THE EFFICACY OF A BI-HORMONAL CLOSED-LOOP SYSTEM AT PREVENTING HYPOGLYCEMIA DURING AND AFTER EXERCISE

by

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A THESIS

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Type 1 diabetes mellitus (DM1) has had a growing incidence over the past decade. This autoimmune disease is characterized by the destruction of beta cells in the pancreas, which makes the individual unable to produce insulin, a hormone required for glucose use in the cells. DM1 patients must check their blood glucose levels many times throughout the day, and administer a carefully calculated amount of synthetic insulin to cover food and maintain a target range of blood glucose levels.

The closed-loop system is a compilation of DM1 control devices that calculates the correct amount of insulin (and in the case of a bi-hormonal system, glucagon) needed to maintain a target range of blood glucose readings. This thesis seeks to determine whether it is necessary for an exercise announcement option to be programmed into the algorithm so that the system can prevent hypoglycemia during and after exercise.

It was found that using the closed loop with an exercise announcement is no more efficient at preventing hypoglycemia during and after exercise than a closed loop system without an exercise announcement or an open loop system ($p=0.57$ and 0.55, respectively). However, it is important to note that these results are only preliminary

results of the Artificial Pancreas Control (APC) study in progress at Oregon Health and Sciences University; this thesis will present results from the first seven subjects of the APC study. Hardware errors, failed infusion sites, and early termination of individual subject studies make for a small sample size, and thus insignificant results. However, closed loop technology is promising, and once the APC study is completed it will act as a guide for future research in the field. Artificial pancreas technology is ever moving forward, and will eventually create a device or system that allows type 1 diabetics to live without constantly thinking of diabetes care and blood glucose control.

Acknowledgements

I would like to thank Dr. Jessica Castle for opening up her study at OHSU and allowing me to ask questions and tag along, not only to learn about the bi-hormonal system and how it works, but also to learn about the process of research studies and the work that goes into making a study visit successful and comfortable for the participant.

I would also like to thank Dr. John Halliwill and Professor Mark Carey for guiding me through the thesis process and assisting me in writing and defending my thesis. Their generous help and willingness to meet with me whenever needed has been a lifesaver. Without the help of Dr. Halliwill, I would had never come in contact with Dr. Castle and her closed-loop study, and would not have been able to produce the following thesis.

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Introduction

There are twenty-six million people living with diabetes mellitus in the United States. Of these twenty-six million, twenty-three million are living with type 2 diabetes, which is characterized by insulin resistance primarily due to genetics with lifestyle and diet components. The other three million are living with a disease characterized by insulin deficiency, related to genetic risk and other unknown causes: type 1 diabetes mellitus (DM1). DM1 is an autoimmune disease that occurs when the insulin-producing cells of the pancreas are destroyed by a person's immune system, causing patients to rely on synthetic insulin to be taken subcutaneously[1] through injections or via an insulin pump.

Many advances have been made in the treatment and management of DM1. In the 1960s, type 1 diabetic patients had to rely on urine testing for blood glucose measurements and multiple-use glass needles to administer insulin. The 1970s introduced the first blood glucose meter, and with the late '70s came the first insulin pump—a large device that had to be carried in a backpack (Hurley, 2010). As technology continued to improve, medical devices became smaller, more convenient, and more accessible to the public. Now, there are many different insulin pumps and devices called continuous glucose monitors[2]. DM1 control has become decreasingly invasive and increasingly user-friendly, allowing DM1 patients to spend less time thinking about calculations and numbers.

Currently, all methods of DM1 control are known as "open-loop" systems, meaning that a patient or caregiver must input information in order for the system to

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[1] Under the skin

[2] Devices that measure interstitial fluid glucose levels and display them in real time

work properly. However, clinical trials are being completed on "closed-loop" systems[3] (systems that take information and determine the amount of insulin or glucagon to deliver). The purpose of these systems is ultimately to replicate the mechanisms of a working pancreas in non-diabetic individual.

This thesis will present a brief background of type 1 diabetes mechanisms and current known control methods, as well as the design of the closed loop system that is currently being tested under the guidance of Dr. Jessica Castle and Dr. Peter Jacobs of the Harold Schnitzer Diabetes Center at Oregon Health and Sciences University. The results that are presented are preliminary results (subjects 001-004, 006-007) of the ongoing Artificial Pancreas Control (APC) study.

