Artificial Pancreas: Components, Function, and State of the Art

Shawn Klein, BASc

ABSTRACT
Diabetes and its progressive neurovascular complications have had a staggering impact on the health of individuals all over the world. Current strategies for managing diabetes include daily insulin injections, oral anti-hyperglycemic medications, close blood glucose monitoring and a strict exercise and nutrition regimen. The literature has been clear that such approaches are not only burdensome to the patient, but also not conducive to adequate blood glucose control. Due to the deficiencies of current diabetes treatments, there is a need to develop a new treatment modality for diabetes that will better succeed in helping patients maintain tight blood glucose control. One promising engineering feat is the development of an innocuous artificial pancreas that is programmed to provide physiologic insulin delivery, while keeping patients’ blood glucose levels within the recommended range. The artificial pancreas has the potential to become a revolutionary treatment option for diabetes by reducing the severity of disease complications through tight glucose control, as well as decreasing the treatment burden on patients. The main beneficiaries of an insulin-delivering artificial pancreas will be type 1 as well as insulin-dependent type 2 diabetics. Although the artificial pancreas is still in the prototype stage of development, preliminary results offer hope that further research can lead to the development of a viable artificial pancreas.

DIABETES – A GLOBAL EPIDEMIC
It is estimated that 171 million people worldwide had diabetes in 2000, and by 2030 this number is expected to reach 366 million. Diabetes is a chronic disorder of impaired blood glucose control which can be classified into two major categories, mainly type 1 and type 2 diabetes. Type 1 diabetes is caused by the autoimmune destruction of beta-cells in the pancreas, causing an absolute loss of insulin production by these cells. The pathophysiology of type 2 diabetes stems from systemic insulin resistance in the body’s cells, which essentially establishes a state of relative insulin deficiency.

The frequent high blood glucose levels found in diabetics is associated with a number of devastating long-term complications that may lead to amputation and systemic infection, as well as pathological changes of the eyes, kidneys, nerves, heart and blood vessels. In fact, individuals with diabetes have a 3 to 7.5 times greater incidence of death from cardiovascular causes, and the disease is currently the fourth leading cause of acquired blindness in the United States. In addition, approximately 30% to 40% of all diabetics will develop diabetic nephropathy, and more than 75% of type 1 diabetics with nephropathy will eventually develop end-stage renal disease. Yet, in the midst of such statistics, the Diabetes Control and Complications Trial (DCCT) has demonstrated that proper control of blood glucose levels reduces the risk of long-term complications of both type 1 and type 2 diabetics.

Insulin is a physiological hormone that works to lower the blood glucose concentration in the body. Since diabetics have a defect in their insulin pathway, their blood glucose levels can often be elevated above the normal glucose range for the blood, a term referred to as hyperglycemia. Normal blood glucose levels values vary depending on the time they are measured. A fasting blood glucose test carried out with no caloric intake for at least eight hours should return a glucose value between 3.9 and 5.5 mmol/L. A glucose measurement taken two hours after meal consumption (postprandial) is normal if it is between 3.9 and 8.1 mmol/L, and a
random blood glucose measurement should be between 3.9 and 6.9 mmol/L.4

Current strategies for regulating blood glucose levels vary depending on the type and severity of the disease. The standard medical treatment for type 1 diabetes is centred around multiple daily insulin injections, a strict dietary plan and a regular exercise regimen.3,5 Although most patients with type 2 diabetes are initially placed on medications that aid in lowering blood glucose levels or provide improved glucose control, type 2 diabetes is a progressive disorder and ultimately requires the addition of insulin to the treatment regimen.3

GLUCOSE SENSORS IN BLOOD GLUCOSE REGULATION

In order to help patients achieve their blood glucose control targets, self-monitoring of blood glucose concentrations must often be carried out multiple times per day.3 This is accomplished by using a sensor that analyzes a drop of the patient’s blood (usually obtained by pricking the fingertips) and provides an instantaneous measurement.3 Diabetic patients must try to maintain blood glucose levels within normal limits during the day, after meals, as well as during the night as there is the potential risk that a large dose of insulin may cause hypoglycemia, which can lead to hospitalization, coma or, rarely, death.6

