Published in final edited form as:

Endocrinol Metab Clin North Am. 2010 September ; 39(3): 609–624. doi:10.1016/j.ec1.2010.05.005.

Toward Closing the Loop: An Update on Insulin Pumps and Continuous Glucose Monitoring Systems

Tandy Aye, MD,

Department of Pediatrics, Stanford Medical Center, G-313, 300 Pasteur Drive, Stanford, CA, 94305-5208, Phone: 650-723-5791, Fax: 650-7258375

Jen Block, RN, CDE, and

Department of Pediatrics, Stanford Medical Center, G-313, 300 Pasteur Drive, Stanford, CA, 94305-5208, Phone: 650-723-5791, Fax: 650-7258375

Bruce Buckingham, MD

Department of Pediatrics, Stanford Medical Center, G-313, 300 Pasteur Drive, Stanford, CA, 94305-5208, Phone: 650-723-5791, Fax: 650-7258375

Tandy Aye: taye@stanford.edu; Jen Block: jblock@stanford.edu; Bruce Buckingham: buckingham@stanford.edu

Synopsis

In this paper we review current pump and continuous glucose monitoring therapy and what will be required to integrate these systems into closed-loop control. Issues with sensor accuracy, lag time and calibration are discussed as well as issues with insulin pharmacodynamics which result in a delayed onset of insulin action in a closed-loop system. A stepwise approach to closed-loop therapy is anticipated where the first systems will suspend insulin delivery based on actual or predicted hypoglycemia. Subsequent systems may “control-to-range” limiting the time spent in hyperglycemia by mitigating the effects of a missed food bolus or underestimate of consumed carbohydrates while minimizing the risk of hypoglycemia.

Keywords

CSII; insulin pumps; CGM; continuous glucose monitoring; type 1 diabetes; closed-loop therapy; artificial pancreas; nocturnal hypoglycemia

Background

Diabetes is a chronic disease which currently can only be controlled by constant vigilance. Chronic elevations, and likely fluctuations, of the blood glucose are associated with long term complications (blindness, kidney failure, heart disease, and lower extremity amputations). Perversely, tight glucose control increases the risk of serious hypoglycemia. Despite insulin infusion pumps and programs which promote intensive diabetes management, the average A1c

Financial Disclosures

Dr. Aye has no financial disclosures. Mrs. Block has received honoraria and/or consulting fees from Medtronic MiniMed and Unomedical. Dr. Buckingham receives research support from Medtronic Minimed, Abbott Diabetes Care, and Dexcom, and he is on medical advisory boards of Medtronic Minimed, Unomedical, Bidel, Animas, Novo-Nordisk, and Bayer.

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at major diabetes treatment centers remains higher than 8%¹, well above the recommended goal of 7% for adults and for age adjusted pediatric goals 2 (Table 1). Many factors contribute to this failure: 1) the difficulties in correctly estimating the amount of carbohydrates in a meal, 2) missed meal boluses, and 3) anxiety about hypoglycemia resulting in under-treatment, especially overnight. It has always been difficult to achieve compliance with complicated medical regimes, whether it is taking pills three or four times a day, or administration of insulin 3 or more times a day. As long as diabetes treatment demands constant direct intervention, the vast majority of people with diabetes will not meet treatment goals. By taking the patient out of the loop or closing the loop, an “artificial pancreas” would allow the person with diabetes to go about their daily activities without the need to constantly remember to check their blood glucose, count carbohydrates, and take insulin multiple times each day.

An artificial pancreas consists of three components: an insulin infusion pump, a continuous glucose sensor, and an algorithm which translates data from the glucose sensor and determines insulin delivery. The most likely first closed loop system would use a subcutaneous sensor and insulin infusion pump. However, an implantable system is also feasible. The main difficulties in optimizing a SQ system are: 1) Accuracy of the SQ continuous glucose sensors, 2) Lags in interstitial SQ glucose measurements when the glucose is changing rapidly, 3) Delays in the onset of insulin action after a SQ injection, 4) Prolonged insulin action of 4–6 hours following a SQ injection and 5) Lack of algorithm models that exactly mimic islet physiology. Thus, with current technology, a SQ sensor-SQ insulin delivery system does not fully mimic normal beta cell function, however initial studies indicate that excellent diabetes control can be achieved using such a system on a short term basis³.

