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Progress of artificial pancreas devices toward clinical use: the first outpatient studies

Steven J. Russell

Massachusetts General Hospital Diabetes Research Center, Boston, Massachusetts, USA

Abstract

Purpose of review—This article describes recent progress in the automated control of glycemia in type 1 diabetes with artificial pancreas devices that combine continuous glucose monitoring with automated decision-making and insulin delivery.

Recent findings—After a gestation period of closely supervised feasibility studies in research centers, the last 2 years have seen publication of studies testing these devices in outpatient environments, and many more such studies are ongoing. The most basic form of automation, suspension of insulin delivery for actual or predicted hypoglycemia, has been shown to be effective and well tolerated, and a first-generation device has actually reached the market. Artificial pancreas devices that actively dose insulin fall into two categories, those that dose insulin alone and those that also use glucagon to prevent and treat hypoglycemia (bihormonal artificial pancreas). Initial outpatient clinical trials have shown that both strategies can improve glycemic management in comparison with patient-controlled insulin pump therapy, but only the bihormonal strategy has been tested without restrictions on exercise.

Summary—Artificial pancreas technology has the potential to reduce acute and chronic complications of diabetes and mitigate the burden of diabetes self-management. Successful outpatient studies bring these technologies one step closer to availability for patients.

Keywords

artificial pancreas; bionic pancreas; continuous glucose monitoring; glucagon insulin; sensor-augmented pump

INTRODUCTION

Type 1 diabetes is unique in the amount of responsibility that patients must assume for disease management. They walk a tightrope, taking risks with each of an endless series of

Correspondence to Steven J. Russell, Massachusetts General Hospital Diabetes Research Center, 50 Staniford Street, Suite 301, Boston, MA 02114, USA. Tel: +1 617 72[0-9] x [0-9]848; sjrussell@mgh.harvard.edu.

Conflicts of interest

I have a patent pending on aspects of a bihormonal (insulin and glucagon) bionic pancreas; received honoraria or travel expenses for lectures from Tandem Diabetes, Sanofi Aventis, Eli Lilly, Dexcom, and Biodel; consulted for Medtronic and Sanofi Aventis; have received support for an investigator-initiated study from Abbott Diabetes Care; received technical advice and loaned equipment from Dexcom, Tandem Diabetes, SweetSpot Diabetes, International Biomedical, Abbott Diabetes Care, Insulet Corporation, and Medtronic; serve on scientific advisory boards for Tandem Diabetes and Companion Medical.

calculations and decisions. Maintaining blood glucose concentrations close to the nondiabetic range (a mean blood glucose less than 154 mg/dl) reduces the risk for complications including blindness, kidney failure, peripheral nerve damage, myocardial infarctions, and stroke, and for death [1–4]. However, reaching this glucose control target is very difficult, and most patients are not able to do so [5–7]. Even though the mean blood glucose of most patients is above goal, hypoglycemia is common, can be life-threatening, and is a barrier to further lowering of the mean glucose [8–12]. The level of effort required and the difficulty in achieving glycemic targets can lead to fatigue and burnout [13–15]. Use of continuous glucose monitoring (CGM) can improve glucose control [16]. However, this is at the cost of increased demands on the attention of the patient, and CGM use has not been associated with improved quality of life in randomized trials [17] – likely an important reason that less than 10% of patients with type 1 diabetes are CGM users [6].

There is a large unmet need for strategies to improve glycemic control that also reduce the demands upon patients. A device that combines a minimally invasive CGM with algorithms to automatically determine the dosing of insulin (and in some cases, glucagon) and administer these hormones is called an artificial, or bionic, pancreas. Dozens of feasibility studies performed in inpatient research ward settings have tested and refined a variety of algorithmic approaches over the last 10 years [18–19]. These studies were required to support the testing of artificial pancreas systems in outpatient environments, which present a much broader array of challenges than tightly controlled inpatient settings. This article focuses on outpatient studies that began appearing in 2013. Table 1 provides the glossary of useful terms.