In addition to the discrete blood glucose sensors mentioned above, there is ongoing work to develop glucose sensors that can continuously measure patients’ glucose concentrations through an indwelling catheter.3 There are a variety of technologies that have been developed for the purpose of continuous glucose sensing including near-infrared and mid-infrared spectroscopy, photoacoustic phenomena, optical coherence tomography, thermo-optical techniques and fluorescence measurements.11 Most of these technologies, however, are still in the research stage of development.11

Although the use of commercially available continuous blood glucose sensors in routine diabetes management is still limited, some diabetic patients have recently started to use these devices. There are three U.S. Food and Drug Administration (FDA)-approved continuous glucose sensors that are currently being sold commercially.11,12 Such commercially available continuous glucose sensors employ electrochemical sensing technology which use glucose oxidase to measure the electric current generated when glucose reacts with oxygen. These devices are designed to measure the equivalent of subcutaneous glucose levels. These sensors are also relatively stable and can provide a good glucose signal for three to seven days. They also all contain alarms to alert the user when hyper- or hypoglycemia glucose concentrations are detected.11 A brief overview of the three commercial continuous glucose sensors is provided below:

- The Medtronic MiniMed “REAL-Time Continuous Glucose Monitoring System” is a a sensor connected to a small wireless transmitter that continuously sends subcutaneous interstitial glucose levels to a receiver for monitoring. The sensor measures glucose concentrations from 2.2 to 22.2 mmol/L, and calibration is recommended four times a day.11

- The DexCom STS sensor measures glucose in a range of 2.2 to 22.2 mmol/L, and glucose trend data from the sensor are displayed on a visual receiver in graph format. The sensor needs to be only calibrated twice a day.11

- The “TheraSense FreeStyle Navigator” by Abbott Diabetes Care transmits glucose concentrations wirelessly every minute to a receiver which can display data trends over 2-, 4-, 6-, 12- and 24-hour time periods. Glucose is measured by the device over a range of 1.1 – 27.8 mmol/L.11,12

Current continuous glucose sensors offer considerable technological advancement toward controlling blood glucose, although there are several remaining challenges that have yet to be fully solved.9 For instance, the sensing accuracy of modern continuous glucose sensors is still considered insufficient when compared to discrete blood glucose sensing meters.9,11 Even the most precise glucose sensors demonstrate a median absolute error deviation around 16%.9 However, unlike discrete glucose meters, continuous glucose sensors certainly provide additional valuable information such as the direction and rate of change in blood glucose concentration.11 Another concern relates to reliability. At the present time, glucose sensors do not alarm the user when they fail, therefore sensor failures can only be assessed retrospectively.9 This deficiency will need to be corrected before safe operation of the artificial pancreas can be assured.

Despite the wide range of current treatment options available, research shows that the majority of people with diabetes are not keeping their glucose levels within the recommended ranges.6 Despite the established importance of blood glucose self-monitoring in diabetes management, few patients with type 1 diabetes actually measure their glucose levels after eating meals or overnight.7 As a result, even patients with well-controlled type 1 diabetes regularly experience postprandial hyperglycemia or overnight hypoglycemia.7 Poor patient compliance with their diabetes management strategies may be partially attributed to burdensome nature of such treatment plans.3 In addition, due to the inability of insulin injections and current glucose lowering medications to precisely control blood glucose levels, even a fully compliant diabetic patient may not always be able to maintain their blood glucose levels within the recommended range.6
THE ARTIFICIAL PANCREAS – THE NEED