Before a functional artificial pancreas (AP) will receive FDA approval, clinical safety in an outpatient setting must be demonstrated. The most important safety issue in the short term will be the avoidance of severe hypoglycemic events. Fortunately, when subcutaneous glucose sensors fail, they generally indicate falsely low glucose readings. A falsely low glucose would cause under-delivery of insulin in a closed-loop system resulting in hyperglycemia, not hypoglycemia. Hypoglycemia can also be avoided by aiming for a slightly higher glucose target. As an example, if the target is set to 120 mg/dl, and the sensor was inaccurate by 50%, glucose values would still be above 60 mg/dl. Current glucose sensors are more accurate above 70 mg/dl^{4–6}, and since a closed-loop would generally maintain glucose levels above this level, the system would be functioning in a glucose range where sensors have greater accuracy, which is another safety feature to prevent hypoglycemia. As algorithms improve, the amount of time spent above 200 mg/dl can also be progressively decreased. Currently, children with an average A1c of 6.9% spend an average of 6 hours with glucose readings above 200 mg/dl each day⁷. With a closed-loop system it should be possible to significantly decrease the time spent in hyperglycemia without increasing hypoglycemia, and thereby decrease glycemic variability. Glycemic variability, independent of HbA1c levels, has recently been described as an independent risk factor for diabetic complications^{8–9}, although this concept is controversial¹⁰.

Sensors

A number of devices and technologies have been proposed for continuous glucose monitoring including the use of near-infrared and mid-infrared spectroscopy, erythrocyte scattering, photoacoustic phenomenon, optical coherence tomography, thermo-optical techniques, Raman spectroscopy, and fluorescence measurements¹¹. Currently commercially available continuous glucose sensors are based on measuring subcutaneous (interstitial) glucose levels. These are electrochemical sensors which utilize glucose oxidase and measure an electric current generated when glucose reacts with oxygen. They are coated with specialized membranes to make them biocompatible, generating almost no tissue reaction, and providing

a barrier to potential cross reactants such as acetaminophen. These sensors are relatively stable and generally provide a good glucose signal for 3 to 7 days.

There is a lag time between blood glucose readings and CGM readings. The lag time is due to three components: 1) a physiologic lag time between blood and interstitial glucose levels of about 3–8 minutes, 2) delays in the electrochemical sensor due to transit times for glucose to diffuse across the membranes coating the sensor of 1–2 minutes, and 3) processing of the sensor signals since these signals can be noisy and require digital filtering which generally introduces an additional 3 to 12 minute delay in CGMS readings¹². As sensor technology improves, the sensor noise is reduced which allows for less filtering and more rapid response times. A more rapid sensor response time is very important when using the sensor signals to drive a closed-loop system. In pigs, the temporal changes in interstitial blood glucose levels correlate better with changes in the CNS glucose than to changes in the blood glucose¹³. Perhaps interstitial glucose levels would correlate better with CNS function than blood glucose levels, although this remains to be determined in humans.

Although real-time continuous glucose monitoring (CGM) is not as accurate as discrete blood glucose monitoring, CGM values are generally within 15% of the discrete measurement. A discrete blood glucose has been compared to a snapshot, and real time monitoring to a video, where there is less information in each frame but the video provides the added dimension of glucose change over time that the snapshot cannot provide. There have been significant improvements in the accuracy of sensors over the last 6–10 years. In a study assessing the use of CGM in non-diabetic children in 2004, 20% of CGM readings were < 60 mg/dl, and 54% of CGM values were >150 mg/dl, whereas the range of reference glucose values was 60–140 mg/dl¹⁴. In a recent study conducted by the Juvenile Diabetes Research Foundation (JDRF) in non-diabetic children and adults using current CGM sensors the sensor glucose concentrations were 71–120 mg/dL for 91% of the day and sensor values were ≤60 or >140 for only 0.2% and 0.4% of the day, respectively¹⁵. Glucose sensors can also be “tuned” to be more accurate in various glucose ranges. For example the Medtronic Veo Glucose sensor uses the same sensor technology as the Medtronic Paradigm REAL-Time but the sensor calibration has been adjusted to improve hypoglycemia sensitivity from 55% in the Paradigm REAL-Time to 82% in the Veo¹⁶.

