

Can We Really Close the Loop and How Soon? Accelerating the Availability of an Artificial Pancreas: A Roadmap to Better Diabetes Outcomes

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Abstract

Development of a closed-loop artificial pancreas has been a long-time goal that could transform diabetes management. The primary limitation until recent years was the lack of a robust and portable continuous glucose sensor. There has been significant progress over the past 5 years in the development and commercialization of continuous glucose monitoring (CGM) devices. Used adjunctively, CGM has been demonstrated to add significant value in improving diabetes management by increasing time spent in glycemic targets and improving overall glycemic control. However, these benefits are limited by the human user's finite capacity to respond to the data provided by the device. By automating even a portion of the insulin delivery functionality of combined sensor/pump systems via computer algorithm, impending excursions could be handled more quickly and effectively. This review will describe very promising preliminary closed-loop studies, describe a potential roadmap to an artificial pancreas that will be safe and effective, and propose a solution—a hypo- and hyperglycemia minimizing control-to-range approach—that may allow for near-term delivery of a semiautomated system to people with diabetes.

Introduction

IT HAS BEEN MORE THAN 15 YEARS since the publication of the landmark Diabetes Complications and Control Trial (DCCT).¹ The DCCT found that improved glycemic control resulted in a significant decrease in risk of diabetes complications. The DCCT changed the standard of care in diabetes and ushered in widespread use of self-monitoring of blood glucose, insulin pumps, and novel forms of insulin. Although these new tactics have produced significant decreases in average blood sugar values, glycemic control in patients with diabetes remains suboptimal. Today, the majority of people with diabetes are not achieving recommended target glycemic control levels,² and hypoglycemia continues to be a major barrier to tight glycemic control.³ For many years, hope has been held that a mechanical solution for diabetes management could be developed that would restore near-physiologic glycemic control automatically—a so-called artificial pancreas.⁴ Such a system would require three main elements: insulin delivery, continuous glucose sensing, and a controller or algorithm that, like the beta cell, regulates the proper amount of insulin delivery at the proper time. But, with no such systems commercially available today, the simple question remains: why hasn't an artificial pancreas been realized?

The answer to this question lies with the need for patient safety. Food and Drug Administration approval to deliver an artificial pancreas system to market in the United States hinges on the system being proved safe and effective. Preliminary studies of prototype closed-loop systems have shown outstanding efficacy,^{5,6} but there is still the risk that sensor inaccuracies could result in misleadingly high interstitial fluid glucose readings when the blood glucose is actually much lower. This scenario could lead to overdosing of insulin and the risk for the induction of severe hypoglycemia.

Here it is proposed that this risk can be mitigated significantly and an artificial pancreas can be developed in the near future with existing glucose sensor technology, as long as the specifications of the system are properly defined. A fully automated, completely hands-off closed-loop embodiment of an artificial pancreas would likely require glucose sensor technology that is more reliable and accurate, contains redundant components, and minimizes the risk of miscalibration. It would also likely require insulin with improved (faster) pharmacokinetics and pharmacodynamics.⁷ But a semi-automated, partial closed-loop system that is less aggressive in the target glucose control could be deployed with existing continuous glucose sensor technology in the near future and result in significant improvements in glycemic control by

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reducing both the frequency and severity of high and low glycemic excursions. Such a path to a partial closed loop, as compared with the more challenging fully automated system, calls to mind the old adage of not letting the perfect be the enemy of the good.

Rationale

The Juvenile Diabetes Research Foundation (JDRF) Artificial Pancreas Project (APP), which launched in 2006, is an effort to accelerate the delivery of technologies that improve glycemic control to people with diabetes, culminating in a fully automated artificial pancreas. There have been vigorous debates about which is the proper or most likely approach to achieve closed-loop control. In the JDRF APP, the “form factor” that is envisioned is the combination of an external insulin pump and continuous glucose monitor—the so-called subQ-subQ approach.^{8,9} While there may be conceptual and physiologic benefits to other approaches, e.g., implanted pumps with intraperitoneal insulin delivery, development of a system that takes already developed technologies and maximizes their potential may allow for the delivery of such a system to market in an accelerated time frame. Continuous glucose monitoring (CGM) and continuous subcutaneous insulin infusion are both powerful approaches to improve diabetes control, but either approach alone has limitations that make achievement of target glycemic control levels incredibly difficult for the majority of people with diabetes.