[3] Also known as an artificial pancreas

Background

Type 1 diabetes history and mechanisms

The word *diabetes* comes from a Greek word meaning "to pass through." This refers to one of the cardinal signs of diabetes: frequent urination. Later, the word *mellitus* was added to the title. Mellitus is the Latin word for "honey-like," which referred to the taste of diabetic patients' urine. It wasn't until the late 19th century that diabetes mellitus type 1 was associated with the pancreas. Prior to the discovery of insulin by Frederick Banting and James Macleod in 1921, DM1 patients controlled their health by adopting a starvation diet at the recommendation of their doctors, and would not eat until their urine tested free of sugar (Hurley, 2010). Prior to the creation of blood glucose monitors, urine was tested either by the appearance, the taste, or urine strips that would turn a different color depending on the level of glucose (Hurley, 2010; Daneman, 2006). DM1 patients that underwent the starvation diet were in constant ketoacidosis, and were bed-ridden until they passed away at a young age. The starvation diet did not treat DM1, instead, it served to prolong a patient's life until the cellular starvation became to be too much for the body tissues to handle (Hurley, 2010).

Type 1 diabetes results from cell-mediated autoimmune destruction of the beta cells—insulin-producing cells—of the pancreas. There are many possible autoantibodies[4] that can be found in a DM1 patient, including islet cell[5] autoantibodies, insulin autoantibodies, glutamic acid decarboxylase (GAD_{65}) autoantibodies, and

[4] A "marker" that immune cells use to signal the destruction of tissues
[5] Islet cells contain both beta (insulin-producing) and alpha (glucagon-producing) cells

tyrosine phosphates IA-2 and IA-2β autoantibodies. A diagnosis DM1 occurs when one or more of these autoantibodies are present in an individual with fasting hyperglycemia[6]. The rate of beta cell destruction varies from patient to patient, but once severe hyperglycemia or ketoacidosis[7] occurs, it is highly probable that insulin production has ceased and the patient must rely on the synthetic[8] insulin administration (Daneman, 2006).

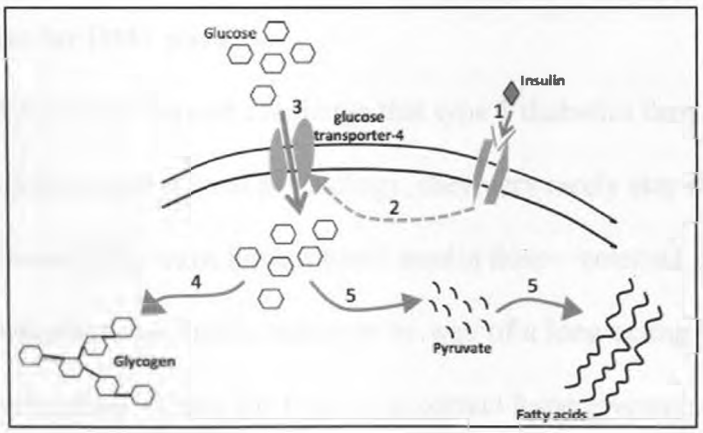

Figure 1: A target cell (Kleck)

This image outlines the effect that insulin has on cells in need of glucose. Once insulin binds to the insulin receptor, the cell goes through a cascade of reactions that ultimately leads to the GLUT-4 transporter translocating to the surface of the cell. This allows glucose to be pulled into the cell and be used for various energy-producing processes

Insulin is required for all DM1 patients to stay healthy and maintain good blood glucose control. In a non-diabetic, insulin, an endocrine hormone is released from the beta cells of the pancreas when the pancreas detects a rise in blood glucose levels. It travels through the bloodstream and attaches to insulin receptors on muscle and tissue

[6] Fasting hyperglycemia occurs when an individual presents with a blood glucose of >126 mg/dL after fasting for at least eight hours
[7] Ketoacidosis occurs when the body cannot use glucose as a fuel source and instead breaks down fat for energy, and produces ketones
[8] Also known as insulin aspart

cells causing the target cell to go through a cascade of chemical reactions. This ultimately leads to the translocation of a GLUT-4[9] transporter to the cell surface. This translocation allows glucose to be pulled from the bloodstream into the cell to be used as energy (Roth & Zick, 2000). This mechanism works similarly in people with type 1 diabetes, except that they must take insulin manually instead of producing it in their body.

