The roles of open loop insulin delivery system and the artificial pancreas in diabetes treatment

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“The Roles of Open Loop Insulin Delivery System and the Artificial Pancreas in Diabetes Treatment”

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Dedication

I’d like to dedicate this project to all my family and friends. The support, love and advice you’ve provided over the past 27 months have allowed me to be where I am today. A thousand “thank you’s” and “I love you’s”.
I’d like to thank April Gardner for all of her help with this project. Her suggestions and support allowed this project to become a reality. Thank you for encouraging me to search the research deeply and for all the smiley faces on my drafts, which made the project more enjoyable. Thanks again!
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Introduction

Diabetes mellitus results when the body is unable to maintain normal blood glucose levels (Morran, Omenn & Pietropaolo, 2008). It is a group of disorders including type 1 diabetes, type 2 diabetes and gestational diabetes. In 2007, there were 17.9 million people diagnosed with diabetes and an additional 5.7 million undiagnosed diabetics living in the United States (Centers for Disease Control and Prevention, 2008). Diabetes affects people of all ages, genders and races and its prevalence is expected to increase. Huang, O'Grady, Basu and Capretta (2009) predict the number of Americans suffering from diabetes will rise to 44.1 million over the next 25 years. They also predict annual spending for diabetes treatment will reach $336 billion in 2034.

Regardless of the type of diabetes, prolonged elevation of blood glucose causes detrimental damage to the body (Morran et al., 2008). Poorly controlled diabetes leads to increased risk of vision disorders, neuropathy, kidney disease, peripheral vascular disease, heart disease, stroke, digestive diseases, infections and periodontal disease (National Diabetes Data Group, National Institutes of Health and National Institute of Diabetes and Digestive and Kidney Disease, 1995). By understanding the risk factors and the pathophysiology of this condition, treatments can be developed and utilized to prevent or delay complications from emerging.

Type 1 diabetes occurs when the body’s natural defense system attacks the pancreatic cells that produce insulin (Morran et al., 2008). After the activation of the immune system, antigens are presented to T cells, which then produce direct damage to the β cells or indirect damage through the release of cytotoxic molecules. As with all
autoimmune diseases, the question of what triggers the body to mount a response against itself is an important topic to discuss.

The development of type 1 diabetes is hypothesized to have both genetic and environmental links. The human leukocyte antigen (HLA) region on chromosome 6 has been linked to the development of type 1 diabetes (Morran et al., 2008). Defects in this region contribute to the development of familial type 1 diabetes in 42% of the cases.

Environmental factors leading to type 1 diabetes include dietary factors, possible toxins and viruses. The list of potential dietary agents that may trigger the immune response include cow’s milk, soy, wheat gluten and vitamin deficiencies (Akerblom & Knip, 1998). In addition to dietary components, toxins such as N-nitroso compounds may also contribute to development of the disease. Despite the prevalence of dietary and toxic agents in the environment, viral diseases have been considered the major environmental trigger (Morran et al., 2008). Several viruses have been linked to development of type 1 diabetes including cytomegalovirus, mumps, hepatitis C, rubella, rotavirus, enterovirus, Coxsackie B and adenovirus. Morran et al. (2008) explains that exposing a cell to a virus changes the cell’s makeup and increases its susceptibility to destruction by the immune system. This alteration leads to the destruction of the β cells and formation of the disease.

In contrast to type 1 diabetes, type 2 diabetes does not result from an autoimmune reaction. Blood glucose levels are elevated in this condition because of insulin resistance in muscle, liver and adipocytes, as well as, impaired insulin secretion (DeFronzo, 2004). The current belief is genetic and environmental factors have roles in its development. Obesity, intra-abdominal fat storage, physical inactivity and increased
caloric intake predispose individuals to develop this disease (NIH, 1995). In some populations, the connection between obesity and diabetes is so strong that the term “diabesity” has been coined to delineate this link (DeFronzo, 2004).

As previously mentioned, the risks associated with prolonged hyperglycemia remain consistent despite the disease classification. Patients with diabetes have increased risk of developing microvascular complications such as retinopathy, nephropathy and neuropathy, as well as, macrovascular complications such as myocardial infarction, stroke and peripheral arterial disease (Krentz, Clough & Byrne, 2007). This increased risk is linked to the metabolic abnormalities associated with the condition (Creager, Luscher, Consenino & Beckman, 2003). Hyperglycemia, increased free fatty acids and insulin resistance contribute to vascular dysfunction by decreasing nitric oxide levels, increasing oxidative stress, altering signal transduction, causing platelet dysfunction and increasing clotting factors (Creager et al., 2003). Nitric oxide is made by the endothelial cells and is essential for vascular health. It promotes vasodilation, as well as, hindering platelet and leukocyte interaction with the cell wall. In hyperglycemic states, reactive oxygen species are produced in large amounts which inactivate nitric oxides and limit their vascular protecting effects. All of these dysfunctions contribute to the damage of the endothelial cells and formation of atherosclerotic plaques.

Despite all that is known about the pathophysiology of diabetes, many diabetic patients continue to have poor blood glucose control and the incidence of complications continues to be high (Weinzimer et al., 2008). To combat these potential complications, treatments have become more sophisticated in hopes of better controlling blood glucose
levels. Two such advancements were the insulin pump and the continuous blood glucose monitor.

In addition to functioning on their own, these two components can be combined in both a closed or open loop fashion. The open loop system provides continuous blood glucose readings which are transmitted to an insulin pump (Peyrot & Rubin, 2009). The patient then adjusts insulin delivery in response to the blood glucose levels (Mastrototaro & Lee, 2008). In contrast, the closed loop system provides adequate insulin infusion without patient input. This “artificial pancreas” has been an ongoing project for many years, but only recently have advancements allowed a convenient version to become a reality.

With the current financial state of the healthcare industry, the cost-to-benefit ratio must be taken into account when determining treatment options for diabetes care. Sophisticated glucose monitoring and insulin delivery methods are costly and many components are not covered by insurance (Mastrototaro & Lee, 2008). This will likely be the case with the artificial pancreas once it is released onto the market.