CGM Today

In the past 3 years, continuous glucose monitors from three manufacturers have been approved by the Food and Drug Administration. Each of these monitors utilizes a similar mechanical approach with a wire-based sensor that sits between 6 and 12 mm subcutaneously and measures interstitial fluid glucose levels. Continuous monitoring had for many years been extremely appealing in concept: rather than a limited number of individual measurements every day, a continuous glucose monitor provides readings every 5 min (288 readings per day) or every 1 min (1,440 readings per day), which allows for trend analysis in real-time. CGM devices also provide hypo and hyperglycemia alarms—and in some models, predictive alarms—that forewarn of the potential to cross high or low thresholds.

A number of studies have demonstrated the power of CGM to improve glycemic control.^{10–13} Recently, the JDRF CGM study group demonstrated in a large randomized trial that patients utilizing a continuous glucose monitor achieved significantly better glycemic control than those who did not and, importantly, did so without an increase in hypoglycemia.¹³ This study may signal a transformation of the treatment of diabetes from a multi-single-point measurement paradigm to a continuous and trending prospective paradigm.

While CGM is proving to be a major advance, there are limitations with this relatively nascent technology. One limitation of all diabetes devices, which continues with CGM, is ease-in-use and wearability. One finding in the JDRF CGM Study and others¹² is CGM underutilization in children and young adults and decrease in use over time. Smaller and easier-to-use devices will likely promote increased adoption and more consistent and effective use over time.

Another challenge that faces diabetes devices, CGM included, is the patient’s limited ability to react to the information at all times. While CGM provides patients a much more detailed view of glycemic control in real-time, including alarming the patient when glucose levels deviate from target ranges, patients do not or cannot always respond to deviations for a number of reasons. Figure 1 highlights a significant and unfortunately common problem that could be addressed with improvement of today’s technologies. In this is a 24-h glucose tracing of a patient wearing a real-time continuous glucose monitor. Note that there was non-responsiveness to eight hypoglycemia alarms in this 17-year-old girl over a period of approximately 150 min overnight. Also note that during this non-responsive time the pump not only continued to dispense insulin at the rate of 1.5 U/h, but ramped up to a higher basal rate during this time of profound hypoglycemia. Unfortunately, the rebound seen after the last alarm was due to treatment of a hypoglycemic seizure. It is disappointing that our best-available therapy still continues to deliver insulin when the system should ostensibly “know” that there is profound hypoglycemia and non-responsiveness. Data from Buckingham et al.¹⁴ suggest that, despite both vibration and audible alarms at nighttime, patients (and parents) fail to awake the majority of the time. Prevention of nocturnal hypoglycemia by automatically reducing or stopping insulin delivery may be readily achievable quickly with a partially closed-loop system.

As with hypoglycemia alarms, patient response to hyperglycemia alarms is not always ideal. Non-responsiveness to repeated hyperglycemia alarms can lead to accumulation of time spent hyperglycemic and negatively impact long-term glycemic control. Below, a road map will be presented to address these limitations of current CGM device/pump treatment and do so with quantifiably low risk and significant potential benefit.

Can We Close the Loop?

