Artificial pancreas: the bridge to a cure for type 1 diabetes

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Summary

Tight glycaemic control in type 1 diabetes mellitus has been shown to be important for the prevention of long-term microvascular complications. Consequently, intensive insulin treatment has been advocated in the attempt to achieve normal glycaemia. This has proven challenging mainly due to an increased risk of hypoglycaemia associated with the intensive insulin regimen. Closed-loop systems for glucose control, designed to mimic the endocrine action of the healthy pancreas without human intervention, may provide a solution.

The vital component of a closed-loop system, often referred to as an artificial pancreas, is a computer-based algorithm. Other components include a real-time continuous glucose monitor and an infusion pump to titrate and deliver insulin. The role of the control algorithm is to translate, in real-time, the information it receives from the glucose monitor and to compute the amount of insulin to be delivered by the pump.

This review article describes the individual components of the artificial pancreas, and aims to highlight existing clinical evidence from studies performed on available artificial pancreas prototypes. Current limitations and obstacles facing this technology are reviewed, together with its potential direction in the future. By achieving normal glycaemia and reducing the risk of hypoglycaemia, the artificial pancreas could potentially improve the lives of patients with type 1 diabetes and act as a 'bridge' until a cure for type 1 diabetes is found.

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Key words

type 1 diabetes mellitus; artificial pancreas; closed-loop insulin delivery

Introduction

The incidence of type 1 diabetes in adults and children is increasing worldwide.[1,2] It is well known that tight glycaemic control reduces the risk of diabetes related complications.[3] For patients with type 1 diabetes, however, achieving tight glycaemic control through intensive insulin therapy remains challenging. This is mainly due to the ever present risk of hypoglycaemia, which is one of the most feared complications of insulin therapy as reported by patients, caregivers and health care professionals.[4,5]

In the last decade, the field of therapeutic devices for type 1 diabetes mellitus has evolved significantly and has led to significant improvement in the quality of life for patients. Current conventional insulin pump therapy, however, still requires the patient's decision and input to deliver the amount of insulin required. The 'holy grail' is to deliver insulin in an automated and continually glucose-responsive fashion. By integrating subcutaneous continuous glucose monitoring sensors (CGMS) with a subcutaneous insulin pump, it may be feasible to mimic the endocrine action of the pancreas, hence the term 'artificial pancreas'.[6] The artificial pancreas, also known as a closed-loop insulin delivery system, delivers insulin under the direction of a computerised control algorithm according to real-time continuous glucose sensor levels (see Figure 1). The artificial pancreas could potentially act as a 'bridge' until a cure for type 1 diabetes is found, while improving the lives of patients with type 1 diabetes.

The aim of this article is to describe the individual components of the artificial pancreas, and to highlight existing clinical evidence from studies performed on available artificial pancreas prototypes. The limitations and obstacles facing this technology are also reviewed, together with its potential direction in the future.

Components of the artificial pancreas

As previously stated, the artificial pancreas or closed-loop delivery system differs from conventional insulin pump therapy through the use of a control algorithm which directs insulin delivery according to real-time sensor glucose levels. The individual components of the artificial pancreas are described below.

Continuous glucose monitors

Modern continuous glucose monitors (CGMs) used in clinical practice are portable devices that continuously measure the patient's interstitial glucose level in 'real-time'.[7] New glucose readings are displayed every 1–5 minutes for up to seven days of continuous wear per sensor insertion. This provides more complete data on glucose levels and pattern, which otherwise would not be attainable using conventional self-monitoring glucose

meters. Using this information, patients can make immediate adjustments to their insulin doses, food intake and physical activity by inspecting glucose values and trends. In addition, most CGM sensors have built-in low and high glucose alarms, which provide an additional layer of safety for patients to respond and take the appropriate course of action.[8]

Examples of the present generation of CGMs include the Enlite® (Medtronic MiniMed, Northridge, CA, USA), Dexcom® SEVEN® PLUS (DexCom Inc, San Diego, CA, USA) and FreeStyle Navigator® (Abbot Laboratories, Alameda, CA, USA). These sensors utilise an amperometric enzyme electrode, which measures interstitial glucose concentration by detecting changes in current flow caused by the enzymatic catalysation of glucose.[9] Patients can wear the sensors for up to seven days, before needing to replace them. All CGM devices require the patient to calibrate the device, by performing approximately one to two finger stick blood glucose measurement(s) daily.

The main value of CGMs in clinical practice is in identifying trends in glucose values, thereby reducing the frequency and severity of hypoglycaemia events. A meta-analysis evaluating CGM use in adults and adolescents with type 1 diabetes reported a significant reduction in HbA_{1c}.[10] However, this finding was limited to those who used the sensors daily and with the highest HbA_{1c} at baseline. This highlights the importance of appropriately selecting patients for CGM use, if the benefit of this technology is to be realised.