**Impact on Physician Assistant Profession**

A physician assistant (PA) is a midlevel practitioner that practices medicine under the direction and supervision of a physician. Based on the 2009 American Academy of Physician Assistants’ census, approximately 73,000 PAs practice medicine in the United States (AAPA, 2010). PAs are trained under the medical model with a focus on primary care and serve in both ambulatory and inpatient settings (Cooper, Henderson & Dietrich, 1998). Because of this training, PAs are able to decrease the patient load of their supervising physician, while continuing to earn money for the practice. Atwater,
Bednar, Hassman & Khouri (2008) stress the affordability of midlevel practitioners by focusing on their salary which is 40-50% lower than a primary care doctor. In addition, Roblin, Becker, Adams, Howard and Roberts (2004) found that patients were as satisfied with the care they received from PAs as they were from MDs. The abilities of the PA and the cost savings they provide will likely be factors that contribute to the continued growth of the profession in the years ahead.

With the expected rise in diabetes, PAs should be aware of the treatment options available to combat this disease. The development of an artificial pancreas will provide a means for blood glucose control that will likely be used by many patients with diabetes. Because PAs have more time to provide education, they will often assume the role of educator to both patients and their families on this new technology.

**History of Diabetes Treatment**

Prior to the 1920s, lack of treatment options caused the diabetic patient to have a shortened life span and a poor quality of life. However, a research breakthrough in 1921 changed the prognosis and fate of patients suffering from this disease. In 1921, Fredrick Banting and Charles Best began injecting atrophied pancreatic cells into dogs lacking pancreases and subsequently observed a decrease in blood glucose after the injection (Joshi et al., 2007). In 1922, physicians in Toronto injected this same solution into a young boy suffering from severe diabetes and immediately noticed a decrease in his blood glucose and in the spilling of glucose and ketones into his urine (Joshi et al, 2007). These initial positive findings ultimately led to the development of insulin and its regular use in patients suffering with diabetes.
Since its discovery, different types of insulin have been engineered for and used in the treatment of diabetes. By adding proteins to insulin or by altering its amino acid sequence, scientists have been able to alter its peak action and duration of action (Joshi et al, 2007). Combining different types of insulin allows better mimicking of the physiologic secretion provided by the normal human pancreas. To this day, insulin remains the mainstay treatment for type 1 diabetic patients.

For patients suffering from type 2 diabetes, there are additional options to help achieve blood glucose goals. Oral hypoglycemic agents fight the insulin resistance and impaired insulin secretion seen with this form of diabetes. Agents that cause increased insulin secretion include the sulfonylureas and the meglitinides, while the biguanides and thiazolidinediones promote insulin sensitivity (DeFronzo, 1999).

In addition to these classes, several new drugs have been introduced that act on intestinal hormones or their degradation enzymes. These drugs help stabilize glucose levels, reduce glucagon secretion, maintain normal gastric emptying, decrease appetite and maintain β cell mass (Unger, 2008). One drug, Exenatide, is similar in structure and function to glucagon-like peptide-1 (GLP-1), which is a major intestinal hormone affecting glucose concentration and the insulin response (Unger, 2008). Another drug, Sitagliptin, inhibits the enzyme that metabolizes GLP-1 (Unger, 2008). By inhibiting its breakdown, plasma GLP-1 concentration rises and the beneficial effects of this hormone are prolonged (Unger, 2008). Exogenous amylin is another new treatment being used to control diabetes. Amylin is a naturally occurring substance that is secreted from the pancreas with insulin and decreases glucagon secretion, prolongs gastric emptying and decreases appetite (Unger, 2008).
Although there are treatment options for type 2 diabetic patients, insulin is still the gold standard for glucose control (Unger, 2008). Most patients with type 2 diabetes will eventually need insulin therapy to reach blood glucose goals. When this time comes, the use of insulin should not be looked at negatively by the patient or the provider (Unger, 2008).

To promote the ease of insulin administration, pens and pumps were developed, which allow nearly painless administration of the drug (Unger, 2008). The subcutaneous insulin pump delivers insulin just below the skin and allows adjustment of both basal and bolus insulin rates based on patient factors (Scheiner et al., 2009). With subcutaneous insulin administration, absorption and distribution must occur before the effects of insulin can be seen. An alternative is the intra-peritoneal or implantable insulin pump, which is implanted into the body and provides a quicker absorption of insulin and a more physiologic response (Renard, Costalat, Chevassus and Bringer, 2006). Intra-peritoneal insulin pumps are available in Europe, but are not FDA approved because current insulin formulations unfold and aggregate causing occlusion of the insulin catheter (Nelson, 2010).

Combining lifestyle changes with pharmacologic therapy provides added benefit to the diabetic patient. In fact, lifestyle changes should be the first line treatment for patients with type 2 diabetes (Unger, 2008). Lifestyle modifications include carbohydrate counting, exercise and self monitoring of blood glucose (Unger, 2008).

Self monitoring of blood glucose (SMBG) is recommended for all diabetic patients, especially those using insulin. Monitoring provides confirmation of hypo or hyperglycemic status and allows patients to adjust their behavior to correct glucose
abnormalities (Renard, 2005). Studies have shown reduced hemoglobin A1c (HbA1c) levels when type 1 diabetic patients test greater than or equal to 3 times per day and when insulin treated type 2 diabetic patients test greater than or equal to 1 time per day (Renard, 2005). Although, SMBG remains the most common blood glucose monitoring method, compliance is often poor because of the cost of testing, as well as, the inconvenience of this approach.

The inconvenience of SMBG was addressed with the emergence of the continuous subcutaneous glucose monitor. This device records interstitial glucose levels numerous times per day, which eliminates the need for multiple needle sticks on a daily basis (Rya et al., 2009). In addition to improved convenience, patients using continuous blood glucose monitors have improved HbA1c levels compared to patients using SMBG methods (The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, 2009).

Despite their advantages, continuous subcutaneous glucose monitors provide only short term accuracy of glucose readings because of body reactions that occur at the site of the sensor (Renard et al., 2006). On average, sensor accuracy decreases after 3 days and the sensor must be replaced. Likewise, since the glucose level is derived from the interstitial fluid, not the blood, it takes time for the true blood glucose value to register. Kulcu, Tamada, Reach, Potts, and Lesho (2003) demonstrated a 5 minute physiological lag between blood glucose levels and recorded interstitial glucose levels. They also reported lower interstitial glucose readings compared to actual blood glucose values when the blood glucose levels were rising rapidly. This is explained by the time needed for equilibration between the interstitial and intravascular
compartments. Similarly, when blood glucose levels were falling, interstitial glucose readings were lower than blood glucose levels because of the effects of insulin on cells. Insulin initially lowers interstitial glucose levels and subsequently lowers blood glucose levels through equilibration.

