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ABOUT CADRE

CADRE (the Council for the Advancement of Diabetes Research and Education) is a nonprofit organization committed to reducing the devastating complications of both type 1 and type 2 diabetes through achievement of tight metabolic control.

To achieve this goal, CADRE provides health care professionals with scientific information and evidence-based educational programs to enable them to manage and empower their patients with diabetes.

Scientific and technological advances continue to expand the treatment options available to clinicians, as well as the management strategies available to patients with diabetes. The following articles approach these advances from very different angles but, taken together, create a complete picture of the components of successful diabetes management: monitoring of glucose fluctuations, appropriate and adequate insulin delivery, and the collection of data to support the use of these methods in broader populations.

Real-time continuous glucose monitoring is discussed, from the evidence supporting its use to physiologic challenges and key patient education messages. Advances in insulin pump therapy continue to build the case for the role of newer technologies in improving the care of patients with diabetes. But first, this issue's editorial raises important questions about the applicability of current diabetes research design and implementation standards to people with diabetes.

▲ Melissa Miles, Executive Director

GUEST EDITORIAL

CANDIDATES FOR NEW DIABETES TECHNOLOGIES: IMPLICATIONS FOR CLINICAL TRIALS AND PRACTICE

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made, and the answer to this question is often to offer the new technology to the most capable, organized, and responsible patients. Narrow inclusion and exclusion criteria are often formalized in clinical trials, such as the Diabetes Control and Complications Trial, with the intent of limiting enrollment to medically appropriate candidates who are thought to be able to fulfill the behavioral demands of trial participation. These patients are often the most educated about emerging technologies and the most vocal about gaining access to them. Offering new technologies to this subset of patients is most defensible for very early demonstrations of the merits of specific

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Recent years have seen a parade of advances in diabetes management. These have included technologically improved glucose meters with continuous glucose monitoring (CGM); better insulin pumps, some of which are augmented with CGM; synthetic human insulin; insulin pens; inhaled insulin; intensified diabetes regimens; carbohydrate counting; correction factors; diabetes video games; automated blood ketone testing; point-of-care A1C testing; and diabetes management software. Certainly, the future will see even more.

With each promising advance, researchers and clinicians face a challenging question: Which patients should be offered the new medical option? I have been involved in clinical trials of new diabetes technologies, read reports of numerous similar trials, and observed many such clinical decisions being

IN THIS ISSUE:

GUEST EDITORIAL

CANDIDATES FOR NEW DIABETES TECHNOLOGIES: IMPLICATIONS FOR CLINICAL TRIALS AND PRACTICE

DIABETES TACTICS

CURRENT ISSUES IN INSULIN PUMP THERAPY

LITERATURE CORNER

CURRENT DEVELOPMENTS IN GLUCOSE SENSORS/MONITORING



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medical advances. As these technologies enter broader clinical dissemination, however, there are valid arguments to be made in favor of more inclusive candidacy criteria.

In this article, I analyze the logical, scientific, and ethical context of this issue, consider its research and clinical ramifications, and offer what I hope is a challenging perspective. In addition, I provide practical ideas about how researchers and clinicians can safely and responsibly offer medical advances to a more diverse cross-section of patients.

Predictive Validity of Restrictive Candidacy Requirements

Is it really possible to accurately predict who will and will not adhere to the requirements of randomized clinical trials? How effectively do restrictive enrollment criteria achieve the objective of minimizing noncompliance with proto-

col demands? How valid are clinicians' predictions of patient adherence to medical advances?

I have not been able to find studies that definitively answer these questions, and conducting such studies would require a major undertaking. In my opinion, however, clinicians and researchers are often overly confident of their ability to predict how patients will behave when they are offered a new treatment option. Noncompliance, dropouts, loss to follow-up, and selective attrition are limitations that plague even the most carefully designed clinical studies. It is well established that adherence to complex medical regimens is neither a global nor a stable personality trait. Instead, adherence is variable across regimen components and across time among patients. It is therefore not surprising that prediction of adherence in a new treatment situation will be imperfect. Designing candidacy criteria that seek to minimize these problems by screening out likely treatment failures is a defensible approach, but this need not be the only strategy for optimizing the benefits obtained from new technologies.