Insulin pump

There are currently a variety of insulin pumps available in the market. Most modern insulin pumps are around the size of a pager, and comprise an insulin reservoir, a small battery-operated motor and a subcutaneous infusion set (cannula and tubing system). The insulin pump normally delivers rapid-acting insulin analogues. It mimics insulin delivery in a normal pancreas by infusing insulin at preselected rates – normally a slow basal rate with patient-activated boosts at mealtimes.[11]

Modern 'smart' pumps have a built-in customisable bolus calculator that allows the patient to input the amount of carbohydrate consumed and accounts for 'insulin on board' to reduce the risk of insulin 'stacking'. More recently, sensor-augmented insulin pumps have appeared on the market, such as the MiniMed Paradigm® Veo™ (Medtronic MiniMed, Northridge, CA, USA), which feature integration with CGMs.[12] An additional feature of sensor-augmented insulin pumps is the low glucose suspend (LGS) feature which automatically suspends basal insulin delivery for up to 2 hours when the CGM detects hypoglycaemia. This has been reported to reduce the risk of nocturnal hypoglycaemia, especially in patients who are most at risk.[13]

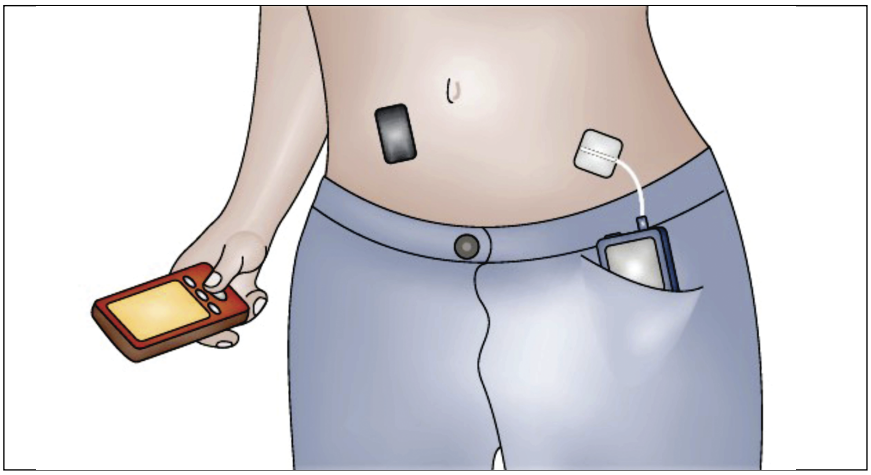

Figure 1. Illustration of a closed-loop system comprising a glucose sensor (rectangle on the left-hand side of the abdomen), an insulin pump (device in the pocket connected to patient via an infusion set) and a mobile-sized device containing the control algorithm (in patient's hand). Each component communicates with each other wirelessly. (From: Hovorka R. Closed-loop insulin delivery: from bench to clinical practice. *Nat Rev Endocrinol* 2011;7:385–95)[6]

Control algorithm

At present, the two main categories of control algorithm employed in closed-loop clinical studies are the model predictive control (MPC)[14–17] approach and the classical feedback proportional integral derivative (PID)[18–20] approach. The MPC controller uses a gluco-regulatory model which links insulin infusion and meal ingestion to glucose excursions.[15] It can be a physiological model representing fundamental gluco-regulatory processes and be adapted to different insulin-glucose relationships. The PID controller adjusts the insulin infusion rate according to departure from target glucose (the proportional component), the area under the curve between the ambient and the target glucose (the integral component) and the change in ambient glucose (the derivative component).[19] The total insulin delivery is the sum of all three components, and this is balanced by a set of numerical constants that may be derived from the subject's estimated insulin daily dose.

Several groups are currently studying the efficacy and safety of these control algorithms. In-silico testing or computer simulation

models are currently being used in closed-loop studies to provide preclinical testing of control algorithms.[21] Using this method, a virtual population of patients with real-life clinical information is created, using data comprising blood glucose levels, insulin delivery and carbohydrate content of parenteral and enteral nutrition. The computer simulation model will then evaluate, compare and optimise glucose control algorithms using the information available to it.[22,23]

Artificial pancreas prototypes

To date, several artificial pancreas prototypes have been studied in children and adults with type 1 diabetes. Research in closed-loop systems adopting the subcutaneous route includes the Artificial Pancreas Software (APS), a modular system supporting the wireless connection to a range of glucose sensors and insulin pump.[24] Medtronic's physiologic insulin delivery (ePID) system utilises the PID algorithm coupled with Medtronic's glucose sensor and pump.[25] The Florence platform from Cambridge uses Navigator CGM, the Aviator insulin pump and an MPC controller[26] (see Figure 2). The Boston artificial pancreas prototype delivers both insulin and glucagon by utilising manual closed-loop control adopting venous blood glucose measurement (GlucoScout®, International Biomedical), and an MPC algorithm for insulin delivery and a PID controller for glucagon delivery.[16] The Oregon prototype also adopts a dual hormonal delivery approach, using manual closed-loop control with a fading memory proportional derivative controller.[20]

