemia may be more efficient than those that look for changes in A1c.

Satisfaction and Lifestyle Compliance

Other factors that affect the impact of CGM technology are the satisfaction levels and lifestyle issues that patients have with the glucose sensors. Unfortunately, these factors are usually assessed using questionnaires, which are sometimes not very sensitive to the issues being measured.

One of the best ways to measure how well subjects like a given device is to track how long they continue to use it after the study has finished. Many people will wear a device during the trial period but discontinue wearing it once the trial is over if they find that it is painful, inconvenient, or not worth the hassle.

GlucoWatch Evaluation

For example, the DirectNet group conducted a 6-month randomized trial to measure the effects of the GlucoWatch continuous sensor on blood glucose control, hypoglycemia, and quality of life as compared to standard care.[4] The GlucoWatch sensor provides glucose readings every 10 minutes over a 13-hour period. At the end of six months, there was no difference in blood glucose control between the experimental and control groups, as measured by A1c and mean glucose using the Medtronic retrospective CGMS device. The results also showed that use of the device had no positive or negative psychological impact on the subjects in the experimental group.

These results were puzzling until we reviewed the usage data, which tracked the number of times per week subjects actually used the device. During the first month, 64% of subjects used the device at least twice per week (2.1 ± 0.8). However, by the third month, average use was only 1.6 ± 0.7 times per week, and 7 of the 99 subjects had discontinued use altogether. By the sixth month, average use was 1.5 ± 0.6 times per week, and 26 of the original 99 subjects had discontinued use. In essence, differences in clinical outcome failed to materialize because an increasing number of subjects stopped using the device.

Data gathered from our questionnaires revealed that families felt the information gained from the device was not worth the discomfort and adhesive problems encountered with its use. This study demonstrates the importance of evaluating how people feel about the devices being tested during trials, since patient satisfaction and usage will affect the data collected and can provide guidance on how to improve the device.

FreeStyle Navigator Evaluation

DirectNet recently completed a pilot trial using the FreeStyle Navigator continuous glucose monitoring device. The trial involved 30 children with an average A1c of 7.1%. Subjects wore a "smart" insulin pump and were asked to use the continuous glucose sensor daily. The study used an algorithm-based set of adjustments to guide families regarding changes in insulin infusion rates. This created some challenges because the algorithms had to vary somewhat depending on each subject's insulin regimen, increasing complexity to the study.

As a measure of satisfaction, we looked at device usage over the study period. More than 80% of the subjects wore the device for more than 50 hours per week, while 40-50% of the subjects wore the device for more than 125 hours per week. This high usage rate remained fairly constant over the study period. These data strongly suggest that there was high acceptance for the device. Data from a satisfaction questionnaire supports this conclusion. The high usage rate continued during a 13-week trial extension in which subjects continued to wear the sensor.

Opportunities

Management Issues

Patients and clinicians need guidance from researchers about the best algorithms for using CGM data to improve diabetes management.

Clearly, there is a benefit to being able to view glucose data. In our general clinical population, we have seen that patients who download data from their glucose meters at home tend to improve their control. However, we need a lot more experience in developing and testing regimens that use CGM technology. We also have to be very careful not to raise unreasonable expectations about the technology as it will not result in perfect glucose levels all of the time.

Another challenge is deciding how to use the data. On the one hand, use of real-time continuous data allows patients to make immediate changes in therapy to address prospective acute needs; on the other, use of retrospective data probably has a more profound impact on basal rates. Because both types of data are important, we will need to combine retrospective and prospective algorithms.

Device Issues

The size of the continuous glucose sensor is a key issue for pediatric patients; it is difficult to adequately secure a flat device on these patients because they are small and have a fairly tight curvature. In addition, longer wear time will continue to be an important issue. Because of the longer calibration times required, we need to look at ways of attaching a second device while the first is still monitoring glucose. In such a case there would have to be a way for the two devices to interact with each other. And, of course, we still have issues with tapes and adhesives; they must be made more effective and less irritating.

Alarm Issues

As discussed earlier, one key issue is when to alarm. Are we looking for severe hypoglycemia with a very high risk of a serious outcome, or simply a threshold level that has been crossed? Other alarm issues involve how the device alarms (does it actually wake the patient/parent?) and how to track alarms. It would be valuable to know whether and how patients respond to alarms.

Conclusions

Interest in improving diabetes management is increasing among those who fund research and who care for children with diabetes; a closed loop would help resolve many of the issues discussed in this presentation. The Juvenile Diabetes Research Foundation (JDRF) is strongly advocating research in this area.

Although considerable demand exists for algorithms to address the many insulin regimens currently being used, I suspect that these types of algorithms may be less practical than a closed-loop, sensor-controlled insulin pump. Because sensors are relatively inaccurate in the low range, it makes more sense to use them in the range where they are more accurate: the range where we would like to manage the insulin pump.

Clearly, detection of nocturnal hypoglycemia in the classic sense (not severe hypoglycemia) requires accuracy in the lower range. However, as discussed earlier, perhaps point-in-time accuracy is not what we should be looking for, but rather ways to detect when a hypoglycemic episode is severe and has persisted long enough to cause a serious event.

With insulin pump control, it is possible to provide effective treatment with less accurate glucose readings. There are already a number of studies demonstrating that the loop can be closed. Our challenge will be to optimize the closing of the loop and determine the best algorithms for controlling the pump.

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