IV enzymatic glucose sensors or implantable glucose monitoring systems are long term sensors that may combat these problems (Renard et al., 2006). Implanted close to the right atrium, they determine glucose readings based on the differences in oxygen pressure between two sensors (Renard, 2008a). Placement is established by a qualified health care provider through a direct jugular or a subclavian approach, while the patient is under general anesthesia (Renard, 2008b). Once placed, one sensor contains glucose-oxidase, which breaks down glucose into its metabolites when exposed to oxygen (Renard, 2008a; Renard, 2008b). The other sensor does not contain glucose-oxidase and provides a baseline blood oxygen concentration. Blood glucose levels can then be determined by comparing the differences in oxygen concentration at the two sensor sites. Compared to continuous subcutaneous glucose monitors, small studies have shown that the IV enzymatic glucose sensor can be operational for 90 – 431 days after implantation (Renard, 2008b). Although not available for clinical use, researchers are assessing the benefit of combining this device with an intra-peritoneal insulin pump.

Advancements in blood glucose monitoring, insulin and oral hypoglycemic agents have improved care for the diabetic patient. To further reduce the burden of self care placed upon the diabetic patient and to enhance blood glucose control, the open loop
insulin delivery system was developed, in hopes that the artificial pancreas would soon follow.

This paper will explore the history of the open and closed loop insulin delivery systems, as well as real and potential advantages and disadvantages of these treatments. What is the current role of the open loop insulin delivery system in diabetes care? Based on this and current research, what will be the role of the artificial pancreas?
Methods

PubMed, The National Institutes of Health, The Center for Disease Control and Prevention and Medtronic Diabetes were used to search the following terms: artificial β cell, artificial pancreas, closed loop insulin delivery system, continuous blood glucose monitor, continuous subcutaneous insulin infusion, insulin pump, open loop insulin delivery system, Paradigm + Medtronic, pathophysiology of macrovascular/microvascular disease in diabetes, pathogenesis of type 1 diabetes and type 2 diabetes, physician assistant + diabetes, physician assistant’s role, sensor augmented pump therapy.

Articles not available in English were excluded from this project. Articles published prior to 2005 were only used to provide historical information on the physician assistant profession, diabetes treatment and the artificial pancreas.
Literature Review

Open Loop Insulin Delivery System Outcomes

As previously mentioned, the open loop insulin delivery system combines a continuous blood glucose monitor with an insulin pump. Blood glucose levels are displayed every 1-5 minutes, allowing the patient to readily adjust the pump’s administration of insulin (Peyrot & Rubin, 2009). The MiniMed Paradigm REAL-Time System was launched in 2006, while the second generation of this system, the MiniMed Paradigm REAL – Time Revel System, was approved by the FDA in March 2010. These are currently the open loop systems being used in the United States (Figure 1) (Mastrototaro & Lee, 2009). These systems provide a means for control over hyperglycemic and hypoglycemic episodes through increased frequency of glucose monitoring, alarms when blood glucose levels are out of an acceptable range and graphics to indicate glucose trends (Peyrot & Rubin, 2009).

Blood glucose levels.

The open loop insulin delivery system may be beneficial in decreasing the HbA1c of patients using the device. A study by Halvorson, Carpenter, Kaiserman and Kaufman (2007) on ten type 1 diabetic children showed a decrease in HbA1c levels from 8.1% +/- 0.9% to 7.8% +/- 0.9% after 4 weeks of open loop insulin delivery treatment. In another study of 20 type 1 diabetic patients, the open loop system reduced the patients’ HbA1c from 7.4% to 6.3% over a 1 year period (Mastrototaro, Cooper, Soundararajan, Sander & Shah, 2006). No statistical analyses were reported on these studies; however, both studies demonstrate the potential clinical benefit of this device in controlling blood
glucose. A 1.1% decrease in HbA1c corresponds with a 38.5 mg/dL decrease in average blood glucose.

Several studies compare the use of traditional therapies to the open loop insulin delivery system. In one study, 14 patients using the open loop insulin delivery system had a 0.7% decrease in HbA1c compared to 14 patients using SMBG with multiple daily injections (MDI); however, these results were not statistically significant (Peyrot & Rubin, 2009). Similarly, a 6 month randomized control trial by Raccah et al. (2009) showed a HbA1c decrease of 0.81% in 55 patients using the open loop insulin delivery system compared to a 0.57% decrease in the 60 traditional insulin pump patients. These results were not statistically significant; however, when the patients who failed to wear the sensor >70% of the time were eliminated from the data, HbA1c was reduced by 0.96 +/- 0.93% in the open loop insulin delivery system group, while the traditional insulin pump patients demonstrated a 0.55 +/- 0.93% reduction. These results were statistically significant with a $P < 0.001$. In addition, Raccah et al. (2009) did observe significantly decreased mean glucose concentrations in the intervention group compared to the control group. This may be due to the fact that they also observed significant decreases in duration and amplitude of hyperglycemic events.

Statistical significant ($P < 0.05$) was seen by Peterson et al. (2009) during their study of 42 diabetic patients. After 1 month of treatment, the 17 open loop insulin delivery system subjects had average HbA1c levels of 5.98 +/- 0.45 compared to average HbA1c levels of 7.32 +/- 0.43 in the 25 control patients ($p = 0.041$). After 2 months, HbA1c averages were 5.96 +/- 0.45 in the intervention group compared to 7.71 +/- 0.39 in the control group ($P = 0.006$) and after 3 months, HbA1c averages were 6.17
+/− 0.36 for the intervention group and 7.63 +/- 0.41 for the control group (P = 0.016).

Open loop insulin delivery produced significant decreases in HbA1c.