Can we close the loop today given the state of the art, and what will it take to restore euglycemia with a mechanical system? A fully “closed loop” would be a system that doses insulin automatically, unlike today’s “open loop” systems in which patients must interpret multiple variables and make insulin dosing decisions themselves. In the following discussion and figures a pathway will be presented that aims to close the loop using a series of *clinically significant* steps that will be improved upon as the various technological components of the system evolve. Note in Table 1 a brief summary of some studies that report the relative time a person with type 1 diabetes spends in the hypoglycemic, euglycemic, and hyperglycemic ranges each day. It is startling that well-controlled patients (judged by average hemoglobin A1c) spend significant time each day hyperglycemic and over an hour each day with hypoglycemia. Furthermore, data from Nathan et al.¹⁶ suggest that the average person with diabetes in the United States has a mean blood glucose that is twice that of a person without diabetes. Given these statistics, efficacy will likely be easier to demonstrate than safety. The risk in all closed-loop research is that a control algorithm may signal for the delivery of insulin when not needed and potentially drive a subject into severe hypoglycemia. This scenario can be avoided with a system with the proper specifications and control targets

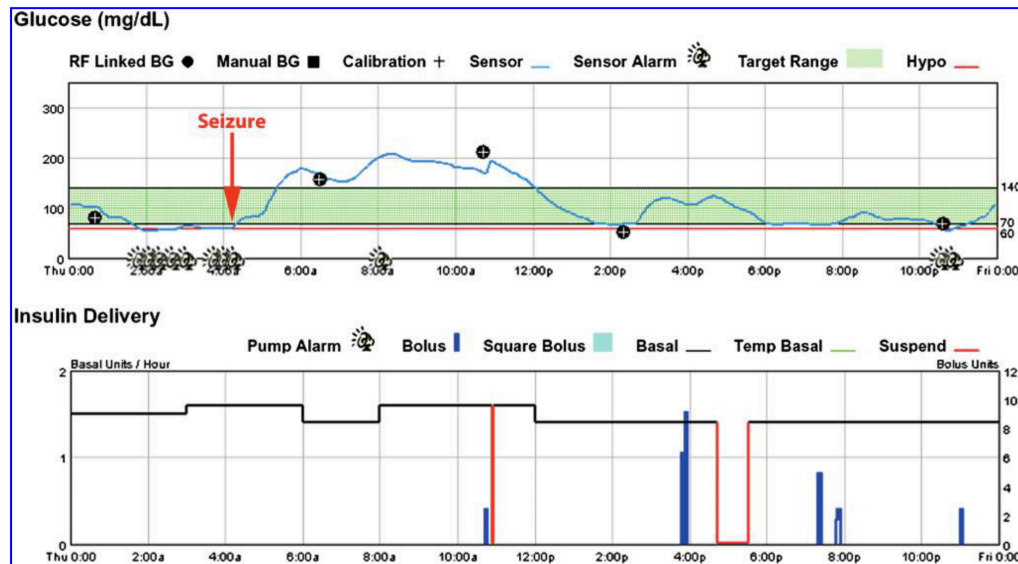


FIG. 1. Non-responsiveness to severe hypoglycemia. A 24-h glucose and insulin delivery profile for a 17-year-old girl with type 1 diabetes highlights non-responsiveness to multiple low glucose alarms and simultaneous automatic increase in basal insulin delivery during this profound hypoglycemia. RF, radio frequency.

with sufficient buffers to significantly reduce risk of a dangerous failure.

Today

The baseline for a roadmap for closing the loop will be the accuracy, robustness, and feature set of today's CGM devices and insulin pumps. Figure 2, curve A shows a 24-h glucose tracing and highlights the functionality of the three devices currently on the market in the United States. All three devices offer a variety of features that are system dependent (which unfortunately are not standardized), but may include high and low thresholds, predictive alarms, trend arrow, and a very low alarm.

TABLE 1. GLYCEMIC EXPOSURE

	HbA1c in reference				
	NR in Bode et al. ¹⁵	7.1% in DirecNet ¹²	JDRF CGM Study ¹³		
			7.6%	8.0%	8.0%
Average age (years)	45.3	11.2	42.9	18.5	11.5
Exposure					
<70 h	2.3	1.1	1.4	1.7	0.9
70–180 h	14.5	12.5	13.9	11.6	11.3
>180 h	7.2	10.4	8.7	10.7	11.8

Exposure in hours to hypo- and hyperglycemia in three studies demonstrates significant exposure in well-controlled patients. NR, not reported. Numbers in bold type highlight time spent hypo- and hyperglycemic, respectively.