Consequences of a Highly Selective Approach

The conventional approach of evaluating medical advances with highly selected patients has important scientific and clinical implications. To optimize the scientific rigor and internal validity of a clinical trial by limiting enrollment to highly selected patients may invoke certain methodological and interpretive complications. Restriction of enrollment to patients who are already at or near target plasma glucose levels may limit the range of variation in the primary outcome measure and limit effect sizes. If the achievable effect size is small, more patients are needed to yield adequate statistical power, thus increasing the cost and complexity of the study. An underpowered study may underestimate the true effect size and lead to an erroneous interpretation that the intervention is less effective or cost-effective than if it were tested with a more diverse

sample of patients. By enrolling a sample of patients with limited diversity, the generalizability of the study findings may be questioned, and treatment effects obtained in research settings may dissolve upon translation into clinical practice where patients cannot be scrutinized so carefully. When these selection criteria enter into clinical practice, they may exacerbate racial and socioeconomic disparities in health status and access to care. Physicians who strive to practice evidence-based medicine may not be inclined to offer medical advances to patients whose characteristics differ from those of participants in controlled clinical trials.

From an ethical standpoint, one must consider the hidden costs of questions that are not asked and opportunities that are not given. Thus, a variety of plausible methodological, interpretive, practical, and ethical considerations suggest that efforts should be made to enroll more diverse patients in clinical trials and in clinical translation of that research. Many reports in diabetes alone provide support for this position.

My colleagues and I conducted an 18-month randomized trial of intensive therapy versus usual care in youth with type 1 diabetes mellitus in which 147 children and adolescents (6 to 15 years old) were enrolled. The primary aim of the study was to identify predictors of treatment outcome from these two regimens. To our surprise, patients with the lowest baseline scores for self-management competence and parental involvement in diabetes management actually derived the greatest glycemic benefit from the extra support and resources that come as part of a clinical trial of intensive therapy. Similarly, in a recent trial of a family problem-solving intervention with adolescents with poor glycemic control, we found that glycemic benefits obtained from this intervention were greater for patients with baseline A1C >9.0% than for those with better control.

The Diabetes Research in Children Network (DirecNet) pilot studies of the

Continued

Navigator CGM showed that patients with baseline A1C >7.5% derived greater glycemic benefit from use of the Navigator than those with better baseline control. Similarly, the European GuardControl trial yielded a mean A1C improvement of 1.0% after 3 months' use of the Guardian Real-Time CGM device among patients with baseline A1C >8%. Several other trials have found similar effects.

For example, Deiss and colleagues followed 50 youths who were starting insulin pump therapy while also using CGM for the first 6 weeks. Poor baseline glycemic control (A1C ≥8.9%) predicted greater glycemic improvement over this period. Pickup and colleagues showed that high glycemic variability and high A1C predicted subsequent glycemic benefit upon transition from multiple daily injections to insulin pump therapy. Finally, Rodrigues and colleagues reported that 15 patients for whom pump therapy was contraindicated in fact enjoyed substantial reductions in A1C and hospitalizations for diabetic ketoacidosis after a mean of 20.5 months of pump therapy. These studies suggest that patients who are not routinely considered ideal candidates for medical advances have realized legitimate therapeutic benefits when technological advances were incorporated into care.

If this evidence and the preceding arguments are convincing, how can a responsible and reasonably cautious clinician safely and effectively offer medical advances to more diverse patients?