Due to the challenges inherent in current diabetes management, there is a need to develop better treatments that will allow patients to maintain tight blood glucose levels without compromising the patients’ quality of life. The artificial pancreas shows promise in fulfilling this need and in effect could revolutionize the management of diabetes as we know it. Essentially, an artificial pancreas is an electromechanical system that employs negative feedback to autonomously release insulin into the body in such a way that physiologically mimics the insulin producing-activity of healthy pancreatic beta cells. The logic behind such a device is the idea that by delivering insulin into the body in the same way that a healthy pancreatic beta-cell would do, normal blood glucose levels can be achieved in a diabetic patient. The artificial pancreas will ideally require very little manual input from the user, and thus also significantly decrease the treatment burden of diabetes.

Due to their complete inability to produce insulin, patients with type 1 diabetes will be the main beneficiaries of an insulin-delivering artificial pancreas. However, because type 2 diabetics become insulin dependent at later stages of their disease, an artificial pancreas may be beneficial to these patients as well.

THE ARTIFICIAL PANCREAS – HOW IT WORKS

The artificial pancreas essentially consists of three important components: a glucose sensor/monitor, an insulin pump to store and deliver insulin, and a control algorithm to compute the amount of insulin to be delivered and communicate between the sensor and the pump. Figure 1 shows an overview of the three components that comprise an artificial pancreas and how these components interact with one another.

Before, during and after meals, as well as at night, glucose levels are continuously monitored by a sensor in a patient’s blood or interstitial fluid. The glucose sensor determines the patient’s blood or interstitial glucose concentration, and it sends this information to the control system of the artificial pancreas. The control system then uses a mathematical algorithm to compute the required insulin dosage that needs to be administered to return glucose levels back to baseline. This information is then forwarded to the insulin pump, which releases the appropriate amount of insulin into the bloodstream. There may also be a feature for the patient to manually program their insulin pump to inject themselves with a customized dosage of insulin if the need arises.

“THE USER’S INPUT” - PATIENT CENTERED OPTIONS IN INSULIN DELIVERY

There are two types of insulin delivery modes which can be implemented in an artificial pancreas: closed-loop or semi-closed-loop. In a closed-loop insulin delivery system, the artificial pancreas will continuously and automatically deliver insulin to the patient without any manual input by the patient. The artificial pancreas will simply continuously monitor the patient’s glucose concentrations and autonomously deliver the appropriate insulin dose in order to keep the patient’s glucose concentration within the normal range.

Alternatively, the artificial pancreas may also operate in a semi-closed-loop insulin delivery mode (also known as meal announcement mode), where it will function completely autonomously, except for when the patient is intending to consume a meal or engage in exercise. During these times, the device will require the patient to provide it with information regarding the size and composition of their upcoming meal or the intensity level of their planned exercise regimen. The artificial pancreas then uses this information to immediately modify the amount of insulin being delivered to the patient in order to pre-compensate for the anticipated fluctuations in glucose concentration.

BODY INTERFACE DESIGNS FOR SENSOR AND INSULIN PUMP

There are three major types of artificial pancreas devices based on the location of the glucose sensor and insulin delivery pump within the body: 1) The subcutaneous (SC) sensing and SC delivery (SC-SC) system.
2) The intravenous (IV) sensing and intraperitoneal (IP) delivery (IV-IP) system.

3) The intravenous (IV) sensing and IV insulin delivery (IV-IV) system.