There are other glucose sensing technologies other than the current glucose oxidase based needle sensors which can also measure blood and subcutaneous glucose levels. One such technology uses a boronic acid matrix which binds glucose and measures glucose levels by quenching of a fluorescence photophore. Results from GluMetrics¹⁷ indicate that this technology has the potential to be more accurate than the current glucose oxidase based sensors in the hypoglycemic range. One possibility in the future would be to combine two different glucose sensing technologies on a single platform, allowing for redundancy in the glucose measurements and sensing technology which has complimentary regions of greater sensor accuracy (glucose oxidase based sensors in the hyperglycemic range, and fluorescent sensors in the hypoglycemic range).

Current needle-like continuous glucose sensors pass through the skin, so there is always the potential for an infection at the insertion site. Current sensors have a transmitter attached to them once they are inserted. The transmitter provides a source of energy to power the sensor, as well as allowing transmission of the glucose signal to a receiver using a radiofrequency (RF) signal. These sensors often take from two to ten hours to stabilize to the local interstitial environment before they generate a reasonably accurate glucose signal. Because of the differences in interstitial and blood glucose levels when glucose values are changing rapidly, it is generally considered better to calibrate the sensor when blood glucose levels are stable (ideally when changes are < 0.5 mg/dl/min)¹⁸. Unfortunately, when patients enter their first

calibration value, they are “blind” to the data from their continuous glucose sensor and their glucose rate of change. After their initial calibration they are able to “see” their glucose trends and assess their rate of change before entering subsequent calibration values. The calibration system could be significantly improved if sensors internally evaluated the stability of the glucose signal, and only requested calibration values when the glucose signal was stable.

There remain multiple factors that affect the patient’s use of the sensors. Because sensors require a continuous source of power, the transmitter cannot be detached from the sensor for any length of time, or the sensor must be recalibrated. One of the biggest user issues with these devices has been the adhesive required to secure the sensor and transmitter to the skin. The adhesives can be irritating to some wearers and others will develop a true tape allergy. A big issue for prolonged sensor wear (greater than 3 days) is maintaining the adhesive. For those who use continuous SQ insulin infusions (CSII; pump), there are two insertion sites (one for the insulin infusion cannula and one for the sensor), and two areas for potential tape related issues. Wearing the tape repeatedly in the same area can temporarily disrupt the usual skin barriers to infection. Future devices may be able to combine a continuous glucose sensor with an insulin infusion set into one platform adhering to the skin.

One way to avoid the topical skin issues associated with adhesives is to implant the sensor. Implanted sensors are attractive to patients since they are not visible, they do not have to insert a needle-like sensor under their skin repeatedly, and they would not interfere with daily activities such as showering, swimming or exercising. There is one published report of a long term implanted subcutaneous continuous sensors¹⁹. The sensors were surgically implanted into the abdomen under local anesthesia. Two months after implantation 13 of the 15 implanted sensors were functioning and had a mean absolute relative difference of 25% when compared to YSI (Yellow Springs Instrument Glucose Analyzer) glucose levels. For implanted devices to be acceptable they will probably need to function for at least 1 year once they are implanted, and ideally their insertion and removal could be performed in a physician’s office and not require a surgical referral. Another approach would be an intravascular continuous glucose sensor. This technology was initially developed by Dr. David Gough²⁰ and similar technology has been used in clinical trials conducted by Minimed in France²¹ and the United States. This sensor has about a 20 minute delay in reported glucose levels, which has created difficulties when trying to integrate the sensor information into an artificial pancreas.