LOW-GLUCOSE AND PREDICTIVE LOW-GLUCOSE SUSPENSION OF INSULIN DELIVERY

The simplest form of automation is suspension of insulin delivery at a low glucose threshold. In 247 patients randomized to sensor-augmented pump (SAP) with a threshold suspend feature vs. SAP alone (in which patients have access to CGM data but must act on it themselves) for 3 months, the hypoglycemia exposure (hypoglycemia area under the curve) was reduced by 38% at night and time less than 60 mg/dl was reduced (3.1 vs. 1.8%) without an increase in the hemoglobin A1c [20▪]. This technology is now commercially available in the USA. A further refinement of this approach is to suspend insulin delivery based on predicted hypoglycemia. In 45 patients randomized to SAP with predictive threshold suspend vs. SAP alone, the hypoglycemia exposure was reduced by 81% and time less than 60 mg/dl was reduced (4.8% vs. 1.5%) with a modest but significant increase in overnight mean glucose (125 vs. 132 mg/dl) [21▪]. A commercial device with a similar predictive low-glucose suspend technology is currently under study.

NIGHT-TIME-ONLY ARTIFICIAL PANCREAS

The first outpatient trials of artificial pancreas devices actively dosing insulin included only the nighttime period. The first of these trials to be published compared SAP with artificial pancreas over a single night each in 56 adolescents at a diabetes camp [22]. The number of episodes with glucose less than 63 mg/dl was significantly reduced from 22 to 7, and there

was a significant reduction in median overnight glucose level (140 vs. 126 mg/dl). A caveat is that the monitoring and hypoglycemic alarms were not the same between the two groups, so these differences could not be entirely attributed to insulin dosing by the artificial pancreas. A home use trial of SAP vs. the same artificial pancreas system in adolescents and young adults followed, and an interim analysis of 15 individuals over four nights each showed a reduction of median time less than 70 mg/dl (49 vs. 4 min per night) without a difference in median glucose level (134 vs. 130 mg/dl) [23▪]. A second, similar home use trial tested SAP vs. the system for 6 weeks each [24▪]. Of 24 subjects randomized, 19 completed the trial and met criterial for analysis. Time <70 mg/dl was significantly reduced (5.2 vs. 2.5%) and mean glucose was reduced (161 vs. 148 mg/dl).

An artificial pancreas system using a different algorithm was tested at night in two home use trials. In an adolescent trial, 16 individuals were randomized to SAP vs. artificial pancreas over 3 weeks each [25▪]. Time in range (70–144 mg/dl) at night was increased (47 vs. 64%) and mean glucose was reduced (151 vs. 137 mg/dl), whereas time less than 70% was not significantly different (0.9 vs. 1.4%). Mean glucose over 24 h was significantly reduced (162 vs. 153 mg/dl) even though the system was only used at night, demonstrating the contribution of the overnight period to overall glycemic control. In an adult trial, 24 individuals were randomized to SAP vs. artificial pancreas over 4 weeks each [26▪]. Time in range at night was increased (39 vs. 53%) and mean glucose was reduced (162 vs. 148 mg/dl), whereas time less than 70% was not significantly different (2.1 vs. 2.8%). Mean glucose over 24 h was significantly reduced (167 vs. 157 mg/dl).

These trials show that artificial pancreas devices can improve glycemic regulation overnight by a number of different metrics, with one system emphasizing reduction in hypoglycemia, the other emphasizing reduction in mean glucose without an increase in hypoglycemia. An outstanding question is whether regulatory agencies will approve a device that has not been shown to be safe for daytime use regardless of its efficacy during the night-time, because there are practical challenges with restricting use to the night-time period.