Automation in Stages

1. Very-low glucose insulin pump shut off, with the goal to reduce severe hypoglycemia exposure/hypoglycemic seizures

A logical first step towards a closed-loop system would be to prevent or minimize exposure to severe hypoglycemia and scenarios such as the one described in Figure 1. Hypoglycemia remains the primary limiting factor to the achievement of tight glycemic control and causes a relative risk of death that is still high.³ Seizures due to hypoglycemia are one of the most feared aspects of diabetes for both patients and parents of children with diabetes. Data suggest that seizures due to hypoglycemia occur after prolonged periods (2.3–4 h) of severe low blood sugar.¹⁷ A logical—and one might argue obvious—first step is a very-low insulin shut-off system. Currently, when a patient is experiencing profound hypoglycemia and is non-responsive to system alarms, the insulin pump will continue dispensing basal insulin. In a very-low shut-off system the pump would suspend insulin delivery upon non-responsiveness to a hypoglycemia alarm or alarms (Fig. 2, curve B₁). This would not prevent hypoglycemia per se, but it may prevent a significant percentage of severe hypoglycemia and hypoglycemia seizures, which can be life threatening (Fig. 2, curve B₂). There would be very little risk in such an approach. The main potential risk would be a pump that turned off when in fact the glucose was not low, potentially leading to hyperglycemia and, in the worst case, ketoacidosis. Studies^{18,19} performed to date have shown this to be a very low risk, particularly if the shut off is limited to a maximum of 120 min. Encouragingly, data were presented at the recent Advanced Technologies and Treatments for Diabetes Meet-

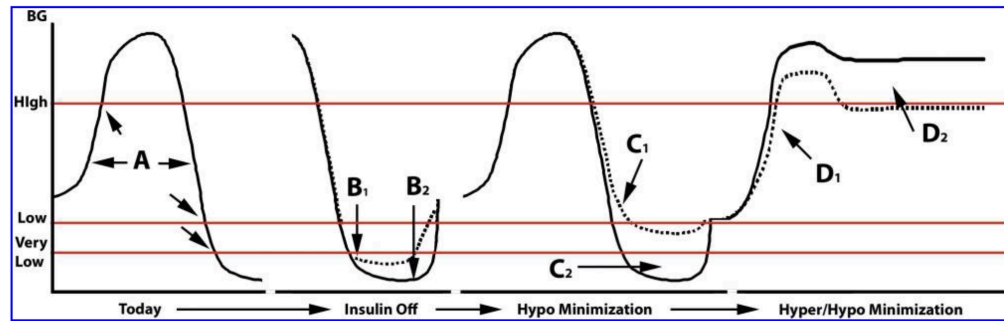


FIG. 2. Pathway from CGM to partial insulin automation: curve A, current CGM alarms including predictive and threshold alarms; curve B₁, insulin-off feature suspends insulin delivery, which would minimize risk for sustained severe hypoglycemia (curve B₂); curve C₁, predictive reduction or suspension of insulin deliver resulting in minimized hypoglycemia exposure (curve C₂). Curve D₁ adds to curve C by automatically dosing insulin to reduce hyperglycemia exposure (curve D₂) in addition to hypoglycemia minimization. Note that this automated insulin delivery aims to reduce exposure but targets reduction back below the high threshold, not to a lower euglycemic target (curve D₂).

ing²⁰ describing preliminary studies of a Medtronic Minimed (Northridge, CA) system with this functionality that is expected to be launched to market in 2009 in Europe.

2. Predictive hypoglycemia minimizing system, with the goal to reduce hypoglycemia exposure from current 1+ h/day average

Another potentially very low-risk, but important, step that may be deliverable to patients as a product in an accelerated timeframe is a predictive hypoglycemia minimizing system (Fig. 2, curve C). When impending hypoglycemia is predicted by such a system and the patient is unresponsive to warning alarms, the system would automatically begin to reduce or cease insulin delivery in an attempt to minimize exposure to hypoglycemia (Fig. 2, curve C₁). In this scenario, an algorithm would continuously monitor glucose levels and would aim for more accurate prediction of impending hypoglycemia. Increased accuracy may come via the combination of algorithmic approaches as described by Buckingham et al.¹⁸ It is very important to be clear that such a system will likely not prevent all hypoglycemia, but instead will significantly reduce exposure to hypoglycemia as compared to current therapeutic options (Fig. 2, curve C₂). The risk of hyperglycemia in such a system, as with Stage 1 above, would in theory be very low. By using an algorithmic approach, the system could resume basal delivery in a time frame that is shorter than some predefined maximum shut-off time (such as 120 min).