Each of the three categories of devices has its own distinct advantages and disadvantages. The SC-SC system has the advantage of being a minimally invasive system when compared to the IV-IP or IV-IV system. The minimally invasive nature of an SC-SC system gives it significant potential to achieve widespread application and, as a result, many of the current research efforts are devoted towards creating such a device. However, because SC-SC devices are inserted into the interstitial fluid of the subcutaneous tissue and not directly into the bloodstream, there are considerable delays associated with SC insulin delivery. These delays are related to the time taken for newly injected insulin to migrate from the interstitial tissue, into the bloodstream and the body’s cells. In addition, there are also delays associated with glucose sensing in a SC-SC system, due to the time lag involved with glucose diffusing from the bloodstream into the subcutaneous interstitial fluid. Due to the considerable delays associated with a SC-SC system, it currently appears that an SC-SC artificial pancreas will have difficulty operating in a completely closed-loop fashion, and users of an SC-SC device may have to manually enter in meal information to assist with insulin delivery. The IV-IP system has lower insulin delivery delays when compared to an SC-SC system. Nevertheless, the delays that remain are still substantial. For instance, there is an approximate delay of 70 minutes from the time that insulin is delivered intraperitoneally to when glucose levels noticeably drop in the blood. Additionally, there are minor glucose sensing delays associated with the IV glucose sensor. Another drawback of the IV-IP technology is that it is considerably more invasive than the SC-SC system, and can result in complications such as intravenous line infections and insulin pump occlusion.

The IV-IV artificial pancreas system is presently used only in special circumstances, such as in critically ill patients, surgical operations, or for research purposes. The benefit of this approach is that there are minimal insulin delivery delays (i.e., approximately 30 minutes due to the delay of insulin action in the blood), which facilitates the development of a fully closed-loop IV-IV system. The drawback of the IV-IV approach is that it is relatively invasive because it requires vascular access for both glucose monitoring and insulin delivery. As expected, IV-IV devices are also associated with a high risk of infection as well as biocompatibility issues.

Artificial pancreas control algorithms need to be adapted based on the continuous glucose sensing interface (subcutaneous, intraperitoneal or intravenous) being employed, because of the associated differences in sensing delays between these interfaces. For instance, any algorithm designed to process interstitial (subcutaneous) glucose measurements will need to account for the delay between the change of blood and interstitial glucose levels when computing the insulin dosage to deliver. Similarly, control system algorithms need to be modified based on the different routes of insulin pump delivery because of their different insulin absorption rates.

**CURRENT ARTIFICIAL PANCREAS DEVICES**

Today, artificial pancreas technology has developed to the point where there are a number of early models currently available in prototype forms. Three prominent prototype models are discussed here.

**Medtronic Minimed**

A SC-SC closed-loop artificial pancreas device has been developed using the Medtronic Minimed (Northbridge CA, US) continuous glucose monitoring system (CGMS), and Medtronic Paradigm insulin pump.

In one study of this device, 10 individuals with type 1 diabetes tested the device in a fully-closed-loop insulin delivery mode over a 28-hour period. During the study, preprandial (before meal consumption) and postprandial glucose levels were measured at 5.6 ± 1.6 and 10.8 ± 2.6 mmol/L (mean ± SD). Patients with diabetes should aim to achieve preprandial blood glucose levels of 5.0 to 7.2 mmol/L, and peak postprandial blood glucose levels of less than 10.0 mmol/L. In total, 17 hypoglycemia events were observed, primarily after meals, suggesting excessive insulin secretion by the device. Under closed-loop control, glucose was within the range of 3.9 to 10.0 mmol/L 75% of the time.

A team from Yale carried out another study of this device in 17 well-controlled diabetics over a 34-hour period. During this study, a comparison was made between the effectiveness of the device operating in a fully-closed-loop approach, and its operation in a semi-closed-loop meal announcement mode, which included manual insulin delivery 10 to 15 minutes before meals. Better results were obtained with the device operating in meal announcement mode, with postprandial peak glucose values of 10.8 ± 2.6 mmol/L (vs. 12.6 ± 2.8 mmol/L for fully-closed-loop) and mean glucose levels of 7.8 ± 2.6 mmol/L (vs. 8.3 ± 3.2 mmol/L for fully-closed-loop).