DAY AND NIGHT INSULIN-ONLY ARTIFICIAL PANCREAS

There have been two randomized trials comparing SAP with insulin-only artificial pancreas devices in outpatient settings during both the night and daytime. These trials exposed the artificial pancreas device to greater challenges than the night-time-only studies, namely meals and physical activity. In one study, 18 adult individuals participated in two 40 h experiments each, in random order, staying in a guesthouse or hotel with some outside excursions [27]. There were no restrictions on diet, and individuals participated in light exercise (walking), but vigorous exercise was not permitted. The artificial pancreas was initialized with each individual’s carbohydrate ratio, correction factor, and basal rate pattern. The carbohydrate count for each meal was announced to the artificial pancreas, and the meal bolus was calculated by the algorithm. The artificial pancreas reduced the mean time with glucose less than 70 mg/dl (1.25 vs. 0.7%) and significantly reduced the need for carbohydrates to treat hypoglycemia (mean of 2.4 vs. 1.2 episodes). However, there was a statistically significant increase in the mean glucose (152 vs. 161 mg/dl).

A much longer study under free-living, home use conditions compared SAP with a different artificial pancreas system over 7 days each, in random order, in 17 adults [28▪▪]. There were no diet restrictions and individuals were allowed to participate in light exercise (walking), but were advised against vigorous exercise. The artificial pancreas was initialized with each individual's basal insulin profile, total daily insulin dose, and weight. The meal bolus in both arms was given by the individuals based on their carbohydrate ratio but could be omitted for meals containing less than 30 g carbohydrate. Median time in the target range (70–180 mg/dl) was significantly increased (62 vs. 75%), and mean glucose was significantly decreased (158 vs. 145 mg/dl), whereas time less than 70 mg/dl was not significantly different (3.7 vs. 5%).

In both studies, the artificial pancreas was initialized with information about the pre-experiment insulin-dosing regimen. This allowed personalization of the algorithm, but is vulnerable to poorly optimized insulin parameters; this problem led to a discontinuation due to hypoglycemia in the first study. An artificial pancreas initialized in this way could not be the initial therapy for a newly diagnosed patient without an established insulin regimen. Although the artificial pancreas can adjust subsequent insulin delivery to compensate for insufficient or excess insulin, the requirement that individuals count carbohydrates leaves the system vulnerable to large errors on the part of the individual and doesn't relieve the burden of diabetes as much as approaches that do not require carbohydrate counting. Finally, artificial pancreas systems designed for use during the daytime will ultimately have to be tested without restrictions on vigorous exercise.

DAY AND NIGHT BIHORMONAL (INSULIN AND GLUCAGON) BIONIC PANCREAS

There have been two reports describing tests of artificial pancreas systems delivering both insulin and glucagon in the outpatient setting. In one, insulin pump therapy monitored with blinded CGM was compared with artificial pancreas over 48 h each in 11 individuals at home [29]. There were no meal announcements or exercise restrictions. The algorithm was initialized with an insulin sensitivity factor based on each individual's total daily insulin dose, and this sensitivity factor could be manually changed after the first 24 h. Median time in range (70–180 mg/dl) was not different on the first day, but was increased by the artificial pancreas relative to insulin pump therapy on the second day (66 vs. 77%), paralleled by a decrease in median glucose (159 vs. 139 mg/dl). However, although time less than 70 mg/dl was not significantly different on the first day (0.7 vs. 2.1%), it was significantly increased by the artificial pancreas on the second day (0 vs. 2.8%).

The other report described two distinct studies with an artificial pancreas that the authors call a bionic pancreas [30▪▪]. In a study of 20 adults, insulin pump therapy with or without unblinded CGM at home (usual care for the individual) was compared with artificial pancreas in a supervised out-patient environment (a hotel at night and free-living during the daytime) for 5 days each in random order. There were no restrictions on diet or exercise. The algorithm was initialized only with the individual's weight and autonomously adapted to each individual's insulin requirements. Meal announcements were encouraged but not required, and took the form of a rough estimate of meal size (typical, less than typical, or

more than typical amount of carbohydrates) rather than a carbohydrate count. Individuals announced approximately two-thirds of meals and snacks. Insulin boluses in response to meal announcements were initially based on body weight and then autonomously adapted toward 75% of the predicted insulin need based on previous meals. After 1 day of autonomous adaptation by the artificial pancreas, the mean glucose relative to usual care was significantly decreased (159 vs. 133 mg/dl), mean time less than 70 mg/dl was significantly reduced (7.3 vs. 4.1%), and mean time in range (70–180 mg/dl) was significantly increased (59 vs. 80%).