Although Hirsch et al. (2008) showed no statistically significant decrease in HbA1c between the open loop insulin delivery group and the control group, they did observe statistical significance in the number of patients achieving the American Diabetes Association’s current recommendation of a HbA1c level less than 7.0% (ADA, 2010). The study participants were both adolescents and adults who had been diagnosed with type 1 diabetes for at least 1 year. There were 66 subjects in the intervention group and 72 subjects in the control group. Mean baseline HbA1c for the intervention group was 8.37% and 8.30% for the control group. After 13 weeks, 30.8% of the intervention group had HbA1c levels < 7.0%, while only 11.1% of the control group had achieved this goal. These results were statistically significant (P = 0.007); however, statistical significance was not seen after completion of the 6 month study. After 6 months, 24.2% of the open loop insulin delivery group achieved the HbA1c goal, while only 19.4% of the control group met the target. As previously demonstrated by Raccah et al. (2009), Hirsch et al. (2008) saw decreased HbA1c with increased treatment compliance. They considered 100% compliance if the patient used the sensor 6 out of 7 days. During their study, there were four subjects who had <60% compliance, 12 subjects who had 60-80% compliance, 32 subjects with compliance between 80 – 100% and 18 subjects with >100% compliance. The researchers compared the HbA1c values of the subjects with <60% compliance to the HbA1c values of the subjects in the three other groups and observed statistically significant
improvements in HbA1c levels from baseline in those patients with >60% compliance ($P = 0.0075$, $P = 0.0020$, $P = 0.0015$).

**Hypoglycemia.**

Hypoglycemia is the main concern and limiting factor in insulin usage (Unger, 2008). Studies demonstrate that patients using the open loop insulin delivery system may have decreased or similar frequencies of hypoglycemic events compared to traditional therapies. Halvorson et al. (2007) reported a decrease in the number of hypoglycemic episodes as the ten type 1 diabetic patients in their study became familiar with the open loop insulin delivery system and its function. When wearing the first sensor, patients experienced 9.4 +/- 21.7, 5-minute blocks of hypoglycemia. This number was reduced to 5.3 +/- 15.1, 5-minute blocks with sensor 7. Although this appears significant, statistical analysis was not reported on these results.

When the open loop insulin delivery system is compared to traditional therapies, Hirsch et al. (2008) found decreased episodes of hypoglycemia in the 66 patients using the open loop insulin delivery system compared to the 72 patients in the control group. Hypoglycemic episodes were measured based on mg/dL below 70 mg/dL multiplied by the time spent at this level. The control group showed a reading of greater than 0.7 mg/dL/min, while the open loop insulin delivery group had a reading of less than 0.4 mg/dL/min. These results were statistically significant. Although statistical analysis was not reported, Peyrot and Rubin (2009) reported three occurrences of severe hypoglycemia in 13 patients using traditional therapy, while the 14 patients using the open loop insulin delivery system had no incidences of severe hypoglycemia.
Insulin.

Patients experiencing bouts of hypoglycemia tend to reduce their insulin use to prevent further episodes, which can lead to inadequate blood glucose control. If the open loop insulin delivery system can decrease hypoglycemic episodes, this will allow patients to use appropriate amounts of insulin with less fear. Raccah et al. (2006) found that 55 patients using the open loop insulin delivery system bolused insulin more frequently and at higher doses than the 60 patients using traditional insulin pump methods. Statistical significance ($P = 0.005$) was achieved in this study but not all studies show similar results. Peterson et al. (2009) observed an increase in insulin use in 17 patients using the open loop insulin delivery system. At the end of their study, this group bolused 43.13 +/- 4.18 iu/day compared to the patients in the control group that bolused 38.05 +/-2.47 iu/day; however, statistical significance was not addressed.

Weight Gain.

In addition to decreasing insulin use, patients commonly increase food intake to prevent hypoglycemic episodes (Joshi & Parikh, 2007). This leads to weight gain, which is another major concern with insulin use. Excessive weight gain can cause insulin resistance and/or poor psychosocial health. Peyrot and Rubin (2009) showed that the open loop insulin delivery system may decrease weight gain. They documented a 2.0 kg weight gain in the 14 SMBG/MDI subjects versus a 0.7 kg weight gain in the 14 open loop insulin delivery system subjects. This difference is not statistically significant; however, the study was only 16 weeks long. Peyrot and Rubin (2009) hypothesize that a significant weight change may occur with a study of longer duration.
Ease of Treatment.

As with any treatment, patients are more likely to follow a patient-friendly regimen. Peyrot and Rubin (2009) explored this aspect of the open loop insulin delivery system by asking 28 participants to complete questionnaires. At the beginning of the study, all participants were asked to complete a questionnaire on their current insulin therapy. At the end of the study, participants in the intervention group evaluated the continuous blood glucose monitor and insulin pump, while participants in the control group evaluated SMBG and MDI. They were asked to assess the convenience, interference, blood glucose burden and control, worries, social burden, well-being, overall satisfaction, desire to switch monitoring and delivery systems, willingness to recommend systems and comparison to prior systems. These were reported on a 0 – 100 scale with 100 indicating more of the characteristic being assessed.

When comparing the ratings of the 14 continuous blood glucose monitor patients with the ratings of the 13 traditional SMBG patients, the perceived blood glucose control with the continuous blood glucose monitor was superior to SMBG with ratings of 76.8 +/- 20.9 and 48.1 +/- 21.1 respectively ($P = 0.026$) (Peyrot & Rubin, 2009). The continuous blood glucose monitor group had higher overall satisfaction with a rating of 73.8 +/- 26.7 compared to 41.0 +/- 30.9 in the SMBG group ($P = 0.007$). They were also more likely to recommend use of the continuous blood glucose monitor to peers with ratings of 83.3 +/- 21.7 versus 61.5 +/- 26.7 in the SMBG group ($P = 0.028$). Although these results were statistically significant, perceptions on convenience (73.7 +/- 23.8 vs. 55.4 +/- 27.3, $P = 0.794$), interference (24.2 +/- 16.5 vs. 28.6 +/- 27.2, $P =$
0.929) and blood glucose burden (28.6 +/- 32.3 vs. 53.8 +/- 38.0, \( P = 0.181 \)) were not significant.