▲ *Formalize measurements of adherence*

Understanding the effects of medical advances on primary outcomes, whether for clinical management or research purposes, should be based on careful, ongoing assessment of adherence to the regimens being compared. In research contexts, treating adherence as a covariate in data analyses can clarify the extent to which the benefit of the medical advance is mediated by adherence, as well as clarify whether between-

group differences in treatment outcomes are attributable to adherence differences. Few controlled clinical trials in diabetes emphasize achieving a careful understanding of adherence to the tested interventions. In clinical trials comparing two or more treatments, different rates of adherence could lead to the inference that the treatments yield different outcomes when, in fact, the apparent treatment effect may be due to adherence differences. Similarly, failing to account for adherence may lead to an underestimate of the treatment benefit, a problem that could be corrected in some cases with a relatively simple behavioral intervention.

Patients not routinely considered ideal candidates for medical advances have realized therapeutic benefits when those advances were incorporated into care.

▲ *Engage a specialist with expertise in behavior modification*

Safe and effective structuring of clinical trials or dissemination of medical advances into clinical practice can be facilitated by using established principles of behavior analysis and behavior modification. Planning (whether a research trial or a clinical program for adding new technologies to diabetes management) can be improved with the participation of a behavior change specialist. Contributions from such a specialist could include identification of likely trouble spots regarding regimen adherence, "incentivizing" patients to negotiate those challenges, careful specification of how financial or other participation rewards are earned, and weighted reinforcement of behaviors that are closest to the primary treatment outcome.

▲ *Gradually relax criteria for candidacy*

Whether designing a clinical trial or translating a medical advance into clinical practice, a reasonable approach would be to gradually and systematically relax

candidacy criteria. As experience grows and clinical safety is confirmed, enrollment criteria could be expanded to a greater number of patients.

▲ *Place greater emphasis on run-in periods than on strict enrollment criteria*

The best predictor of future behavior is past behavior under highly similar circumstances. Unfortunately, observation of such past behavior is often not possible. Establishing a priori enrollment criteria is one way to attempt to ensure the internal validity of a clinical trial or to ensure that clinical use of new methods is safe and responsible. But this physician-driven approach does not give the patient a real role in the decision to try the new advance. In contrast, I would favor imposing more substantive pre-randomization run-in periods, during which no treatment is provided, and relying more heavily on these outcomes than upon preestablished hypotheses regarding which patient characteristics should be prioritized as candidacy criteria. Run-in periods offer marginal candidates a chance to prove themselves. On the other hand, I have seen "excellent" clinical trial candidates drop out during and after run-in periods, convincing me that prediction of clinical trial engagement is a risky proposition lacking in firm empirical support.

▲ *Learn and utilize patient-centered communication styles*

There is extensive empirical support for the effectiveness of motivational interviewing, patient empowerment, and autonomy-supportive communication styles among patients with diabetes. These methods offer practical strategies for helping patients and families define their personal goals for improved diabetes management and are particularly useful for working with patients who have been resistant to more conventional attempts.

▲ *Plan rescue procedures*

Regardless of the predictive validity of evaluating candidates, some patients will invariably not benefit, and some may experience adverse events. Being prepared for these situations and

Continued

having a plan in place that enhances early detection and provides prompt, appropriate treatment can help to minimize harm to those given the opportunity to try new technologies. Rescue procedures may include relaxation of therapeutic targets, more frequent clinical encounters, or referrals for additional education or counseling.

Summary

As new technologies are used in controlled trials and clinical practice, there are valid reasons to expose increasingly diverse samples of patients to these advances. As with any approach, there are challenges to overcome—for example, the considerable costs associated with exposing a greater number of individuals to devices that have yet to be proven. However, the conceivable risks of greater inclusion can largely be anticipated and minimized, and a number of potential methodological, interpretive, and social benefits could result. Time dedicated to the promotion of optimal use of new technologies may be more productive than efforts to screen out those who are thought to be marginal candidates.

Dr. Wysocki has no commercial relationships to disclose.