Clinical Pointers in the Use of CGM Sensors today

Recent studies have demonstrated that when subjects are wearing CGM devices 5–7 days a week they can improve their A1c levels without increasing their risk of hypoglycemia and this benefit can be maintained over 12 months with continued sensor wear^{22, 23}. This benefit was seen across all age groups as long as they wore the sensor at least 5–6 days a week. The main predictors for success in using a CGM at the onset of the JDRF trial was the age of the subject (adults were more successful than adolescents) and the number of home glucose tests subjects were doing prior to entering the study (those reporting at least 6 tests a day were more successful)²⁴. Wearing a CGM does not automatically improve diabetes control, it takes effort to observe glucose patterns and make adjustments to the diabetes routine. The number of glucose tests subject’s were doing prior to entering the study is probably a surrogate maker for their interest in managing their diabetes. Until the loop is closed, CGM performs as a behavior modification tool, and provides alarms for hyper and hypoglycemia.

Currently CGM use is approved only for adjunctive use in the United States. CGM is to be used only in conjunction with traditional blood glucose testing and all treatment decisions should be based on blood glucose test results. Intermittent finger stick blood glucose monitoring is often described as a snapshot of diabetes control and CGM is likened to a movie that provides

dynamic information about glucose control. Perhaps the most exciting component of CGM use is the trend data it provides. This additional information about the rate and direction of glucose change is very important. Take the model of blood glucose testing, a finger stick BG test of 90 mg/dL is considered a safe glucose level, now add the trend data that shows the glucose is going down at a rate of 2 mg/dL/min which means in 20 minutes the glucose may be at or below 50 mg/dL. This additional knowledge may prompt a different response, and in fact the trend data provided by CGM data may be used to prevent the glucose from dropping below or rising above the individual's glucose targets. All of the currently FDA approved CGM systems used in the US have user programmable low and high glucose threshold alarms. These alarms can be programmed to alert the user when the glucose drops below or rises above the individually set thresholds.

While trend data is helpful for the user in day to day life for health care providers (HCP) a distinct advantage of CGM use is the complete glucose profiles it provides. Current CGM systems have software that is available to download and view information on glucose control including reports showing the modal day and statistics. This information, especially the data on nocturnal glycemic patterns, can be used in combination with the blood glucose levels to guide treatment decisions with a higher degree of confidence. The CGM tool can then be used as an adjunctive means of assessing how effective any therapy changes may be.

Advantages of CGM Use

- CGM provides a more complete glucose picture.
- Adds trend data that helps predict where the glucose is headed.
- Provides constant feedback on how multiple variables impact glucose control.
- The immediacy of the feedback helps identify causality of glycemic variations.
- When combined with BG data allows for more confidence in therapy management.
- Alarms, if acted on, can result in increased time within target and fewer glycemic excursions.
- Trend/prospective data may be used to prevent glucose from dropping below or rising above target

Challenges to CGM Use

- Similar to the model for insulin pump instruction, RT-CGM instruction may be best accomplished by well-trained diabetes educators who guide patients.
- Expense to patient and providers.
- Wearability
- Teaching patients how to utilize the data.
- Unrealistic patient expectations. CGM is not an artificial pancreas but does provide a wealth of information that the user can respond to.
- Setting alarms and alerts to maximize utility and minimize patient burden.
- Time and support for intensive diabetes management and CGM is often poorly reimbursed ²⁵.

Strategies to Overcome Challenges

- Using group medical visits to educate patients about CGM technology and potentially for follow up.

- Trial use of a CGM system prior to purchase may help patients and providers make a more informed decision about using the technology and how likely they are to wear it.
- For assistance with reimbursement, the JDRF website offers guidance for seeking CGM coverage and provides information about select insurance carriers and CGM coverage policies.
 - http://www.jdrf.org/index.cfm?page_id=106514
- Access CWD Insurance Forum to learn about what has worked well for others seeking reimbursement.
 - <http://forums.childrenwithdiabetes.com/forumdisplay.php?f=57/>
- Utilize online patient teaching resources like the Continuous Glucose Monitoring School Online created by members of the JDRF sensor study group.
 - <http://cgmteaching.jaeb.org>
 - The tool includes:
 - ◆ Basic information on CGM technology
 - ◆ Device specific teaching modules
 - ◆ Guidelines and exercises for using CGM data
 - ◆ Suggestions on how to integrate DATA algorithms into care.

Key CGM Education for Patients

Initially starting patients on CGM can be challenging as they are often made aware of glucose trends that they were previously unaware of. Remind patients that perfection is not usually attainable but the goal of CGM use is continued improvement ²⁶.