Current control methods for DM1 patients

Blood glucose control is the largest challenge that type 1 diabetics face. Since DM1 patients lack the detection and control physiology, they very rarely stay in a tight blood glucose range[10]. Instead, they must have a basal insulin dose—constant insulin, either through small increments in an insulin pump or by way of a long-acting insulin injection—as well as a bolus dose—doses for food or to correct hyperglycemia. The factors and dose amounts for insulin varies by patient and time of day, and must be calculated for each person. Typically, these ratios are entered into an insulin pump, but are occasionally written down and used for insulin injections. There are two standard ways of measuring blood glucose for DM1 patients: 1) using a blood glucose meter anywhere from 3 – 10 times daily, or 2) using a real-time continuous glucose monitor (CGM). A CGM works by measuring the glucose levels of the interstitial fluid that surrounds the platinum wire that is placed subcutaneously. These values are sent to a receiver every five minutes. While these methods have improved for blood glucose control over the years, they still require a large amount of thought on the DM1 patients'

[9] Glucose transporter-4
[10] Normal blood glucose range for non-diabetics is defined as 70-100mg/dL

part. The ratios for insulin pumps or insulin injections must be calculated and kept up-to-date, and outside information that could affect blood glucose levels must be accounted for.

Patients with type 1 diabetes also fail to release glucagon, a peptide hormone that works to raise blood glucose. Glucagon is produced in the alpha cells of the pancreas, and in non-diabetics is released in small amounts when a drop in blood glucose is detected. Glucagon causes the liver to breakdown glycogen into glucose molecules, effectively raising blood sugar. DM1 patients must be administered glucagon when their blood glucose levels dip dangerously low. However, synthetic glucagon is not as stable as synthetic insulin. It must be mixed before administration, and it must be administered in large doses. Once glucagon is reconstituted, it is only viable for twenty-four hours. Thus, DM1 patients reserve glucagon treatment for extremely dangerous low blood glucose levels, and instead treat hypoglycemia or dropping blood glucose levels with oral glucose forms.

Exercise and DM1

Blood glucose can be affected by any number of factors[11]. Usually, each individual with type 1 diabetes responds uniquely to different stressors, but exercise is one that tends to have the same response across the board. This is due to the physiological response to the body's need for energy when exercise begins. The body uses a few different energy substrates—muscle glycogen, plasma glucose, free fatty acids, and intramuscular triglycerides. When exercise begins, GLUT-4 receptors

[11] These factors can include different types of food, stress, excitement, and exercise.

translocate to the surface of the cell, much like they do when insulin is circulating the bloodstream. During exercise, this process is completed without insulin (Goodyear & Kahn, 1998). DM1 patients tend to become hypoglycemic during and after exercise. GLUT-4 receptors translocate whether or not insulin is present during exercise. If insulin is present, more receptors will translocate and pull more glucose from the bloodstream causing patients to experience hypoglycemia. Since DM1 patients also lack natural glucagon, they have no way of replacing the glucose that was used for energy (Derouich & Boutayeb., 2002). This increase in GLUT-4 receptor availability can last for hours after exercise, which increases the risk for post-exercise hypoglycemia.

Existing research and practice in closed-loop systems

Until recently, methods of treatments have been kept relatively separate from one another, and each treatment requires input from the patient or a caregiver. These systems are known as open-loop systems. Normally, DM1 control is maintained by frequent capillary blood glucose readings, continuous glucose monitors, insulin pumps, or insulin injections. By combining different medical devices with algorithms, researchers have been able to develop a closed-loop system that is able to take information such as a glucose reading, use predictive algorithms, calculate the amount of insulin or glucagon needed to maintain blood glucose measurements in a tight range, and carry out the dosing (Bakhtiani, *et. al.*, 2013; El Youssef, *et. al.*, 2009; Jacobs, *et. al.*, 2011; Pevser, *et. al.*, 2014).