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DIABETES TACTICS

CURRENT ISSUES IN INSULIN PUMP THERAPY

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(T1DM). Much has happened since the commercialization of the first insulin pump in 1980. The most dramatic advance came in June 2006 with the launch of the first insulin pump with continuous glucose monitoring (CGM). The evolution of insulin pump therapy has made continuous subcutaneous insulin infusion (CSII) a safe and viable alternative to conventional insulin therapy or multiple daily injections (MDI). This article will help familiarize health professionals with the current state of insulin pump therapy and its potential benefits for patients.

After the Diabetes Control and Complications Trial (DCCT) concluded in 1993 and the 10-year follow-up results of the Epidemiology of Diabetes Interventions and Complications (EDIC) study were released, it became clear that normalization of

glucose markedly delayed or prevented both microvascular and macrovascular complications of diabetes. Current goals for patients with diabetes are to attain glucose levels as close to normal as possible, without significant hypoglycemia or hypoglycemia unawareness. At the end of the DCCT, 42% of the subjects in the intensive therapy group were using CSII. In that study, CSII correlated with significantly better glycemic control than did MDI. One of the major complications observed in the DCCT was an increased rate of severe hypoglycemia with intensive insulin therapy. Since the completion of the DCCT and the introduction of rapid-acting insulin analogs, studies have shown a significantly lower risk of major hypoglycemia with insulin pump therapy, as well as an improvement in quality of life.

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At the end of the DCCT, there were approximately 10,000 individuals in the United States using insulin pump therapy. Five years after the conclusion of the DCCT, with the realization of the need for better means to lower A1C and minimize the risk of hypoglycemia, use of insulin pump therapy had increased to more than 100,000 patients. Since then, insulin pump use has flourished among adults and children with T1DM, with more than 25% of T1DM patients in the United States now using an insulin pump. Current indications for pump therapy in insulin-requiring adults and children with T1DM are listed in Table 1.

Patient Characteristics

Patients who benefit most from insulin pump therapy are motivated to improve their glycemic control, work with their health care team, and assume responsibility for their day-to-day diabetes care. These individuals should

- Practice frequent self-monitoring of blood glucose (preferably four times a day),
- Perform carbohydrate counting, and
- Attend regular follow-up visits with their health care team.

Prior to starting pump therapy, an assessment by a certified diabetes educator (CDE) can help determine readiness, gaps in skills and knowledge, availability of support systems, and other factors that may affect the overall appropriateness of the patient for initiating pump therapy. In addition, a CDE will ensure that patients and caregivers have realistic expectations regarding outcomes, financial implications, and what is involved in day-to-day care.

Patients who meet the criteria for pump therapy should be referred to a diabetes team or insulin pump trainer with expertise in initiating insulin pump therapy and troubleshooting follow-up problems. Current protocols for initial insulin dose are based on the patient's body weight and/or current insulin requirement. Unless A1C levels are well above target levels, 20% less insulin is typically required

when initiating CSII, with average total starting doses being approximately 0.5 U/kg body weight. The total basal amount should be $\leq 50\%$ of the starting dose, and the remaining insulin should be given as boluses based on the amount of carbohydrate consumed. The patient will also require a correction dose based on how much 1 U of insulin lowers his or her glucose (also known as insulin sensitivity).

A patient initiates therapy by entering all parameters into the pump's bolus calculator setup screen; the bolus calculator function should be used for all meal and correction dosing. Once this function is activated, the patient can either directly transmit the glucose reading from the meter into the pump or enter the glucose meter reading (as well as the number of grams of carbohydrate to be consumed) into the insulin pump. The pump will then calculate the recommended meal and correction dose for an out-of-range blood glucose and subtract any on-board insulin from a prior dose.

After initiation of insulin pump therapy, insulin doses are adjusted based on fasting and premeal, 2-hour postmeal, and nighttime glucose values. Changes to the basal dose should be made in order to keep the blood glucose within

a 30 mg/dL range when not eating. If postmeal glucose is significantly elevated, the carbohydrate-to-insulin ratio should be lowered, and the patient should be encouraged to give boluses approximately 15 to 20 minutes before eating. The patient should report any significant hypoglycemia to his or her diabetes team so that appropriate changes can be made to pump settings.