3. Predictive hypoglycemia and hyperglycemia minimizing system, with the goal to reduce hypoglycemic exposure as above and reduce hyperglycemic exposure from current 9+ h/day average

Perhaps the biggest step in the field of closed-loop research will be the first system that automatically doses insulin. The challenge, as stated above, is the risk that a continuous glucose monitor will provide such a system with a high reading

when the actual glucose level is significantly lower, and thus drive unnecessary insulin delivery and risk causing hypoglycemia. A third stage of automation is proposed here as a potential solution to this problem. In this stage, the system would function exactly as the predictive hypoglycemia minimizing system, but with a mirror capability on the hyperglycemic end. As seen in Figure 2, curve D, upon impending hyperglycemia to which the patient is non-responsive, this system would automatically dose insulin (Fig. 2, curve D₁). The amount of insulin that would be dosed would not be aimed at restoring euglycemia to a low set point, but rather at minimizing exposure to hyperglycemia (Fig. 2, curve D₂).

There have been a number of studies published that demonstrate significant hyperglycemia exposure at given A1c levels (Table 1^{12,13,15}). Perhaps the proposed hyperglycemia minimizing system will have a response threshold of 180 mg/dL, or perhaps higher, depending on the expected clinical benefit. One way to define a safe high point in a more quantitative manner will be the retrospective analysis of paired interstitial glucose and blood glucose readings and a priori definition of a hyperglycemia threshold at which the risk of inadvertent system-caused hypoglycemia is acceptably low. There has been considerable discussion about the accuracy of continuous glucose monitors, particularly in the hypoglycemic range, and whether the current generation of sensors would be reliable enough to control insulin delivery.²¹ Errors in the E portion of the Clarke Error Grid would be particularly problematic. However, errors in the E zone are uncommon, and this conservative approach, likely combined with a number of other safeguards, could provide a significant buffer that may allow for very safe operation.

While a hyperglycemia/hypoglycemia minimizing system would be imperfect, the data referenced above suggest that it could have a considerable and potentially transformational clinical impact. Such a system would maximize the strengths of today's CGM devices, while appreciating that to set more aggressive targets the sensors may likely need to evolve. Such an approach will allow for a quantitative empirical definition of the hyperglycemia threshold. This risk of system-driven

hypoglycemia can be mitigated by a number of safety features led by the appropriate conservative set point. Research in the JDRF APP has begun to define and quantify the associated risk as the hyperglycemia threshold is varied. Appealingly, this hyperglycemia minimizing approach may be most effective in those patients who struggle the most to realize the potential of newer technologies such as CGM—i.e., adolescents and young adults.

4. Overnight control: hybrid closed-loop, with the goal to automate to a euglycemic set point overnight with some meal announcement to achieve further reduction in hyperglycemic exposure

A challenge to achievement of non-diabetes-like euglycemia with a subQ-subQ approach that has become obvious in preliminary closed-loop experiments is the very slow action of insulin delivered subcutaneously—including insulin analogs—relative to a pancreas that produces insulin and delivers it directly into the portal bloodstream.⁷ Evolution from the proposed antihypoglycemia/antihyperglycemia system to a system that targets a lower set point will likely require additional improvement of the sensor component of the system, perhaps incorporating redundancy in the data collection, to ensure safety. However, even with a perfect sensor, insulin kinetics will remain a challenge. Weinzierl et al.⁶ have demonstrated the feasibility of using a “hybrid” approach with very promising results. By bolusing approximately one-third to one-half of the anticipated insulin just prior to meal consumption, the group found significant reduction in postprandial hyperglycemia and maximum glucose level. This approach would be the first mostly automated approach, which in addition to improved glycemic control may lessen the burden of diabetes management significantly.