**Roche Diagnostics**

An SC-SC artificial pancreas prototype has been developed by Roche Diagnostics GmbH (Manheim, Germany). The device operates in a semi-closed-loop insulin delivery fashion with meal announcement, and employs a unique “empirical” control algorithm which administers an insulin bolus every 10 minutes according to a set of clinically...
derived rules. The prototype is designed to monitor subcutaneous interstitial glucose levels for up to 4 to 5 days.\textsuperscript{5}

The Roche system was tested on 12 type 1 diabetic subjects over a period of 32 hours and compared to results obtained with regular self-directed therapy. Overall, the device achieved similar mean glucose concentrations when compared to self-directed therapy (6.9 vs. 6.2 mmol/L). The prototype reduced the number of hypoglycemia events per day from 3.2 to 1.1 per subject. In addition, during the evaluation, 60\% of glucose readings obtained with the device were within the desired 5.0 to 8.3 mmol/L range, compared to only 45\% of readings with self-directed therapy.\textsuperscript{5}

**EVADIAC Group**

A fully closed-loop IV-IP device is being developed by the “Evaluation dans le Diabete du Traitement par Implants Actifs” (EVADIAC) group, a team of French doctors and researchers. Their artificial pancreas system employs an intravenous long term sensor system (LTSS) developed by Medtronic MiniMed. The LTSS, an enzymatic oxygen-based sensor, is implanted in the superior vena cava through direct jugular access and is connected by a subcutaneous lead to an intraperitoneal insulin pump implanted in the abdominal wall. An external wireless transmitter-receiver is used to communicate with the intraperitoneal pump (Figure 2).\textsuperscript{5}

The EVADIAC prototype was tested in four elderly type 1 diabetics over a 48 hour period. During this evaluation, blood glucose levels were within 4.4 to 13.3 mmol/L 84.1\% of the time. In fact, excluding meals, glucose levels were below 13.3 mmol/L for 98\% of the time.\textsuperscript{5}

**WHERE DO WE GO FROM HERE?**

Initially, the artificial pancreas is likely to find wider use in a supervised hospital environment, such as at the intensive care units, rather than in home settings. However, it is anticipated that home setting application will follow, with a gradual decrease in the supervision of the device as experience and comfort with it increases.\textsuperscript{1} In fact, due to the commercial potential of a safe and effective home-use artificial pancreas, much of the current research is aimed towards the development of such a device.

Although present day technology has made considerable advances toward the development of a true artificial pancreas, there is further work that needs to be done.\textsuperscript{1} For instance, most of the prototypes developed in recent years are fairly effective in maintaining normal glucose levels between meals, but are not as effective in containing blood glucose levels during and immediately after meals.\textsuperscript{8} In reality, early generations of the artificial pancreas are unlikely to produce near-normal glucose levels.\textsuperscript{10} Development of the device will likely occur in stages, with each subsequent release progressively reducing the risk of hyper- and hypoglycemia.\textsuperscript{10} An optimistic projection envisions the first generation of a commercial artificial pancreas to become available around 2011 to 2012.\textsuperscript{10}

Since the artificial pancreas is still in the prototype stage of development, it is difficult to accurately estimate the cost of such a device. However, because a safe and effective artificial pancreas will revolutionize the management of diabetes, when such a device is released to the general public, it is expected that most health care insurance plans will be updated to include coverage for it.

Despite the limitations of current artificial pancreas devices, their development offers considerable hope to millions of patients with diabetes worldwide. These devices offer patients the prospect of a future in which diabetes is easier to manage and attaining ideal blood glucose targets does not pose undue annoyances in individuals’ busy schedules. This technological advancement raises the possibility of a future in which tight blood glucose control is an achievable goal, and the disease’s devastating vascular, renal and nervous system complications are kept to a minimum. Moreover, a safe and effective artificial pancreas will not only provide significant benefits to diabetic patients, but also offer significant financial relief to a health care system which comprises burgeoning shares of our country’s gross domestic product.
REFERENCES


Author Biography

Shawn Klein earned his Bachelor of Applied Science degree from the University of Waterloo and is currently a second year medical student at McMaster University.