Aside from hypoglycemia, there are two adverse event concerns with insulin pump therapy: (1) interruption of the insulin infusion can lead to ketoacidosis, and (2) a lack of appropriate insulin infusion site care can lead to site inflammation, infection, and lipohypertrophy. Significant hyperglycemia typically occurs when the insulin set cannula becomes dislodged without the patient noticing. Frequent blood glucose monitoring and appropriate responses to elevated blood glucose can easily prevent most episodes of serious metabolic decompensation. If a patient develops significant hyperglycemia that is not responsive to a pump correction bolus, the patient must manually inject insulin and then replace the infusion set and reservoir. If nausea and vomiting persist, the patient should proceed to the emergency room for potential treatment of impending

Continued

Table 1. Indications for continuous subcutaneous insulin infusion (CSII) in adults and youths with type 1 diabetes mellitus

CSII should be considered in patients with

- Recurrent severe hypoglycemia
- A1C greater than target range for age
- Wide fluctuations in blood glucose levels regardless of A1C
- Microvascular complications and/or risk factors for macrovascular complications
- Insulin regimens that compromise lifestyle

CSII may also be beneficial in

- Young children, especially infants and neonates
- Managing the dawn phenomenon
- Children with needle phobia
- Ketosis-prone individuals
- Competitive athletes
- Preconception or pregnancy

diabetic ketoacidosis. Inflammation and infection at the infusion site usually only occur in carriers of *Staphylococcus*; these individuals may need to clean the site with antistaphylococcal solutions (eg, Hibiclens™). Lipohypertrophy can also occur if the injection site is not rotated on a routine basis (as with injected insulin).

Pediatric Pump Usage

One of the most disappointing aspects of the history of insulin pump treatment is the limited number of children and adolescents with T1DM who used this therapy in the past. During the last 8 years, however, young people with T1DM have been the fastest growing segment of the diabetes population to adopt this therapy. Teenagers with well-established T1DM were among the first to adopt insulin pump therapy, and pediatric diabetes specialists have increasingly offered the treatment to ever-younger patients, earlier and earlier in the disease. In fact, some pediatric diabetes programs in Scandinavia now treat all patients with CSII at the time of diagnosis. Because of their unpredictable eating and activity patterns, infants and toddlers (and their parents) ultimately benefit more from this therapy than older children and adolescents.

Most of the evidence that has fueled the increase in insulin pump use among children comes from nonrandomized studies documenting clinical outcomes after switching patients from MDI to CSII therapy. In all of these studies, A1C levels fell by 0.3% to 0.7% (mean, ~0.5%) and approached average values in the pediatric target range (ie, ~7.5%). Additionally, the rate of severe hypoglycemia was reduced, better metabolic control was attained, there was no excessive weight gain, and both patients and parents preferred CSII to MDI.

Functions of the newest pump models that are particularly useful in very young children include the ability to adjust basal and bolus doses in increments as low as 0.025 to 0.05 U and the ability to give an unlimited num-

ber of small meal bolus and correction doses. In adolescents, the basal insulin infusion can be suspended or reduced to prevent hypoglycemia during exercise and delayed hypoglycemia on nights after exercise, and alternate basal infusion profiles can be programmed for sleeping late on weekends. The bolus history function is especially useful to assess adherence among adolescents with increasing A1C levels.

Some pediatric diabetes programs in Scandinavia now treat all patients with insulin pump therapy at the time of diagnosis.

A Pediatric Diabetes Consensus Forum was recently convened to review the current state of knowledge about CSII in children and adolescents with T1DM. A review of the recommendations regarding indications for CSII in children and adults shows that virtually every child and most adults with T1DM may be eligible (Table 1).