Statistically significant results were also seen when comparing the insulin pump to MDI (Peyrot & Rubin, 2009). Compared to the 13 MDI patients, the 14 insulin pump patients felt the device was more convenient (52.1 +/- 21.6 vs. 80.5 +/- 16.4, \( P < 0.001 \)), increased blood glucose control (42.9 +/- 22.5 vs. 80.1 +/- 19.5, \( P = 0.001 \)) and reduced blood glucose burden (61.5 +/- 41.6 vs. 28.6 +/- 32.3, \( P = 0.036 \)), social burden (37.9 +/- 21.4 vs. 21.8 +/- 13.0, \( P = 0.001 \)) and worries (54.5 +/- 20.2 vs. 38.4 +/- 15.2, \( P = 0.009 \)). Overall satisfaction and recommendation to peers was significantly higher in the insulin pump group compared to the MDI group with ratings of 83.3 +/- 21.7 vs. 33.3 +/- 22.6 (\( P < 0.001 \)) and 97.6 +/- 8.9 vs. 57.1 +/- 27.5 (\( P < 0.001 \)) respectively. The insulin pump group was also less likely to switch to other insulin delivery systems (7.1 +/- 14.2 vs. 83.3 +/- 21.7, \( P < 0.001 \)). Two areas that did not reach statistical significance when comparing the insulin pump group to the MDI group were interference (34.3 +/- 32.5 vs. 39.5 +/- 19.6, \( P = 0.937 \)) and well-being (49.5 +/- 8.9 vs. 48.4 +/- 6.7, \( P = 0.193 \)).

Based on the survey results, the open loop insulin delivery system received superior ratings compared to the SMBG/MDI group (Peyrot & Rubin, 2009). Patients’ perceptions of the open loop insulin delivery system are good, which may lead to increased treatment compliance and improved blood glucose control.
Disadvantages.

Hypoglycemia.

Despite studies showing a reduction in hypoglycemic episodes, the risk of hypoglycemia remains a concern with the open loop insulin delivery system. Hirsch et al. (2008) reported 11 severe hypoglycemic events in 66 open loop insulin subjects and only three events in the 72 traditional self monitoring subjects. This result was statistically significant ($P = 0.04$). A severe hypoglycemic event was defined as, “a clinical episode of hypoglycemia, resulting in seizure or coma, requiring hospitalization or intravenous glucose or glucagon, or any hypoglycemia that required assistance from another person” (Hirsch et al., 2008, p. 378). Only five of the open loop insulin hypoglycemic episodes were linked to possible device problems. The other six instances were likely due to patient noncompliance.

Raccah et al. (2009) reported one episode of hypoglycemia with loss of consciousness in the 55 subjects using the open loop insulin delivery system. This episode was linked to improper calibration and alcohol intoxication. Mastrototaro et al. (2006) documented three self reported episodes of hypoglycemia in 20 patients receiving open loop insulin therapy for an average of 317 days. Halvorson, Carpenter, Kaiserman and Kaufman (2007) defined a hypoglycemic event as a 5 minute block of time when blood glucose readings were less than 50 mg/dL. Although they reported a decrease in hypoglycemic episodes after several months of open loop insulin therapy, nine out of ten patients experienced a hypoglycemic episode over the study period.
**Other adverse effects.**

In addition to hypoglycemia, diabetic ketoacidosis (DKA), pump malfunction, needle/catheter occlusion and infection have been linked to the insulin pump component, while bleeding/bruising, pruritis/skin irritation and pain are side effects associated with the continuous blood glucose monitor (Pohar, 2007). Raccah et al. (2009) reported two incidences of DKA in the 55 open loop insulin pump participants. They linked this to lack of patient response to hyperglycemic alarms. Hirsch et al. (2008) also reported one episode of DKA with the 66 open loop system participants. In addition, one of their subjects developed abscesses at the insulin infusion site. Mastrototaro et al. (2006) reported 67 adverse events during their study of 20 diabetic patients using the open loop insulin delivery system for an average of 317 days. Of these adverse events, 46% (n = 30) were bleeding/bruising, 42% (n = 28) were itching/skin irritation, 7% (n = 5) were pain related and 1% (n = 1) was infection. Large studies are lacking on the likelihood and frequency of these adverse effects.

**Cost.**

As with any new technology, one of the major disadvantages of the open loop insulin delivery system is increased cost. The initial costs to purchase the components of the MiniMed Paradigm REAL-Time System are approximately $7000.00 for the insulin pump and $999.00 for the continuous glucose monitor (Rosalee, Medtronic Diabetes, personal communication, May 6, 2010). In addition, the patient’s monthly costs are approximately $500.00 which includes: $120.00 per month for pump infusion sets, $35.00 per month for insulin reservoirs and $350.00 per month for continuous glucose monitor sensors. Although insurance may cover a portion of this cost, unless
additional public assistance becomes available, the system will be unattainable for many individuals including the uninsured or poorly insured (Pohar, 2007).

Studies have revealed the possible advantages of reduced blood glucose levels, reduced hypoglycemia, reduced weight gain, increased insulin use and ease of treatment and disadvantages of hypoglycemic episodes, other adverse effects and cost associated with the open loop insulin delivery system. With research underway on the closed loop system, the question remains, how will it compare to the open loop system and the traditional insulin delivery methods?

**History of the Artificial Pancreas**

Insulin, the breakthrough in diabetes treatment, is less than 100 years old, but the idea of a closed loop insulin delivery system or artificial pancreas has existed nearly as long as its discovery. Professor E. Perry McCullagh presented the concept of an implantable artificial pancreas in 1959 (Nishida, Shimoda, Ichinose, Araki & Shichiri, 2009).

The first clinically useful artificial pancreas was developed in 1974 by Albisser *et al.* in Toronto, Canada and in 1975 by Shichiri *et al.* in Osaka, Japan; however, these devices were cumbersome and impractical for everyday clinical use (Nishida et al., 2009). Additional research and advancements allowed the development of the bedside artificial pancreas.

The bedside artificial pancreas draws blood from an indwelling catheter into a bedside blood glucose analyzer (Nishida et al., 2009). This information is sent to a bedside computer that analyzes the results and determines output instructions based on programmed algorithms. The computer instructs bedside pumps to administer insulin or
glucagon based on blood glucose levels. Despite its more compact form, multiple components inhibit patient movement and normal life functions. The primary use for the bedside artificial pancreas is for research, but it has been used to control blood glucose during DKA, dialysis, surgery and delivery (Nishida et al., 2009). Figure 2 shows an example of the bedside artificial pancreas.

Further advancements have allowed models of the portable and implantable artificial pancreases to be developed internationally. Research is currently underway in the United States to develop efficacious and safe models of the portable and implantable artificial pancreas. Like the bedside artificial pancreas, the portable artificial pancreas consists of a glucose monitor, an insulin pump and an algorithm that determines the amount of insulin to administer (Weinzimer, 2008). Its compact size makes it wearable and will allow patients to continue normal life functions. Similarly to the portable system, the implantable artificial pancreas provides patient freedom with added aesthetic benefit because the device is hidden inside the body. Researchers are attempting to develop an implantable device that provides intraperitoneal insulin delivery or delivery through the portal vein which may promote a more physiologic insulin response compared to subcutaneous administration (Nishida et al., 2009; Renard, Costalat, Chevassus and Bringer, 2006).