- CGM is adjunctive technology and patients will still need to perform blood glucose tests to calibrate the system and to use as the basis for therapy decisions.
 - They will need to understand
 - ◆ The pharmacodynamics and role of basal/meal insulin coverage.
 - ◆ The Difference between interstitial glucose and BG and this difference will be more pronounced when the BG is changing rapidly.
 - ◆ It is not realistic to expect the BG and CGM values to be identical all the time.
 - ◆ Data interpretation (done with HCP team with retrospective analysis of results).
 - ◆ How to utilize trend data (real-time data) in combination with the BG data.
 - Adjust insulin doses based on the glucose trend ²⁷

In our experience, ideal CGM candidates are patients who

- Are prepared to see the data.

- Are willing/able to make changes based on the data.
- Are willing to wear the CGM system.

Pumps

Continuous subcutaneous insulin infusion (CSII) or insulin infusion pumps have been commercially available for almost 30 years²⁸. Since the initial pumps were developed there have been progressive improvements in their software features, and improvements in their size and the insulin infusion sets. Most pumps are attached to the subject using an infusion set catheter. A newer pump (a “patch” or “pod” pump) eliminates the need for infusion set tubing and manual insertion of the infusion set catheter. Two such pumps are the OmniPod and Solo™ Micro Pump. Current pump software features include the ability to calculate different carbohydrate to insulin ratios and different insulin sensitivities for correction doses at different times of the day. They also feature a calculation of residual insulin activity following an insulin bolus. Most pumps can now automatically receive data from a glucose meter (by radiofrequency (RF), or they have a glucose meter built into the pump), so glucose values do not need to be manually entered. A conscientious pump user can often achieve very good glycemic control if they monitor their blood glucose frequently, adjust their insulin doses based on an accurate assessment of the quantity and type of meals they are eating, and compensate for the effect of physical activity on glucose levels. This may require a prolonged bolus (square wave) for foods which are gradually absorbed, and often requires a pre-meal bolus of insulin prior to eating, especially in the morning, and temporary changes in basal infusion rates to account for physical activity. If the user also makes additional adjustments for activity level even better control can be achieved. However, dose delivery needs to be activated by the user. As with all chronic, lifelong conditions, the problem is the “human factor” with people remembering to give an insulin bolus before all meals, and knowing the amount of carbohydrate, protein and fat in the meal, and how rapidly the food will be absorbed. In a review on downloaded pump data at the Barbara Davis Center, 65% of adolescents were missing at least one meal bolus a week and their HbA1c was 0.8% higher than those not missing a meal bolus²⁹.

A pump with the ability to store and deliver more than one hormone would better mimic islet physiology and its mechanism of glucose control. Even the option of two hormones, for instance the addition of the counterregulatory hormone such as glucagon would be an added counter measure to prevent hypoglycemia. In fact, Dr. Edward Damiano and Firas El-Khatib have conducted studies using pigs and a dual infusion system and model predictive control, where small doses of glucagon, are given to prevent impending hypoglycemia. They found that glucagon was stable in an insulin infusion pump attached to the pig for at least 7 days³⁰. The onset of action of subcutaneous glucagon was very rapid, allowing for quick prevention of possible hypoglycemia. This therapy, of course, depends on the patient having adequate glycogen stores. Epinephrine has also been tried in the treatment of hypoglycemia, but was relatively ineffective³¹. Amylin, or islet amyloid polypeptide, can also be added to delay gastric emptying resulting in a slower rate of glucose change following a meal, since meals with their rapid rate of change present the greatest challenge to a SQ insulin/SQ sensor closed loop.