The most important recent advance in the field of intensive diabetes management has been the development of real-time continuous glucose monitoring (RT-CGM). Traditional self-monitoring of blood glucose consists of obtaining a blood glucose measurement at set time points; with this method, however, a patient cannot tell whether glucose values are currently rising or falling. With RT-CGM of interstitial fluid, however, a patient and his or her health care team can glean a more complete picture, including the direction and speed of changes in glucose values. RT-CGM gives the user continuous glucose updates, trend graphs, and rate-of-change arrows, which empower the user to observe the effects of lifestyle, food, activity, and treatment on glucose control. For more information on RT-CGM, see the article by Dr. Howard Wolpert in this issue of *CADRE's Current Diabetes Practice*.

Trials are under way using closed-loop devices in which the sensor will automatically adjust insulin delivery from the pump in order to maintain euglycemia over a 24-hour period. The most promising substitution for physiologically normal β -cells would incorporate an insulin delivery device, glucose sensor, and glucose controller in the form of RT-CGM and an external insulin pump. To compensate for the delay in insulin absorption associated with subcutaneous delivery, a small "priming" bolus of insulin, provided 15 minutes before a meal, can improve postprandial glycemic excursions. Preliminary work at Yale University using this approach in children with T1DM has shown that these patients can achieve fasting glucose in the 110 mg/dL range without hypoglycemia, as well as minimal glycemic excursions with meals. Additional work, such as that examined in the Long-Term Sensor System project, involves the use of a fully implantable device. Research in this area promises to improve the autonomy, quality of life, and risk of long-term complications for patients with either T1DM or T2DM.

Dr. Bode serves as a consultant for and has received grant support from Abbott Laboratories, DexCom, Johnson & Johnson, and Medtronic, Inc.

Ms. Fredrickson owns stock in Medtronic, Inc.

Dr. Tamborlane serves on the advisory boards of Abbott Laboratories; LifeScan, Inc.; Medtronic, Inc.; and Novo Nordisk A/S.

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LITERATURE CORNER

CURRENT DEVELOPMENTS IN GLUCOSE SENSORS/MONITORING

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Real-time continuous glucose monitoring (RT-CGM) devices provide detailed information on glucose patterns and trends (including postprandial and overnight glucose measurements rarely obtained by conventional means), information on the direction and rate of glucose change, and alarms that alert the patient to both hyper- and hypoglycemia. RT-CGM may dramati-

Table 1. Key patient education points for starting real-time continuous glucose monitoring (RT-CGM)

- Physiologic lag between interstitial and blood glucose levels, implications for device calibration, and interpretation and use of data
- Practical considerations with the use of sensor alarms and caveats in the setting of alarm thresholds
- Potential risk for hypoglycemia related to excessive postprandial bolusing by RT-CGM users, and the practical implications for patient training

cally improve a patient's day-to-day diabetes management and can be an important tool for reshaping eating behavior.

Randomized clinical trials indicate that this new technology can lead to a reduction in both hyper- and hypoglycemic excursions. The GuardControl study showed that use of RT-CGM is associated with a statistically significant reduction in hemoglobin A1C levels. At the end of the study, 50% of patients using RT-CGM reduced their A1C by $\geq 1\%$, and 26% of patients using RT-CGM reduced their A1C by $\geq 2\%$. Data from the Star 1 trial indicated there is reduced risk for hypoglycemia when glucose control is intensified using continuous sensors alongside intermittent fingerstick monitoring.

For practitioners and patients to derive full potential benefit from the safe and effective use of RT-CGM, practitioners must have a thorough understanding of several physiologic and technological issues, and patients must have or should be provided with the necessary education to develop good diabetes self-management skills (Table 1). In addition, key educational messages that should be communicated to patients using RT-CGM are discussed.

Interstitial Glucose and Lag Implications for Sensor Users

Whereas fingersticks measure capillary glucose, currently available RT-CGM devices measure interstitial glucose. Due to the physiologic lag in equilibration between these two compartments, glucose level changes are usually first detected in the blood. This

physiologic lag between blood and interstitial fluid—which can be as long as 30 minutes—has important implications for the accuracy of continuous sensors and the use of RT-CGM in diabetes self-management.