Artificial pancreas studies

It is anticipated that the artificial pancreas will go through several developmental phases with increasing technology sophistication and more realistic treatment objectives.[27]

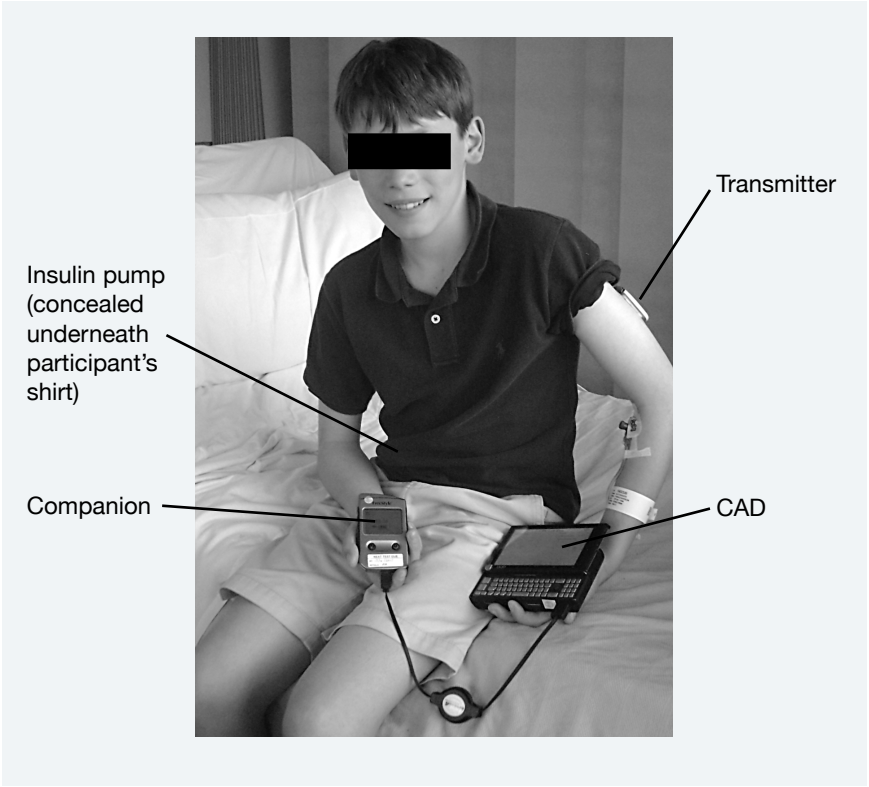

Figure 2. A study participant displaying the Florence closed-loop insulin delivery system, consisting of a handheld device (Companion) which receives and displays glucose value data from the FreeStyle Navigator Transmitter, communicating with the Control Algorithm Device (CAD) and controlling the subcutaneous insulin pump

The first generation is likely to provide benefits in terms of reduction of hypoglycaemia. An example of this is the low glucose suspend function, which is the first commercial application of the closed-loop insulin delivery. An insulin pump with an integrated continuous glucose monitoring (Paradigm Veo, Medtronic Diabetes, Northridge, CA, USA) is currently available, automatically suspending insulin delivery for up to 2 hours when hypoglycaemia is detected and hypoglycaemia alarm is not acknowledged by the patient. The aim of low glucose suspend is to reduce the severity of hypoglycaemia. Post-marketing studies in adults and children to date have documented significant reductions in the frequency and duration of nocturnal hypoglycaemia.[13,28]

Prevention of hypoglycaemia by discontinuing insulin delivery when pending hypoglycaemia was predicted has been tested by an algorithm developed by Buckingham *et al.*[29] This approach was able to prevent hypoglycaemia during the majority of the study nights (75% of nights) without causing rebound hyperglycaemia. Suspension of insulin delivery by up to 4 hours is reported to be safe in children and adolescents, based on safety and efficacy studies performed for PID and MPC controllers.[30,31]

As most severe hypoglycaemic events occur at night-time,[32] the potential for overnight closed-loop insulin delivery to reduce the incidence of nocturnal hypoglycaemia may provide a solution to an important clinical problem. When overnight closed-loop control was compared with conventional insulin pump therapy in randomised controlled studies in children and

adolescents, closed-loop control was associated with greater time spent in glucose target range, and the incidence of nocturnal hypoglycaemia was significantly reduced.[17] Similar results were shown in adults as well on overnight closed-loop insulin delivery.[26]

Closed-loop control during daytime is more challenging, as a variety of factors come into play such as variable dietary and physical activity patterns. The delay in absorption of subcutaneously delivered insulin, coupled with variable glucose appearance of meals, makes the postprandial period particularly challenging. If the closed-loop system delivers too much insulin in an attempt to correct high postprandial glucose levels without taking into account the delay in insulin absorption, late postprandial hypoglycaemia can occur. The phenomenon of 'insulin stacking', which can be seen in conventional insulin pump therapy, is potentially an issue with closed-loop control as well.