Advantages of pump use

- Provides flexibility of dose delivery
- More closely mimics pancreas physiology
- Accuracy of dose calculation
- Recorded data of insulin delivery

- Lower incidence of severe hypoglycemic events ³²
- Improved Quality of Life particularly in the pediatric population ³³
- Improved A1c ³²
- Decreased glycemic variability
- Possible cost effectiveness since lowers incidence of complications ³⁴

Challenges to pump use

- Similar to the model for CGM, insulin pump instruction may be best accomplished by well-trained diabetes educators who guide patients.
- Expense to the patient and providers
- Wearability
- Unrealistic patient expectations: the pump is not an artificial pancreas and must be activated by the user for delivery of insulin at mealtimes.
- Time and support for intensive diabetes management and pump use is often poorly reimbursed.
- Possibility of infusion set failures
- Possibility of weight gain

Strategies to Overcome Challenges

- Using group medical visits to educate patients about CGM technology and potentially for follow up
- Trial use of various types of insulin pumps prior to switching from MDI may help make a more informed decision about using the technology and how likely they are to use it.
- Most insurance plans will cover the cost of a pump if there is proper documentation Utilize online and each manufacturer's pump training program

Key Pump Education for Patients

- Initially starting patients on an insulin pump may be challenging as they are given a large possibility of insulin dose options. Before switching a patient from MDI be sure
 - The patient is able to wear a device continuously on the body
 - There is mastery of carbohydrate counting
 - Acknowledgement that pump therapy will intensify diabetes management
- Remind patients that perfection is not usually attainable immediately and doses may continually need to be adjusted;
- They will also need to understand the pharmacodynamics and role of basal and meal insulin coverage.

In our experience many patients who are on MDI and use real-time CGM become frustrated with the insulin delivery options using MDI and switch to pump therapy to allow easier meal coverage, more frequent correction doses, and the ability to use dual wave boluses to cover a meal.

Infusion sets

Currently infusion sets are generally used for 3 days, whereas continuous glucose sensors are generally functional for 5⁶, ³⁵ to 7 days. Patients would prefer to have one device attached to their body which could serve as both the sensor and insulin infusion pump. For both to be merged onto a common platform it would require a longer duration of insulin infusion set function, or the ability to insert several infusion sites on or into a common sensor platform. Another proposal is to use microneedle arrays ³⁶ to deliver intradermal insulin.

Insulin

One of the problems with the current “rapid-acting” insulins is that they are relatively slow for the purposes of a closed loop. They reach ½ their maximum activity in 20 minutes and do not reach full activity for 45 minutes ³⁷. When this is coupled with a 12–30 minute delay in the algorithm detecting the onset of a meal (based on the rate of change of glucose levels)³⁸, meal delivery of insulin becomes very difficult. This can be partially compensated for by having the patient give a pre-meal bolus of insulin, but then it is no longer a closed-loop system. Another approach would be to use an insulin with a more rapid onset of action. This can be accomplished by keeping the insulin in a monomeric (instead of hexameric) state. A new insulin developed by Biondi (ViaJect insulin) keeps the insulin in a monomeric state by chelating zinc which allows a more rapid onset of insulin action, reaching peak activity about 10–15 minutes earlier than current analog short acting insulins³⁹. Other possible solutions would be to change the insulin delivery so that it is provided to a more vascular area or the insulin could be delivered into the peritoneal cavity where some of the insulin would directly be absorbed through the portal circulation. Minimed has developed an implanted insulin pump using U-400 insulin and intraperitoneal insulin delivery. The greatest experience with this infusion system has been in France ⁴⁰, but there are currently no plans to market this system in the United States.

Algorithms

Control algorithms are, by definition, designed and tuned based on a model of how a system works, ranging from the simple (knowledge of whether a manipulated input increases or decreases the output) to the complex (sets of nonlinear partial differential equations). This range trades off ease of design and implementation and possibly robustness to uncertainty with performance and ability to fine-tune and learn. These trade-offs become increasingly challenging when delays separate action and effect. Currently available insulin pumps utilize simple algorithms to incorporate current glucose levels into suggestions for bolus doses (the “bolus calculator” or “bolus wizard” features), with the availability of glucose trend from continuous glucose sensors, more sophisticated algorithms can be developed.

The simplest form of a “partial” closed-loop system would be for the delivery of insulin to be suspended when the patient is hypoglycemic and not responding to alarms. Minimed has developed such a system, the Veo[®] Pump which is currently only available in Europe. When the glucose is below the hypoglycemic threshold (determined by the patient) and the patient does not respond to the alarm, insulin delivery is stopped for 2 hours.