There are two types of closed-loop systems: unihormonal and bi-hormonal systems. Unihormonal systems combine a CGM, insulin pump, and a controller with algorithms. This system works by giving insulin when needed, and suspending the

insulin pump when blood glucose falls. Once the CGM predicts a hypoglycemic episode, it sends information to the computer, which then notifies the insulin pump to suspend insulin for ninety minutes (Buckingham, *et. al.*, 2009). The unihormonal system is efficient at preventing quick drops in blood glucose if the predictive alarm occurs far enough in advance and if the only cause for hypoglycemia is too much insulin.

Bi-hormonal systems integrate both glucagon and insulin into the set-up. By using two different hormones, these systems have been more successful at preventing impending hypoglycemia. Some studies "utilize[s] control algorithms that alter output based on proportional (difference between actual and target levels), derivative (rate of change) and integral (time-related summative) errors in glucose" (Youssef, *et. al.*, 2009). In these systems, glucagon was given in smaller doses for smaller drops in blood glucose, and was generally successful at preventing hypoglycemia. However, there were some instances in which the doses of glucagon failed to prevent hypoglycemia. Most of these instances occurred when the subject already had a large amount of insulin in his or her bloodstream. A number of studies have proven that glucagon works less efficiently when insulin is still in the bloodstream (Bakhtiani, *et. al.*, 2013; Castle, *et. al.*, 2010). While insulin works to decrease blood glucose levels, glucagon works to increase blood glucose levels. If there is a large amount of insulin present, the glucagon will be working against the insulin action, and will not work as efficiently.

Artificial Pancreas Control design

Study design

The artificial pancreas control (APC) study uses two Tandem t:slim pumps, one Dexcom G4 sensor, and a Google Nexus 5 phone. The subject is outfitted with both pumps; one with insulin, inserted into the right side of the subject's body, and one with Glucogen—a brand name for glucagon—inserted into the left side of the subject's body. The subject is also paired with a Dexcom sensor (placed subcutaneously) and transmitter. The APC controller is the Google Nexus 5 phone, which runs the algorithm (discussed below). This phone is plugged into a battery case, and connected to the Dexcom G4 receiver. Every five minutes, the Dexcom receiver transmits its glucose reading to the algorithm in the phone, which runs calculations and will send insulin and Glucagen infusion commands to the respective T-slim pumps via Bluetooth (see figure 2).

For study purposes, the phone also communicates via the Cloud with other computers. It steadily uploads the data it calculates, as well as the sensed blood glucose. This data is then portrayed on a password-protected website that is viewable from any browser (IDE, 2014).

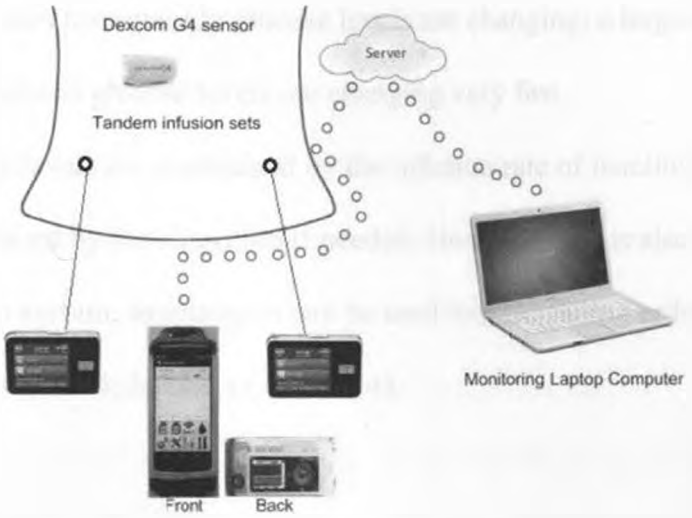

Figure 2: Study design (IDE, 2014)

A schematic of the different components of the APC study and how they connect.

Study algorithm

The APC algorithm utilizes the fading memory proportional derivative controller (FMPD). The proportional portion of this algorithm measures the difference between the sensed blood glucose and the target blood glucose[12,13]. Positive proportional errors mean that sensed glucose levels are above target, and will cause the algorithm to calculate a larger amount of insulin to be infused. Negative proportional errors mean that sensed glucose is below target. The derivative error measures the amount of change in the sensed glucose, calculated over a ten-minute time interval. Positive derivative errors mean that the sensed glucose levels are rising, while negative derivative errors mean that sensed glucose levels are falling. The degree of the

[12] Daytime target blood glucose is set at 115 mg/dl.
[13] Nighttime target blood glucose is set at 140 mg/dl.

derivative error indicates how quickly glucose levels are changing; a large derivative error will mean that sensed glucose levels are changing very fast.