Problems with the artificial pancreas components have prevented the development of a widely useful and convenient artificial pancreas. Previously, the major hindrance in the development of the artificial pancreas was unreliable glucose sensors (Nishida et al., 2009). A glucose sensor monitors blood glucose levels and displays or sends the information to an insulin pump. Prior to 1999, problems with the glucose
sensor included decreased blood glucose sensitivity and prolonged sensor response time after several days of use (Shichiri, Kawamori, Hakui, Yamasaki, & Abe, 1984). These findings were attributed to protein and fibrin deposition on and around the sensor. Technological advancements increased the accuracy of the monitors, and in 1999, the first FDA approved continuous blood glucose monitor was released. Decreased sensor sensitivity over time remains an issue, so most continuous blood glucose monitors require that the sensor be changed every 3 – 7 days depending on the brand (Ellis, Naik, Gemperline & Garg, 2008). In addition, most continuous blood glucose monitors require or recommend calibration of the sensor using SMBG.

The algorithm used to determine insulin dosages has been another concern in the development of the artificial pancreas. The algorithm used in many studies adjusts for the fact that insulin is secreted based on glucose concentration and the rate of change in glucose concentration (Nishida et al., 2009). The algorithm causes the insulin delivery system to infuse insulin based on the actual blood glucose level, while also producing the low-second phase insulin rise and fast first-phase insulin rise that is seen physiologically (Steil, Rebrin, Darwin, Hariri, Saad, 2006). As with all physiologic processes, the exact mechanism of blood glucose control differs from person to person, so the algorithm may function differently in individuals. Large, randomized controlled studies on the artificial pancreas will help to reveal differences in blood glucose regulation that may necessitate changes to the algorithm for specific populations.

In 2006, the Juvenile Diabetes Research Foundation launched the Artificial Pancreas Project whose goal is to develop and promote regulatory approval of the artificial pancreas while making it affordable for all diabetic patients (Juvenile Diabetes
Since its initiation, multiple research studies have been sponsored on the closed loop system and its components. These studies and other research forums, have produced limited outcome data on the artificial pancreas.

**Closed Loop Insulin Delivery System Outcomes**

**Blood glucose levels.**

The ultimate goal of diabetes therapy is to manage blood glucose levels. Several studies showed that the closed loop insulin delivery system provides improved or similar glycemic control compared to other insulin delivery methods.

Weinzimer et al. (2008) placed 17 subjects with type 1 diabetes on open loop control for 3 days, followed by 34 hours of closed loop control during which data was recorded. Throughout the open loop period, 58% of glucose values were between 70 and 180 mg/dL; however, during the closed loop period, 85% of values were in this range. These results were statistically significant ($P < 0.002$).

Steil, Rebrin, Darwin, Hariri and Saad (2006) recruited 10 patients with type 1 diabetes who were utilizing continuous subcutaneous insulin infusion (CSII) for at least 6 months. The subjects were placed on the closed loop insulin delivery system for approximately 24 hours. Although statistical significance was not reached during closed loop control, the subject’s blood glucose levels were between 70 and 180 mg/dL 75% of the time versus 63% of the time during CSII therapy. Despite these differences, the mean blood glucose levels were similar between the two groups; however, the variability in blood glucose levels was reduced in the closed loop participants.
In another study, Renard, Place, Cantwell, Chevassus and Palerm (2009) placed eight type 1 diabetic patients treated with implanted insulin pumps on open loop insulin therapy for 24 hours and on closed loop insulin therapy for 48 hours. Blood glucose levels during closed loop insulin therapy were between 4.4 mmol/L (79.3 mg/dL) and 6.6 mmol/L (118.90 mg/dL) 39.1% of the time versus 27.7% during open loop therapy. These results were statistically significant ($P = 0.05$). Similar to results seen by Steil et al. (2006), mean blood glucose levels were comparable during open loop and closed loop insulin therapy.

Okabayashi, Nishimori, Maeda et al. (2009) recruited 88 hepatic resection patients to undergo either standard sliding scale insulin therapy (SS) or closed loop insulin therapy for the first 18 hours after surgery. The number of patients assigned to both groups was equal (n=44) and the number of previously diagnosed type 2 diabetics was similar between the two groups (31.8% of SS group, 38.6% of closed loop group). The prior insulin therapy of the diagnosed type 2 diabetic participants was not discussed. Results showed that subjects using the closed loop system obtained blood glucose levels between 80 and 110 mg/dL >60% of the time versus < 23% of the time with the SS group. Although the results appear significant, statistical tests were not preformed on this data.

In another postoperative study, Okabayashi, Nishimori, Yamashita et al. (2009) compared the blood glucose control in 13 pancreatic resection patients undergoing SS therapy to 17 pancreatic resection patients undergoing closed loop insulin therapy. Closed loop therapy subjects had blood glucose levels in the 80 to 110 mg/dL range 18
hours after surgery, while blood glucose levels in the SS group were 150 mg/dL 18 hours after surgery. These blood glucose trends were statistically significant \( P < 0.05 \).

**Hypoglycemia.**

As previously mentioned, hypoglycemia is a common concern with insulin administration. To explore the frequency of hypoglycemic episodes, Fatourechi et al. (2009) performed a meta-analysis of 14 randomized control trials comparing CSII to MDI. Of the 611 CSII users, 28 patients experienced greater than or equal to one severe hypoglycemic episode, while 55 of the 602 MDI users experienced greater than or equal to one severe hypoglycemic episode. This correlates to 4.5% of CSII users experiencing severe hypoglycemia compared to 9.1% of MDI users. This meta-analysis found no significant difference in severe hypoglycemic events between CSII and MDI users.

Compared to the hypoglycemic episodes commonly seen in CSII and MDI, some closed loop studies showed a decrease in the incidence or no change in hypoglycemic episodes. For 3 days, Weinzimer et al. (2008) placed 17 type 1 diabetic subjects on open loop control followed by 34 hours of closed loop control. Open loop glucose readings were less than 70 mg/dL 9% of the time, while only 3% of closed loop glucose readings were less than 70 mg/dL. These results were statistically significant \( P < 0.002 \). Although this study defined hypoglycemia as < 60 mg/dL, in clinical practice a blood glucose value of < 70 mg/dL is concerning. A decrease in time spent below this level would be clinically beneficial.