The next step would be to stop insulin delivery based on predictive alarms, i.e. the subject would not need to be hypoglycemic before basal insulin delivery is attenuated or stopped. This would be particularly important overnight, when subjects fail to respond to over 70% of alarms⁴¹. In a clinical research center setting where basal insulin infusion rates were increased to induce hypoglycemia, predictive algorithms which triggered a suspension of basal insulin prevented hypoglycemia 75% of the nights when hypoglycemia was predicted to occur⁴², ⁴³. These algorithms could trigger a pump shut off without waking the patient, thereby also decreasing the incidence of sleep disruption due to alarms. In our reviews of nighttime CGM

monitoring during which a seizure occurred during the night, hypoglycemia was recorded on the sensor for a minimum of 2 ¼ hours prior to a seizure⁴⁴, so with this safety window, a pump shut off over the night should prevent most episodes of nocturnal seizures and dead-in-bed (4 hours of nocturnal hypoglycemia ⁴⁵), unless a large dose of insulin had been given prior to bed. Another retrospective approach would be to have a computer program review 3–6 days of CGM and pump data looking for patterns. This can be done by dividing the day into 3 hour windows with windows beginning when a meal bolus has been given. Time blocks beyond the meal blocks can be used for adjustment of basal insulin infusion rates. For a patient is using an insulin infusion pump this can be accomplished by downloading both the sensor and pump information into a common file. If there is a consistent trend seen over multiple days, this could generate a recommendation to the patient to change either a basal rate or a carbohydrate to insulin ratio for a particular meal. These suggested doses would be more accurate than what physicians initially calculate and would allow for testing of algorithms before fully closing the loop. A third partial approach to closing the loop would be to have an algorithm incorporated into the insulin infusion pump which includes glucose rate of change information as well as insulin action profiles into the bolus calculator. This would allow adjustment of meal bolus doses and basal infusion rates based on glucose trend analysis as well as glycemic targets, but the final decision on insulin delivery is done by the user.

Another partial approach to a closed-loop system would be to have a “control-to-range” algorithm that would only be active when blood glucose levels are projected to be above a user defined upper target (perhaps 160 to 180 mg/dl) or below a lower target (perhaps 70–80 mg/dl). The JDRF artificial pancreas consortium is planning studies in the next year on a “control-to-range” algorithm in a clinical research center setting, and the JDRF has also signed an agreement with Animas to bring such an algorithm to the market in 4 years.

To create a fully functional artificial pancreas there must be an algorithm which determines insulin delivery. Several algorithms have been proposed including a proportional-intergral-derivative (PID) algorithm⁴⁶, model predictive control^{47–49}, and adaptive neural networks⁵⁰. The first of these models to be tested in humans has been the proportional-integral-derivative (PID) algorithm³. At each point in time the controller assesses how far the current glucose is from the desired glucose (proportional), the rate of change in glucose (derivative), and how long the glucose has remained above or below target (integral). In these CRC studies on 10 subjects with type 1 diabetes who were on the artificial pancreas for 30 hours, the PID controller achieved excellent control overnight, but there was mild hyperglycemia following meals, particularly breakfast, and a tendency for hypoglycemia 4–6 hours following meal insulin delivery³. These issues can be partly addressed by using a feed-forward algorithm where a partial meal bolus is given 5–15 minutes before the meal, i.e. a “hybrid” closed-loop. This approach was initially tested at Yale and resulted in a significant improvement in post-prandial hyperglycemia⁵¹. The basal rate can also be decreased several hours after a meal to compensate for the insulin onboard from the meal bolus. With extended hyperglycemia the integral component can become significant, and can only be decreased by a corresponding area under the curve below the target. To prevent this from happening, constraints can be placed on the insulin infusion rates using techniques such as “reset windup”⁵².