Recently, Hovorka²² has presented impressive data from preliminary studies of a fully automated approach to overnight control. His group demonstrated the ability to achieve target glucose levels with significant reductions in hypoglycemia exposure compared to open-loop control studies. Overnight control is currently very challenging when using the current “open-loop” approaches, including CGM, but in preliminary closed-loop studies significantly improved con-

trol, compared to the open loop portion of the experiment, has been achieved.^{5,6,22} Closed-loop control overnight could have a significant clinical impact as well as potentially improve what is often a difficult and sometimes frightening time for patients and parents of children with diabetes. Figure 3 details evolution from current open-loop control, which is represented by the solid black line, to overnight control (dotted black line), to hybrid and ultimately fully closed loop control.

5 and 6. Fully closed-loop and multi-hormone systems, with the goal to minimize/eliminate user interactions for the most part, restore euglycemia, and ultimately mechanically mimic non-diabetes physiology

Evolving beyond proposed Stage 4, the hybrid closed-loop system will mean evolving towards perfection. Stages 1–4 do not really represent an artificial pancreas, but rather the incremental automation of insulin delivery. A more physiologic and truly more “artificial pancreas”-like system will require more robust and accurate continuous glucose sensors. It may require two independent and redundant sensor systems operating simultaneously: one controlling the insulin delivery and the other acting as a sentinel system monitoring the primary sensor and the overall system performance. It may be possible to achieve improved glycemic control with the use of other hormones. In studies performed by El-Khatib et al.,²³ glucose control, with minimal postprandial excursions and no hypoglycemia or rescue carbohydrates, was achieved using a combination of glucagon and insulin in a swine model of diabetes. This group is currently performing human trials and has demonstrated similar outstanding performance in humans.²⁴ Studies are underway examining the effect of other relevant hormones such as the amylin analog pramlintide on the potential design of a fully automated artificial pancreas system. There has been debate regarding glucagon and whether the addition of that hormone will add another layer of safety to a closed-loop system. This possibility must be carefully considered and will require further research. The normal accident theory approach²⁵ suggests that significant caution should be applied when designing a control system that relies upon a rescue approach such as the administration of glucagon. Furthermore, such a multi-hormone approach

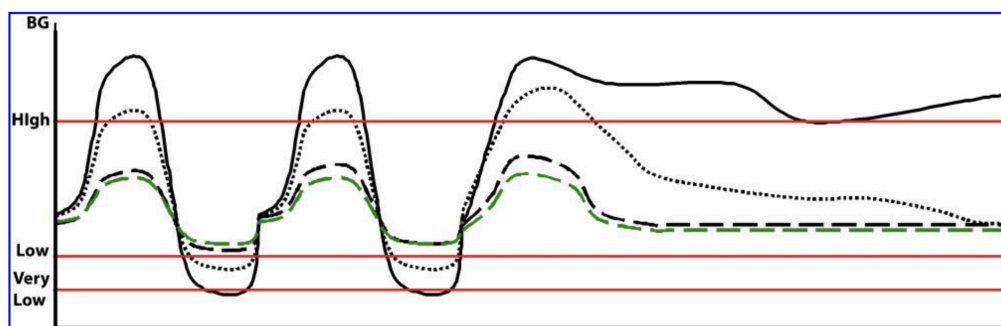


FIG. 3. Evolution towards a fully closed loop. Comparison of theoretical improvements from today (solid black line) to automated control overnight (dotted black line), which would reduce hyperglycemia and hypoglycemia exposure. Subsequent generations of controllers would function 24 h/day, require less human intervention (black dashed line, fully closed loop), and more closely mimic non-diabetes glucose patterns (dashed green, multi-hormone closed loop).

will require dual-chamber pumps to be developed and re-labeling of glucagon or other hormones that may be utilized. Therefore, though the development of a multi-hormone system is very appealing because it may be more physiologic than insulin alone, the time to deliver such a system to market may be longer.