Blood glucose levels are maintained by the infusion rate of insulin; this rate can be increased or decreased by the algorithm if needed. However, this is also a bi-hormonal closed-loop system, so glucagon can be used to raise falling or low blood glucose if needed (IDE, 2014; Jacobs, *et. al.*, 2014).

Insulin infusion

The APC algorithm calculates three different types of insulin infusion rates, and adds them together for a total insulin infusion rate (IIR_T, measured in units/hour). The first rate to be calculated is the basal rate (IIR_B). This is a relatively constant value, and is calculated using 50% of the total daily insulin requirement (TDIR[14]) divided by 24. The IIR_B is constant until blood glucose declines below target. When sensed glucose is below target, the IIR_B is decreased until the sensed glucose reaches 60% of target glucose, at which point the IIR_B is shut off.

The other two rates calculated are the proportional error insulin rate (IIR_{PE}) and derivative error insulin rate (IIR_{DE}). The IIR_{PE} accounts for the difference between the target blood glucose and the sensed glucose level, while the IIR_{DE} takes into account the rate of change of sensed glucose. The actual insulin infusion rates are affected by the gain multiplier, a multiplier that adjusts for differences in insulin sensitivity[15]. There is also a fading memory component to the algorithm, which means that the algorithm

[14] In most cases, TDIR is taken as reported from the subject. However, for every percentage point above 7%, TDIR is increased by 6.67% to take into account poor blood glucose control and common hyperglycemia

[15] The gain multiplier is calculated from the TDIR. The higher the TDIR, the higher the gain multiplier

gives more weight for recent proportional and derivative errors over past proportional and derivative errors.

The IIR_T is calculated by adding IIR_B, IIR_{PE}, and IIR_{DE} together. The IIR_T is the amount of insulin expected to be infused over one hour. However, it may change with subsequent data from the Dexcom sensor, so this value is divided by twelve and given over a five-minute period, to be adjusted with the next input of data.

Meal boluses occur at the start of a meal. The amount of grams of carbohydrates for a given meal is input into the algorithm, and the algorithm calculates a bolus using the grams and TDIR. For the purposes of this study, only 60% of the expected meal bolus is given to the subject.

Once insulin is infused, insulin on board (IOB) must be calculated and taken into account for future IIR_T calculations. Insulin can stay active for hours after delivery. In this FMPD algorithm, IOB levels rise linearly for thirty minutes after delivery, then stay at a maximum level for sixty more minutes. Ninety minutes after delivery, IOB levels decrease exponentially. The IOB levels are calculated every five minutes, with each new IIR_T. If the IOB rises above 10% of TDIR, the IIR_T will be reduced. Once IOB reaches 30% of TDIR, IIR_T will be reduced to 0 (IDE, 2014; Jacobs, *et. al.*, 2014).

Glucagon infusion

Total glucagon infusion rate (GIR_T)[16] is calculated by adding the proportional error infusion rate (GIR_{PE}) and the derivative error infusion rate (GIR_{DE}). There is no basal glucagon. GIR_{PE} takes into account the proportional errors that happened within

[16] measured in micrograms/hour

fifteen minutes prior to the time of calculation using the glucagon set points[17]. GIR_{DE} takes into account the derivative errors that happened within ten minutes prior to the time of calculation. Both the GIR_{PE} and GIR_{DE} have the fading memory component. Once glucagon is delivered, it is expected to decay exponentially over time.

The efficiency of glucagon at raising blood glucose is affected by insulin already in the system (IOB). Therefore, GIR_T must be modified according to the IOB value. If IOB is low, then the maximum GIR_T allowed can be low as well. If IOB is high, the maximum GIR_T will be higher. GIR_T in a fifty minute period can be up to 2.0 mcg/kg. If this maximum dose is fully delivered over fifty-minutes, two things will change in the algorithm. First, there will be a refractory period of fifty-minutes in which no glucagon can be delivered. Second, the IIR_T will be decreased by 75% for forty minutes so as to give the glucagon an optimal environment to work in, and to avoid potential overdose of insulin (IDE, 2014; Jacobs, *et. al.*, 2014).