Steil et al. (2006) reported 13 episodes of hypoglycemia (< 60 mg/dL) in their 10 subjects using closed loop therapy, which was identical to the incidence of
hypoglycemia with traditional CSII therapy. Neither group had episodes of severe hypoglycemia.

Renard et al. (2006) studied four, type 1 diabetic patients for 48 hours using implanted closed loop insulin delivery systems. They reported no incidences of severe hypoglycemia with closed loop control. Similarly, Okabayashi, Nishimori and Yamashita et al. (2009) compared the blood glucose control of 13 pancreatic resection patients undergoing standard sliding scale insulin therapy (SS) to 17 pancreatic resection patients undergoing closed loop insulin therapy for 18 hours postoperatively. They observed no instances of hypoglycemia (< 40 mg/dL) with closed loop therapy. In another study, Okabayashi, Nishimori and Maeda et al. (2009) monitored 44 hepatic resection patients using SS and 44 hepatic resection patients using close loop insulin therapy for 18 hours after surgery. They reported no episodes of hypoglycemia (< 40 mg/dL) in either group.

**Insulin.**

Increased insulin use often leads to improved blood glucose control. Several studies showed that the closed loop insulin delivery system promotes increased insulin use. Steil et al. (2006) started 10 previous CSII patients on the closed loop insulin delivery system for 24 hours and reported daily insulin use of 51 +/- 25 units/day with the closed loop system vs. 41 +/- 13 units/day with CSII. These results were statistically significant ($P < 0.05$). In 44 hepatic resection patients using SS and 44 hepatic resection patients using closed loop insulin therapy, Okabayashi, Nishimori, Maeda et al. (2009) reported use of 175 +/- 93 units of insulin with the closed loop system during the 18 hours postoperatively vs. < 24 units in the SS group. Statistical analysis was not
performed on this data. In the 18 hours after pancreatic resection, Okabayashi, Nishimori, Yamashita et al. (2009) documented mean insulin use of 8 units in 13 patients using SS group and 107 units in 17 patients using closed loop therapy group, which was significant ($P < 0.001$).

**Cost savings.**

One advantage to improved glucose control is decreased overall medical cost. The potential cost savings of the closed loop insulin system was demonstrated by Okabayashi, Nishimori, Maeda et al. (2009). Their hepatic resection patients that used closed loop insulin therapy had significantly shorter hospital stays, as well as, significantly fewer surgical site infections. Because of these reasons, the total hospital cost for the closed loop insulin therapy group were $16,407 per person compared to $21,879 per person in the SS group. These results were statistically significant ($P = 0.047$).

**Disadvantages.**

**Hypoglycemia.**

Similarly to other insulin delivery methods, hypoglycemia remains a concern with the closed loop system. In one study, three out of 17 participants experienced a hypoglycemic episode during 34 hours of closed loop control (Weinzimer, 2008). This correlates to 17.7% of subjects experiencing hypoglycemia. No statistical analysis was performed on this data; however, this result is high compared to the frequency of hypoglycemia with MDI and CSII use that was reported by Fatourechi et al. (2009). It is important to note the small study size. In another study, Renard et al. (2009) reported
16 deviations below 4.4 mmol/L (79.3 mg/dL) in their eight subjects during 48 hours of closed loop insulin therapy.

**Glucose sensor unreliability.**

Although glucose sensors have increased in reliability, studies showed that these sensors are not completely accurate. Weinzimer et al. (2008) used subcutaneous glucose sensors during their study and compared these results to venous levels. The subcutaneous glucose sensors commonly underestimated blood glucose levels compared to venous levels, especially postprandially. Renard et al. (2009) reported relative absolute differences of 15.9 +/- 3.8% and 13.9 +/- 2.9% between subcutaneous glucose sensors and lab blood glucose values. In another study, one of the four, type 1 diabetic patients using implanted closed loop insulin therapy had to withdraw from the study because his glucose sensor was reporting abnormal readings compared to actual blood glucose levels (Renard et al., 2006). Despite advancements in glucose sensors, areas for improvement remain.

**Postprandial hyperglycemia.**

Despite overall improved glucose management with the closed loop system, several studies showed elevated blood glucose levels after meals (Renard et al., 2006; Steil et al., 2006; Weinzimer et al., 2008). One reason for this elevation is likely due to a delay in insulin action from subcutaneous insulin administration (Steil et al., 2006). Renard et al. (2006) attempted to eliminate this problem by using intra-peritoneal insulin pumps; however, blood glucose was still higher 2 hours after meals compared to levels outside of meals. This elevation was attributed to delays in sensor signaling, insulin administration and insulin action. Renard et al. (2009) also attempted to address
elevated postprandial blood glucose levels by instructing patients to manually program an insulin bolus 15 minutes before meals. This bolus consisted of 30% of the amount of insulin the patient would normally administer based on their glucose levels and the carbohydrate content of his/her meal. With this bolus, glucose levels returned to a normal state quicker; however, early postprandial blood glucose levels were still elevated. Steil et al. (2006) reported average two-hour postprandial blood glucose levels of 189 +/- 41 mg/dL at lunch, 172 +/- 61 mg/dL at dinner and 225 +/- 35 mg/dL at breakfast, which all exceed recommended values. Similarly, Weinzimer et al. (2008) showed postprandial glucose levels greater than 180 mg/dL.

**Postprandial glucose variability.**

A common frustration with insulin therapy is the need to personalize the insulin regimen to obtain blood glucose levels in the acceptable range. Environmental factors and severity of disease affect the amount of insulin that is needed. The need for personalized insulin regimens leads to increased health care provider input and increased health care cost. Several studies have shown that the closed loop system maintains blood glucose levels in an acceptable range more often than traditional therapy (Okabayashi, Nishimori, Maeda et al., 2009; Okabayashi, Nishimori, Yamashita et al., 2009; Renard et al., 2009; Steil et al., 2006; Weinzimer et al., 2008). This indicates that the algorithm is able to appropriately determine the insulin need of each patient. Because of this, blood glucose levels were less variable between subjects with the closed loop system than with traditional therapies.