To ensure that RT-CGM provides accurate readings, it is critical that patients follow proper procedure in calibrating the devices. Because RT-CGM devices are calibrated using capillary blood glucose, calibration should only be performed when capillary blood and interstitial glucose are in a steady state, that is, when the glucose level is fairly stable (such as preprandially or at least 3 hours following a bolus). If the RT-CGM device is calibrated postprandially, the sensor reading will be biased upward, thereby decreasing the device's ability to detect hypoglycemia. Calibration should be performed using samples obtained from fingerstick only, not an alternate site. Patients should follow proper procedure regarding fingertip cleaning and glucose monitor coding. For optimal accuracy, currently available RT-CGM devices should be calibrated three to four times a day.

Sensor lag has important implications for the use of RT-CGM data in diabetes self-management. In situations in which the sensor's trend graphs or rate of change arrows indicate that glucose levels are shifting, there may be a physiologic lag in interstitial glucose levels behind blood glucose. In such a case, the patient should verify the glucose level by checking a fingerstick before making any treatment decisions (Table 2). If the glucose level is normal

Continued

according to the sensor but the arrow indicates glucose is dropping, the blood glucose could be low even though the interstitial glucose is normal; this lag is an especially important consideration before driving and/or for patients who are exercising. In short, too much reliance on sensor readings can lead to erroneous decision making. If the sensor indicates the glucose level is normal but there is any reason to suspect that glucose may be low, the patient should perform a fingerstick measurement. Likewise, during recovery from hypoglycemia, an increase in interstitial glucose will often lag behind blood glucose, and use of the RT-CGM device to assess response to hypoglycemia may lead to overtreatment. If a patient's glucose level tends to spike after hypoglycemic events, it is important to find out if he or she is basing decisions regarding how much carbohydrate to take on RT-CGM device readings rather than on fingerstick measurements.

Setting Alarms

Alarms for hypo- and hyperglycemia are a very important feature of RT-CGM devices. To ensure the patient derives full benefit from this technology, the alarm thresholds must be individualized. Table 3 outlines some important considerations in optimizing alarm settings and preventing patients from developing alarm burnout.

Setting alarm thresholds is a stepwise process analogous to setting basal

Table 2. Sensor-related patient teaching points

- If ▲ ▼ indicate changing glucose levels, check fingerstick before adjusting insulin
- If sensor glucose is normal but ▼ indicates glucose is dropping, check fingerstick, especially before driving or during exercise
- If any reason exists to suspect glucose may be dropping but sensor is normal, rely on fingerstick
- Use of real-time continuous glucose monitor device to assess hypoglycemia treatment response may result in overtreatment

rates for an insulin pump. Step 1 entails deciding on initial thresholds when initiating use of a RT-CGM sensor; step 2 entails reviewing continuous glucose tracings over time to assess if the settings are optimal. Individuals with hypoglycemia unawareness or a history of severe hypoglycemic reactions will usually want a high degree of assurance that an alarm will sound whenever glucose is low. For these individuals, the low alarm threshold should be set at ≥ 80 mg/dL. Because of the physiologic lag, by the time the alarm is triggered blood glucose levels are often lower than the sensor measurement indicates; this may be an additional consideration in setting the low alarm threshold. The downside of setting the low alarm at a relatively high threshold is the increased frequency of false alarms. These intrusive and irritating alarms can lead to alarm burnout, with an associated tendency for patients to ignore the sensor alarms.

For individuals without a history of problematic hypoglycemia, the low threshold may initially be set at 55 to 60 mg/dL, and the high threshold may be set at ≥ 250 mg/dL. This ensures that intrusive and irritating alarms will be reduced and risk for alarm burnout will be minimized while the patient initially masters use of the sensor and learns to smooth out glucose excursions. Over time, alarm settings can be brought closer to target glucose levels, which may assist with further tightening of glycemic control.