Exercise announcement programming

There is an exercise announcement option in the algorithm as well. If used, it affects both IIR_T and GIR_T for one and a half hours after the initial start. The announcement should occur at the start of exercise, and is completed by pushing a button on the controller phone. From there, insulin is shut off for thirty minutes and then reduced by 50% for one hour, for a total change of 90 minutes.

[17] Glucagon set point is 95 mg/dl

Two changes occur in the glucagon calculations. First, the maximum dose allowed for glucagon is increased by the same parameters that are used when IOB is high. Second, the glucagon set point is increased, meaning that glucagon can be infused at a higher sensed glucose reading. Instead of an optimal set point of 95 mg/dl, exercise announcement sets an optimal set point of 110 mg/dl. Once these adjustments are made, they will be maintained for one and a half hours after the start of exercise (IDE, 2014; Jacobs, *et. al.*, 2014).

Methods

This study took place through the Harold Schnitzer Diabetes Health Center at the Hatfield Research Clinic (HRC) in Oregon Health and Sciences University (OHSU). It is designed to compare glucose control resulting from 1) open loop control, 2) a bi-hormonal closed-loop system with exercise announcement and 3) a bi-hormonal closed-loop system without exercise announcement. The following procedure is an outline of the APC Study Procedure used at OHSU. with extra information required for the purpose of this thesis.

Subjects

Subjects were adults between 18 – 45 years of age with type 1 diabetes. There were up to fifty subjects screened, with a goal of twenty-one subjects enrolled. Subjects must have a diagnosis of type 1 diabetes for at least 1 year, be willing and able to perform 45 minutes of exercise, and use an insulin pump at the time of screening. Subjects must not have met any exclusion criteria (Appendix A). Subjects were recruited from the OHSU website and clinics, as well as from past clinical trials completed under Drs. Castle or El Youssef. Subjects may also have been recruited by using the diabetes research registry and www.clinicaltrials.gov.

For the purposes of this thesis, data was taken from subjects 001, 002, 003, 004, 006, and 007 for analysis.

Procedure

Subjects made seven total visits to OHSU's Hatfield Research Clinic. These visits were made up of the screening process, three sensor insertion visits, and three 21-hour treatment visits.

Screening Process (visit 1)

Subjects first underwent a screening process. This process took place within 12 weeks before visit 2. Consent forms were signed at this initial visit. Capillary blood glucose was measured and a venous blood sample was taken in order to measure HbA1c, complete blood count, complete metabolic panel, and c-peptide. An EKG was performed, and then subjects underwent VO_2max testing[18] if they met all inclusion criteria and no exclusion criteria.

Sensor insertion (visits 2, 4, 6)

Subjects completed a sensor insertion visit no more than 72 hours before each treatment visit. Subjects were fitted with a Dexcom™ G4 CGM and were trained on how to use and calibrate the CGM. The CGM was inserted into the subject's abdomen or flank.

21-hour treatment (visits 3, 5, 7)

Subjects were asked to avoid exercise for 24 hours prior to treatment visits. Subjects arrived at OHSU's HRC at 8pm. For two of the three visits, the subjects underwent the closed-loop treatment. Upon arrival to the HRC, subjects were instructed

[18] This test was for the purpose of determining optimal exercise level; subjects exercised at 60% of their maximum heart rate.

to disconnect their own insulin pump, and instead used two Tandem® Diabetes Care t:slim infusion pumps for the duration of the visit. One infusion pump was filled with aspart insulin, and the other with glucagon[19]. The subject was also in possession of a Google Nexus 5 phone, which ran the computerized FMPD algorithm every five minutes upon arrival of a new blood glucose reading from the Dexcom sensor. The Google Nexus 5 phone sent instructions wirelessly to the two t:slim pumps, as well as sent data to a cloud server every five minutes. Once the subject was fitted and comfortable with all devices, research staff left the subject's room, but had access to the cloud data, as well as a chat device if they had any questions or concerns. The subject recorded any symptoms and occurrences in a journal. A research technician was monitoring the data and could intervene when necessary.