Challenges and Potential Time Frame

There are a number of challenges that will need to be addressed before closed-loop systems reach patients with diabetes and have a clinical impact. The current generation of continuous glucose sensors are interstitial fluid-based, and by nature interstitial fluid glucose lags blood glucose. Reliability of sensor signal will be an issue. Miscalibration of the system may be the largest concern for such approaches, and more sophisticated algorithms that cue for calibrations at the appropriate time and frequency will almost certainly need to be incorporated into closed-loop control systems. Some studies question the accuracy of CGM devices and whether the current devices are fundamentally suitable for insulin dosing.²¹ Pilot studies referenced above^{5,6,18,22,24} suggest that there is no fundamental problem. Rather, the challenge for initial closed-loop controllers will likely be data quality and calibration. Another important consideration is the algorithms that will drive the automated control of insulin delivery. This review has not focused upon the algorithmic challenges and variety of approaches that show great promise are being developed.^{5,26–28} These approaches will need to be compared to determine which is most robust and suitable for use in a commercial system. However, it may be that approaches such as described by Dassau et al.,²⁸ which combines algorithmic approaches to leverage the strengths of each.

The dynamics of human physiology and the uncertainty of mechanical delivery of insulin will provide a number of challenges to a closed-loop system, particularly as such a system becomes more automated. Just a few such challenges may include gastroparesis, changes in insulin sensitivity/insulin uptake, exercise-induced changes in insulin sensitivity, puberty, menstrual cycle, etc. Such challenges at a high level may initially seem insurmountable. However, again this recalls the old adage of perfection being the enemy of the good and definitions of success. Initially, the goal for first-generation systems would be to add automation in a way that improves upon today's open-loop therapy. Mimicking human physiology may never be fully attainable, but algorithms will likely evolve to become "smart"—learning about each individual and self-tuning to be more aggressive or conservative in response to these physiologic challenges. In the meantime, preliminary experiments of first-generation algorithms, both Proportional-Integral-Derivative and Model-Predictive Control have shown superiority, in the face of many of these challenges, over open-loop control. Outpatient trials in a broader spectrum of patients will be necessary to test many potential scenarios that could prove challenging a closed-loop controller, but if the comparator is open loop control and not non-diabetes, preliminary experiments suggest significant gains can be made, and such challenges are will be better addressed in a more than adequate manner.

Time frames to the realization of such systems are difficult to predict and fraught with potential roadblocks and unexpected challenges. However, this review has argued that

hypoglycemia—particularly severe hypoglycemia—and the first automated system—a semiautomated closed loop—may be attainable with today's currently available components. As noted above, Medtronic Minimed has announced the launch of an "insulin-off" system in 2009 in Europe. This is a very important first step. The roadmap above argues that the pathway to a "hyperglycemia/hypoglycemia minimizing system" may allow for utilization of currently available technologies and may be deliverable to market in a very accelerated manner. In 2009 the JDRF APP Consortium will be testing protocols and algorithms that may be incorporated into industry development plans. Development of a fully closed loop system is likely more than 5 years away. As described above, hardware will likely need to evolve and insulin kinetics will need to improve to realize a fully automated system.

Summary

Since insulin was first administered to save people with diabetes from certain death, significant advances in treatment have allowed for considerable improvements in quality of life and reduction of risk of the devastating short-term and long-term complications. However, challenges still exist. The average person with diabetes still maintains a mean blood glucose that is significantly elevated compared to a person without diabetes and still is challenged with hypoglycemia on a nearly daily basis. A closed-loop artificial pancreas has been a long-time "holy grail" that for many years seemed attainable, but never materialized. In the past 3 years, real-time continuous glucose monitors have ushered in a new era of diabetes management and brought us one step closer to the realization of an artificial pancreas. Preliminary data suggest that this goal is attainable if concerns about safety of such a system can be properly addressed. The pathway put forward here is one such approach. The goal of the JDRF APP is to help accelerate the delivery of such systems.

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