The second study in the same report [30▪▪] was an outpatient study of 32 adolescents in a diabetes camp comparing insulin pump therapy determined by camp physicians with artificial pancreas for 5 days each in random order. There were no restrictions on diet and exercise, and the same algorithm used in the adult study was initialized only with individual weight. The same qualitative meal announcements were used, but nearly all of the meals were announced in the camp setting. After 1 day of adaptation by the artificial pancreas, the mean glucose was significantly decreased (158 vs. 142 mg/dl), and mean time in the target range (70–180 mg/dl) was significantly increased (61 vs. 76%). The difference in the mean time less than 70 mg/dl was not significant (4.9 vs. 3.1%), but the need for carbohydrates to treat hypoglycemia was significantly decreased (once every 2.3 vs. 1.5 days).

INSULIN-ONLY VS. BIHORMONAL BIONIC PANCREAS

An active debate is whether an artificial pancreas should deliver insulin alone or insulin and glucagon. Glucagon is the most important counter-regulatory hormone in normal glucose physiology, and is released by the α cells of the pancreatic islet in response to impending hypoglycemia and exercise [31,12]. Glucagon promotes glycogenolysis by the liver, thereby countering the hypoglycemic effect of glucose clearance by other insulin sensitive tissues and noninsulin-dependent glucose uptake into muscle caused by exercise. The secretion of glucagon in response to hypoglycemia and exercise is lost in patients with type 1 diabetes, leaving them vulnerable to hypoglycemia [32–34]. Deficient glucagon secretion can result in hypoglycemia after autotransplant of normal islets into patients with pancreatitis, emphasizing the importance of glucagon even when insulin delivery (from normally functioning β cells) is optimal and directed to the liver [35▪]. Inclusion of glucagon in an artificial pancreas is intended to mimic the glucose control physiology of the normally functioning islet. A practical argument for use of glucagon is that even if insulin is dosed ‘correctly’ at any given point of time, the slow absorption of subcutaneously administered insulin means that the dosing may no longer be correct by the time it reaches the bloodstream, for instance if the patient starts to exercise in the interval. An insulin-only artificial pancreas can suspend insulin delivery and sound an alarm for impending hypoglycemia, but given the slow absorption of subcutaneously administered insulin suspension of delivery may not be effective to prevent hypoglycemia, and the alarm may not be effective if the patient is asleep [36,37] or does not have access to oral carbohydrates. In contrast, automatic glucagon delivery requires no action from the patient to prevent hypoglycemia. Glucagon is absorbed much more quickly than insulin after subcutaneous delivery (time to peak blood levels 15–20 min), and this increases its utility in preventing hypoglycemia.

An argument against the use of glucagon in an artificial pancreas is that insulin and glucagon may work against each other, thereby increasing the use of insulin. Data from the diabetes camp study [30▪▪], in which the conditions of the two arms were strictly comparable, does not support these concerns, as the insulin utilization was not different in the comparator vs. artificial pancreas arms (0.79 vs. 0.82 units/kg/day) despite a reduction in mean glycemia in the bionic pancreas arm. Another argument is that failure of glucagon delivery without corresponding failure of insulin delivery will increase the risk of hypoglycemia. This risk can be mitigated by appropriate tuning of insulin-delivery by the artificial pancreas algorithm and with engineering approaches to reduce the risk of undetected, isolated failure of glucagon delivery. In most common scenarios, the availability of glucagon will reduce the risk of hypoglycemia, and this must be balanced with the risk of rare glucagon delivery failure. The overall benefits and risks of glucose usage will become more clear in large, long-term free-living studies with the power to detect rare events. In addition, the safety of chronic, intermittent administration of micro-doses of glucagon will have to be established. A practical barrier to the use of glucagon in artificial pancreas systems is the relative instability of current formulations, which have to be freshly reconstituted daily. More stable formulations have been produced, and efforts to qualify them for human use are ongoing [38].