The research technician calibrated the Dexcom sensor every six hours. The subject's blood glucose readings were measured every two hours during the day and every three hours at night. This was a blind measurement, and subjects were not aware of their capillary blood glucose (CBG) measurements for the duration of the study, but could view the sensed glucose on the phone and/or Dexcom. When the subject ate[20], the meal was announced to the Google Nexus 5 phone.

In the morning after arrival at the research center, the subject ate breakfast at 6am. Two hours after the meal, the subject exercised for 45 minutes on a treadmill at a fixed rate of 60% of their maximum heart rate[21]. One closed-loop treatment visit

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[19] Glucagon will be reconstituted to a concentration of 1.0mg/mL using sterile water.
[20] A low carbohydrate meal in which all carbohydrates were measured.
[21] Determined from the VO_2max test at the screening visit

included an exercise announcement to the controller. The other closed-loop treatment visit did not include an exercise announcement. Three hours after exercise, the subject ate lunch. Five hours after lunch the closed-loop system was terminated, the two t:slim pumps and Dexcom sensor were removed, and the subject was released.

The other 21-hour treatment visit consisted of an open-loop treatment. During this visit, subjects wore the Dexcom sensor, but managed their own blood glucose control. There was no suggested protocol for preparing for exercise; subjects were allowed to change their basal rates and meal boluses in order to prepare for exercise.

If the sensed blood glucose fell below 70 mg/dl at any point in the study, a CBG measurement was taken and rescue carbohydrates were given if needed. If the sensed glucose fell below 50 mg/dl at any point in the study, the visit was terminated and the subject was asked to reschedule and start that particular visit over. If the sensed glucose rose above 300 mg/dl, a CBG measurement was taken, ketone levels were measured (if needed), and termination was considered for that visit.

Hypothesis

It is expected that the closed-loop system with exercise announcement will be more successful at preventing hypoglycemia during and after exercise than the closed-loop system without exercise announcement and the open loop system. It is also expected that both closed loop systems will present with tighter blood glucose control (i.e. a smaller standard deviation and a higher percentage between 75-180 mg/dl) than the open loop system.

Results

There was a total of five participants in the open loop and closed loop portion of the study, and six participants in the closed loop with exercise announcement. The average blood glucose reading over nine hours (one hour prior to the start of exercise, and eight hours following the start of exercise) for the open loop condition (OL) was 161.6±54 mg/dl. The average blood glucose reading for the closed loop condition (CL) was 152.4±47.8 mg/dl. The average blood glucose reading for the closed loop with exercise announcement condition (CLX) was 154.6±47.8 mg/dl. Further study into the results and trends follows.

The following three graphs show individual subjects' sensed blood glucose readings over time with the average blood glucose reading (and standard deviation) over time overlaid. The fourth graph is the average sensed blood glucose readings over time from each different condition.