Although the overall variability of glucose levels between patients was reduced, one study showed an increase in variability after meals (Weinzimer et al., 2008). This
may be due to glucose sensor unreliability or the algorithm itself. In order to develop a closed loop system that does not require insulin personalization, the issue of postprandial glucose variability must be corrected. One possible solution is to use implanted insulin pumps instead of subcutaneous insulin pumps because of their ability to promote a more natural insulin response. Renard et al. (2009) showed decreased postprandial glucose variability with intra-peritoneal insulin pumps versus subcutaneous pumps.
Discussion

When evaluating the current research on the open and closed loop systems, several study weaknesses must be considered. The majority of studies had few participants and were limited to patients with type 1 diabetes. Likewise, several studies were sponsored by the device manufacturers and one study was performed on company employees. Because of these two factors, the chance of bias is high and the ability to generalize to all diabetic populations is low. In addition to reducing generalization, small study size makes statistical significance difficult to achieve.
Conclusions

Diabetes is one of the leading causes of death in the United States and its prevalence is expected to rise. Without advancements in diabetes treatment, health care providers should also expect a rise in complications from the disease, which will ultimately increase health care spending. Insulin is one of the oldest options for diabetes treatment and remains the best choice for patients with type 1 diabetes. A reduction in blood glucose levels has also been demonstrated in type 2 diabetic patients who are started on insulin therapy early in treatment. Despite its beneficial properties, insulin is underused in many instances because of the risk of hypoglycemia, weight gain and patient fear. A system that combats these deterrents will likely improve diabetes care. In lieu of the flaws surrounding the research, studies show promise that the open and closed loop systems may provide safe insulin delivery with high patient satisfaction.

The most concerning aspect of diabetes is the risk for long term complications associated with prolonged elevated blood glucose. Based on the research available, both the open loop and closed loop systems provide better blood glucose control compared to traditional therapies. The closed loop system provides added benefits by decreasing glucose fluctuations and increasing the time spent in the normal glucose range.

The improved glucose control seen with the open and closed loop systems may be linked to the increased insulin use which was seen in some of the open loop studies and more consistently in the closed loop studies. Use of adequate insulin is often the best way to improve blood glucose control, especially in patients suffering from type 1 diabetes.
Despite better overall glucose control, elevated postprandial blood glucose levels continue to be a concern. Several studies suggested or used a premeal bolus to counteract this phenomenon (Renard, 2006; Renard et al., 2009; Weinzimer et al., 2008). Requiring a premeal bolus defeats the concept of a completely closed loop insulin delivery system (Weinzimer et al., 2008). The implanted artificial pancreas could be beneficial in maintaining the closed loop while reducing postprandial blood glucose levels due to its ability to better mimic the natural insulin response.

Based on the research, it appears hypoglycemia is still a concern with both systems. Although some studies show hope that the open and closed loop systems will provide better control over hypoglycemic episodes, the results are inconsistent.

In addition, concerns with the accuracy of the glucose sensor will likely slow the development of a reliable artificial pancreas. Although the reliability of the glucose sensor has improved, these devices have a tendency to underestimate blood glucose levels, especially postprandially. For a completely closed loop insulin delivery system, sensor readings must be accurate to prevent hyperglycemic and hypoglycemic events.

The ultimate goal of the loop systems is to provide improved care that is easier for the patient. One open loop study showed evidence that patients preferred this system over conventional therapy. With the open loop system, patients spend less time daily caring for their diabetes, which increases their quality of life. Although not yet tested by research, similar results will likely be seen with the closed loop system.

Because of the reduced need for patient input with the open and closed loop systems, the question arises, is reduced patient input a good idea? With currently used therapies, patients need a sound understanding of the disease process, medications
and how to control blood glucose levels. To help combat diabetes and improve quality of life, health care providers focus on these concepts, in addition to diet, activity and weight control. Will the importance of these treatment components be valued less with the new open and closed loop systems?

Lastly, how will our health care system handle the increased costs associated with the open and closed loop systems? Will these systems be restricted to the wealthy in our society or will the government cover the cost? Most Americans cannot afford an additional $500.00 per month to pay for the open loop insulin delivery system. When faced with the decision, patients are more likely to choose the cheaper route even if more convenient and efficacious methods for diabetic control are available.

Because of the prevalence of diabetes, all primary care providers must be familiar with the treatment options available to diabetic patients. They must weigh the advantages and disadvantages of the treatment before recommending a treatment plan to the patient. Small studies on the open and closed loop systems show potential improvement of blood glucose control; however, the cost of these systems will likely be high. Larger studies should be completed to assess the true cost-to-benefit ratio of the open loop insulin delivery system and the artificial pancreas.

As of September 2010, there were six FDA clinical trials underway or recruiting to further explore the feasibility and roles of the artificial pancreas and its components. In addition to studies that strictly assess the value of the artificial pancreas, there is also a study that will explore of the use of a bi-hormonal artificial pancreas including glucagon and insulin vs. an artificial pancreas with insulin alone. Another study will compare different algorithms to determine which provides the best blood glucose control. These
studies, in addition to studies that will likely emerge in the coming months to years, will help to make the portable artificial pancreas a reality.
References


National Diabetes Data Group, National Institute of Diabetes and Digestive and


Figure 1

Open Loop Insulin Delivery System

Figure 2

Bedside-Type Artificial Pancreas STG-22

Note: Adapted with permission from “Close relationship between tissue plasminogen activator-plasminogen activator inhibitor-1 complex with multiple organ dysfunction syndrome investigated by means of the artificial pancreas” by Hoshino, M. et al., 2001, Critical Care, 5, p. 88-99.
Abstract

Objective: The purpose of this literature review was to examine the roles of the open loop insulin delivery system and the artificial pancreas in diabetes care.

Methods: Sources were located by searching PubMed, The National Institutes of Health, The Center for Disease Control and Prevention and Medtronic Diabetes.

Results: There were 44 references obtained including research articles, government brochures and Medtronic, Inc. product information.

Conclusion: The open loop insulin delivery system and the artificial pancreas show potential to reduce the blood glucose levels in diabetic patients leading to decreased diabetes associated complications. Likewise, the decreased treatment burden placed on the patient will lead to increased patient satisfaction and, hypothetically, increased patient compliance. The cost must be considered before widespread use of these products begins. Larger, randomized control trials utilizing different diabetic populations should be performed to determine the cost-to-benefit ratio of the open loop insulin delivery system and the artificial pancreas.