In model predictive control (MPC) the controller has a model of expected glucose values and responses to insulin which may vary by time of day (dawn phenomenon), meal events, changes in insulin sensitivity. At each point in time the model compares the predicted glucose with the actual glucose and the model is then updated with a new prediction horizon. At each step the model takes into account the previous history of glucose measurements and insulin delivery and model may be updated to learn from discrepancies between actual and predicted values, and then the optimization is repeated. How to best update the model to correct for model mismatch is one of the major challenges to MPC. MPC has been utilized in a simulated

patient⁴⁷, and there are some short term studies in humans^{53, 54}. It should be noted that MPC is a basic strategy or concept, but any number of model types can be used, with many different methods of performing the optimization. Classic MPC uses a fixed linear model, but there have been many formulations using nonlinear models⁵⁵, including artificial neural networks⁵⁶. A nice feature of an optimization-based approach is that different weighting on the control objective can be used depending on whether the glucose is entering hyperglycemia or hypoglycemia conditions. Also, multi-objective optimization techniques can be used to rank order the important objective; for example, the highest ranked objective might be to avoid hypoglycemia.

Potential future applications of a closed loop system

One of the most promising uses for CGM and a closed loop system may be in the intensive care unit. Tight glycemic control in the intensive care unit has produced dramatic improvements in morbidity and mortality⁵⁷. A glucose sensor which provide glucose information to the subject every few minutes (real-time CGM) has functioned well in an ICU setting even with variable changes in the core body temperature, use of inotropes, and body-wall edema⁵⁸. When intravenous glucose infusions are provided at a steady rate, the blood glucose fluctuations associated with oral absorption of meals is avoided. In an ICU setting insulin is delivered intravenously, which significantly improves the pharmacodynamics of insulin delivery in a closed loop system, since it has a more rapid onset of action and a shorter duration of action. The intensive care unit may therefore be one of the initial settings where closed loop delivery of insulin using a continuous glucose sensor will be implemented.

Another use would be to prevent continued glucotoxicity. Islet glucotoxicity occurs at the onset of type 1 diabetes and even occurs with type 2 diabetes. When β -cells are stimulated by hyperglycemia they express increased levels of β -cell antigens^{59, 60, 61, 62, 63, 64, 65}, and are more susceptible to damage by cytokines^{66, 67, 68, 69}. One potential use of a closed-loop system would be at the onset of diabetes to limit glucotoxicity. The effectiveness of this therapy was demonstrated by studies done by Shah and Malone using a Biostator for 2 weeks at the onset of diabetes to preserve c-peptide secretion⁷⁰. Prevention of glucotoxicity at the time of transplantation could also prolong the life of the transplanted islets.

Strict metabolic control of blood glucose levels should be beneficial in many situations in the future treatment of diabetes. Initial applications will need to be in a research setting with further expansion into intensive care units and other inpatient settings. Eventually these studies may provide the basis for the FDA to approve the use of closed-loop for daily outpatient use.

Conclusion

Even with constant vigilance, current diabetes therapy does not prevent the fluctuations in blood glucose values. The most motivated patients find it difficult to achieve good control with a hemoglobin A1c <7% over multiple years, even with the currently available insulin infusion pumps and continuous glucose monitoring systems. A closed-loop insulin delivery system could significantly decrease the patient burden of managing diabetes and should decrease the risks of both hyper and hypoglycemia.

However, there are multiple factors which will eventually determine the feasibility of an ambulatory, outpatient closed loop system. The system will have to be safe, and have a very low incidence of significant hypoglycemia. Currently children with a HbA1c of 6.8% spend about 15 minutes each day with glucose values < 50 mg/dl and about 5 minutes each day with glucose values < 40 mg/dl according to FreeStyle Navigator CGM readings⁷¹. These children had no severe hypoglycemic events recorded. A closed-loop system should do better than this, and there should be no values < 50 mg/dl for it's use to be considered safe.

An initial closed-loop system ready for clinical use may have only limited goals; for example, automatically decreasing or stopping insulin delivery to prevent hypoglycemia rather than aiming for complete normalization of glucose values. Latter models will control nocturnal glucose levels and postprandial hyperglycemia. Much of the progress will be based on demonstrating safety of the proposed algorithms, but much additional work needs to also occur in making the devices unobtrusive, comfortable, and easy to wear and use, perhaps integrating them into smart phones.

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Table 1

Hemoglobin A1c Goals by Age

Age	Target Range*	HbA1c
0–5 years	80–200 mg/dL	7.5–8.5%
6–11 years	70–180 mg/dL	Less than 8%
12–20+ years	70–150 mg/dL	Less than 7%