Both insulin-only and bihormonal artificial pancreas systems have shown benefits compared with comparators in clinical trials, but there are no published studies directly comparing them in the outpatient environment. A recent inpatient study compared a bihormonal artificial pancreas with an insulin-only version of the same system and SAP in a three-way crossover study [39▪▪]. Both the bihormonal and insulin-only artificial pancreas systems significantly reduced time in the hypoglycemic range relative to SAP, with the bihormonal system reducing hypoglycemia significantly more than the insulin-only system. In outpatient day and night studies, a bihormonal artificial pancreas achieved lower mean glucose with either similar or lower levels of hypoglycemia than insulin-only systems, despite fewer restrictions on activity and no requirement for carbohydrate counting [27,28▪▪, 30▪▪]. However, head-to-head trials in free-living settings will be necessary to assess the relative merits of these approaches.

CONCLUSION

Automated glucose control has the potential to dramatically improve glycemic regulation, reducing acute and chronic complications of diabetes, and mitigate the burden of diabetes self-management. Both insulin-only and bihormonal artificial pancreas systems have shown promising results in initial outpatient trials. The relative merits of these approaches should become clear with longer-term, free-living trials. Automated glucose control with an artificial pancreas is no longer a long-term, speculative prospect, but is likely to reach the clinic before the end of the decade.

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KEY POINTS

- There is a large unmet need for strategies to improve glycemic control that also reduce the demands upon patients.
- Automated suspension of insulin delivery in response to actual or predicted hypoglycemia can reduce hypoglycemia exposure.
- Day and night use of insulin-only artificial pancreas systems has been shown to reduce mean glycemia or hypoglycemia but not both in the same trial.
- Day and night use of a bihormonal artificial pancreas system has been shown to reduce both mean glycemia and hypoglycemia.
- Longer free-living, home use trials without restrictions on diet and activity will be necessary to evaluate the relative merits of insulin-only and bihormonal artificial pancreas systems.

Table 1

Glossary

Artificial pancreas	A device that uses glucose information, usually from a CGM, to determine the dosing of insulin, and in some cases glucagon, with the aim of regulating blood glucose levels. The drugs are typically infused into the subcutaneous tissue using insulin pumps and infusion sets.
Continuous glucose monitor	A device that uses a sensor implanted into the skin to measure the glucose in the interstitial fluid. This information is used to estimate the blood glucose level, typically by calibrating the device at intervals with blood glucose measurements. The sensors protrudes 31 cm into the subcutaneous tissue and use chemistry similar to that in glucometer strips. A transmitter connected to the sensor and adhered to the skin sends a wireless signal to a receiving device that displays and stores the estimated blood glucose values, typically every 5 min. The user can set alarms for glucose values above and below threshold values and for large rates of change.
Sensor-augmented pump therapy	A variant of continuous insulin infusion therapy (insulin pump therapy) for diabetes in which information from a continuous glucose monitor is used to inform decision making by the patient. In the United States no CGM is approved to replace capillary blood glucose measurement – the labeling of CGM devices specifies that are to be used for ‘tracking and trending’ purposes and that capillary blood glucose measurements should be used to guide therapy. However, the CGM alarms can be used to detect and deal with problems earlier than would be possible with intermittent BG testing and insulin doses can be adjusted for the blood glucose trajectory in addition to the absolute BG value.

BG, blood glucose; CGM, continuous glucose monitoring.