During follow-up visits, it is important to check specifically whether the alarm went off whenever the patient's glucose was low or markedly high, as well as to inquire whether the patient was troubled by frequent false alarms. If the patient is having frequent highs (especially overnight) and is not being appropriately alerted by the sensor,

Continued

Table 3. Trade-offs in setting continuous glucose monitor alarm thresholds

	Set alarms at the "ideal" level (Example: low = 80 mg/dL, high = 180 mg/dL)	Set alarm thresholds more widely (Example: low = 55 mg/dL, high = 250 mg/dL)
Pros	<ul style="list-style-type: none"> • Patient will be warned of most low and high blood glucose readings 	<ul style="list-style-type: none"> • Fewer false alarms • Fewer irritating and intrusive alarms • Less risk for alarm burnout
Cons	<ul style="list-style-type: none"> • Frequent false alarms • Frustration and irritation • Disruption of sleep • Increased risk for alarm burnout with an associated tendency to ignore sensor alarms 	<ul style="list-style-type: none"> • Patient will not be warned of all high and low blood glucose readings

the high alarm threshold should be reduced. Conversely, if the patient has experienced hypoglycemic reactions without being alerted, the low alarm threshold may need to be set at a higher level. In the context of discussing alarm thresholds with patients, it is often worthwhile to emphasize that it is less important if the alarm went off at the “right” number than if the alarm provided timely warning of low and high glucose levels.

Minimizing Hypoglycemia

When understood and used properly, the alarms and trend information provided by continuous sensors may be of particular value in minimizing hypoglycemia. However, some patients overreact to the postprandial glucose spikes identified by the sensor by taking excessive amounts of insulin, which can increase hypoglycemia risk. Reducing this tendency for postprandial over-bolusing is an important focus in the training of patients using RT-CGM.

It is less important for the sensor alarm to go off at the “right” number than for the alarm to provide timely warning of low and high blood glucose levels.

To minimize the risk of hypoglycemia from postprandial over-bolusing, patients should be educated to consider the amount of residual insulin “on board” from the last premeal bolus before taking supplemental boluses. Insulin pumps with bolus calculators may help determine appropriate dose reductions. The type of carbohydrate eaten—in particular, an understanding of the glycemic index—may help patients decide whether additional postprandial boluses are appropriate. With high-glycemic-index carbohydrates, a mismatch between the absorption of the carbohydrate and insulin bolus action will lead to a rapid spike in glucose levels, and there is a risk for hypoglycemia if correction doses are taken 2 to 3 hours postprandially. Conversely, 2 to 3 hours after a low-glycemic-index

Table 4. Adjusting bolus dose based on rate of glucose change

- If glucose is increasing 1-2 mg/dL/min: add 10% to calculated food/correction bolus
- If glucose is increasing >2 mg/dL/min, add 20% to calculated food/correction bolus
- If glucose is decreasing 1-2 mg/dL/min, subtract 10% from calculated food/correction bolus
- If glucose is decreasing >2 mg/dL/min, subtract 20% from calculated food/correction bolus

carbohydrate meal, a significant proportion of the carbohydrate load will not have been absorbed. In this case, if the glucose level is elevated, a correction bolus would be appropriate. For more information on the glycemic index, see Volume 6, Issue 3 of *CADRE's Current Diabetes Practice*.

The “trend” arrow on the glucose sensor is another factor to consider in this decision making. Table 4 shows the algorithms for adjusting insulin boluses based on rate of change of the glucose level as outlined in the training materials for the Star 1 trial and the Juvenile Diabetes Research Foundation–sponsored randomized controlled trial.

Conclusion

Initial clinical experience and trials indicate that RT-CGM can benefit a substantial number of individuals with diabetes. To derive full benefit from this technology, patients must be motivated and trained in diabetes self-management. Patient education about the technical and physiologic considerations associated with the use of continuous glucose data provides an important foundation for success.

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Suggested Reading

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