Several solutions have been studied to overcome these difficulties. One practical solution is to combine closed-loop insulin delivery with manual delivery of prandial insulin boluses (a hybrid closed-loop system). Significantly better postprandial glucose levels were observed when a fully closed-loop system was compared with the hybrid closed-loop system. Both the MPC[33] and PID[34] control algorithm have been evaluated using the hybrid approach, and the results to date have been encouraging. Another method to overcome the challenges of closed-loop control is to incorporate the delivery of insulin with glucagon,[20] a counter-regulatory hormone. Utilising a dual-hormone or bi-hormonal delivery system has the advantage of mimicking the physiological response of hypoglycaemia without the need for fast-acting oral glucose. The disadvantage of this system is that two separate pumps are required to deliver insulin and glucagon and, although effective, occasional hypoglycaemia can still occur.

Current limitations of closed-loop system

In spite of our increased understanding of the pathophysiology of diabetes and the progressive improvement in technology over the past two decades, there are still several obstacles to overcome before the artificial pancreas can be used safely and effectively in daily clinical practice. These are outlined below, as well as the possible solutions related to these challenges.

Accuracy of continuous glucose monitors

Accuracy and reliability of CGMs remain the biggest obstacle to the development of the closed-loop system.[35] A commercially available CGM has still not replaced the need for self-monitoring of blood glucose due to the need for calibration. Accuracy with CGMs can be affected at times when blood glucose concentrations are changing at high rates, such as periods immediately after a meal. This is due to a degree of lag time which exists between interstitial and blood glucose, which may be up to 20 minutes.[36,37] Other factors that can affect the degree of deviation between interstitial and blood glucose are erroneous calibration, loss or increase of sensor sensitivity and mechanical disturbance of the sensor such as dislodgement.[38] Persistent deviation, especially in scenarios where the CGM overreads (i.e. gives a glucose value higher than the actual blood glucose level) may result in the artificial pancreas system over-delivering insulin, leading to hypoglycaemia. Mitigating this risk would require further improvement in the accuracy and reliability of CGMs.

Insulin absorption

Modern rapid-acting subcutaneous insulin analogues take approximately 90–120 minutes to reach their maximum glucose lowering capacity or peak action. Even then, their action can continue beyond this peak. As a result, 'insulin stacking' can occur if several correction boluses are given in close sequence, increasing the risk of hypoglycaemia. This may pose a hazard for a closed-loop system, if not accounted for by the control algorithm.[39] Other consequences of delayed insulin absorption and action are hyperglycaemia immediately after a meal and hypoglycaemia after exercise. Patients may therefore need to deliver manually meal-time insulin bolus to counter the former, and pre-emptively consume carbohydrate for the latter.

Individual variability

The absorption and action of insulin can vary between subjects (intersubject variability) and within the same subject (intrasubject variability).[40] Among the causes of intersubject variability are body mass, age, gender, physical activity and smoking. Intrasubject variability can be influenced by acute illness, stress, alcohol,[41] physical activity and variations in counter-regulatory hormone levels during the day.[42] To perform optimally, closed-loop systems will have to be able to adapt and compensate for these variations.

Outlook for the future

Research into the development of the artificial pancreas has progressed rapidly in the past decade. The next step is to test the artificial pancreas at home, out of the confines and controlled environment of a research facility. This will likely be performed in stages, with short-term overnight studies comparing closed-loop with conventional insulin therapy initially, followed by more intensive use of the closed-loop system (i.e. day and

night, exercise conditions). The system will have to be proven to be safe and effective in the home environment before it can be widely used in clinical practice. The early clinical applications of the closed-loop system will also have to be practical and realistic, with early studies focusing on mitigating hypoglycaemia events especially at night-time. Clinically meaningful targets such as tighter glycaemic control and reduction of HbA_{1c} may occur gradually. In order to support the wider use of the closed-loop system, appropriate technical and clinical infrastructures should be in place for patients and health care professionals.

Although the ideal situation would be a biological cure for type 1 diabetes, where damaged beta-cells could be replaced with healthy ones and be viable, the interim role of the artificial pancreas might be to act as a 'bridge' until that cure is found. It is therefore hoped that the advent of the artificial pancreas in the near future would lead towards better care in the management of patients with type 1 diabetes.

Declaration of interests

There are no conflicts of interest declared.

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