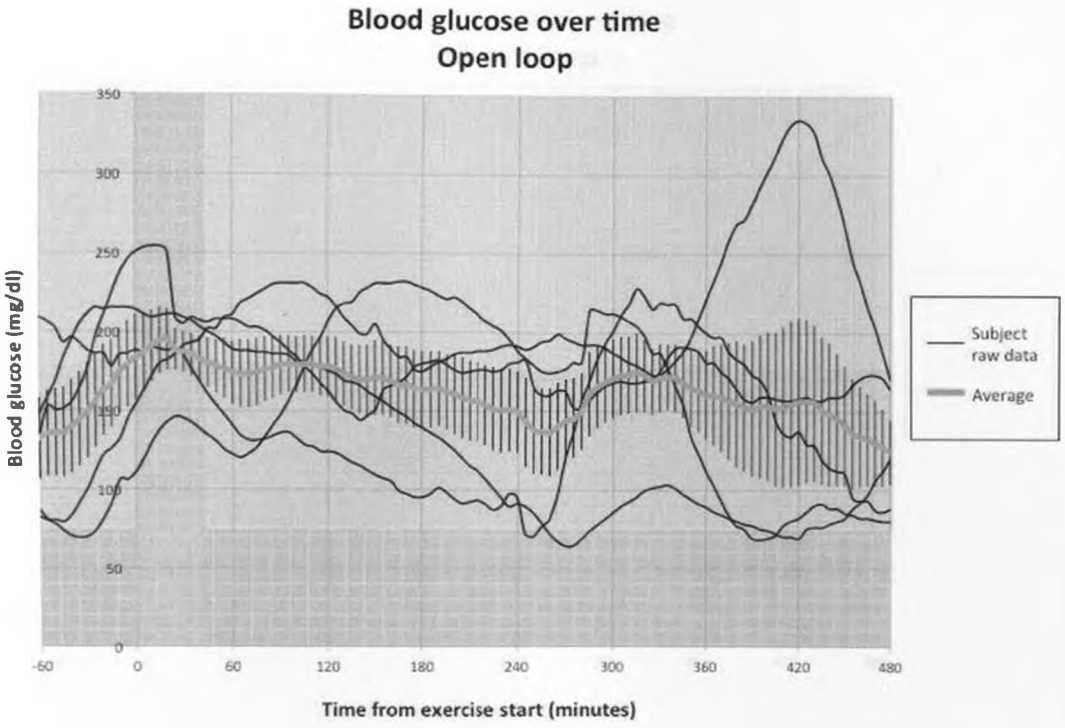

Figure 3: Open loop graph

This graph is the compiled data from the open loop portion of the study. Each black line represents the raw data of a study participant; the blue line represents the average blood glucose readings of each five-minute increment. The red portion of the graph represents hypoglycemia, the green portion represents target blood glucose, and the orange portion represents hyperglycemia. The purple portion of the graph represents the time the subject was exercising.

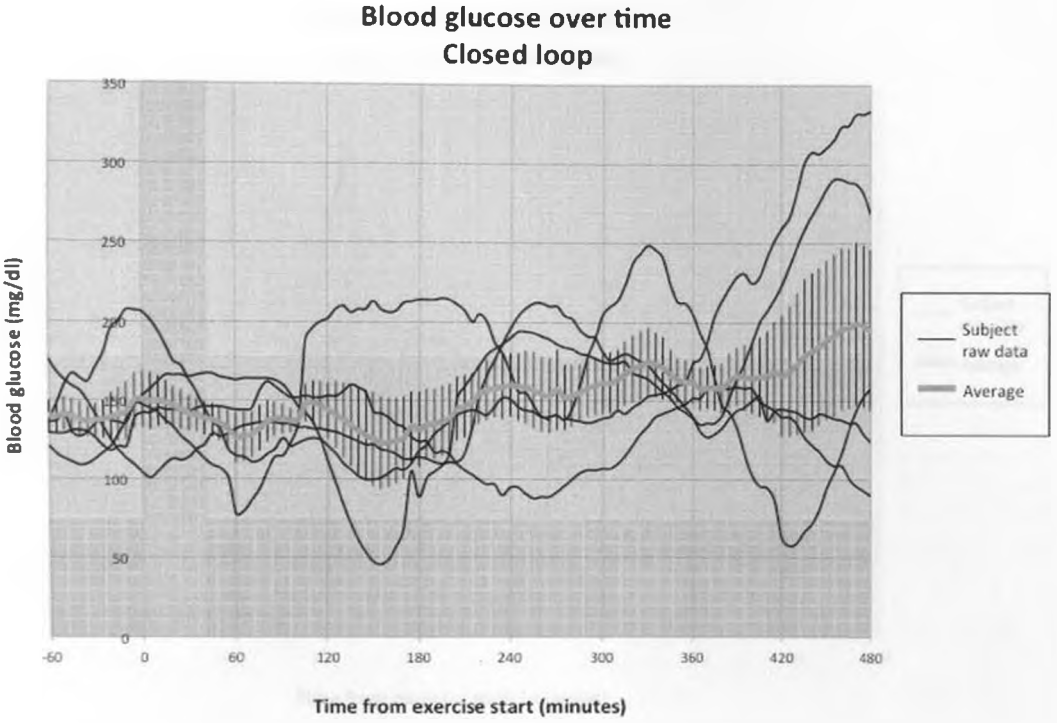

Figure 4: Closed loop graph

This graph is the compiled data from the closed loop portion of the study. Each black line represents the raw data of a study participant; the blue line represents the average blood glucose readings of each five-minute increment. The red portion of the graph represents hypoglycemia, the green portion represents target blood glucose, and the orange portion represents hyperglycemia. The purple portion of the graph represents the time the subject was exercising.

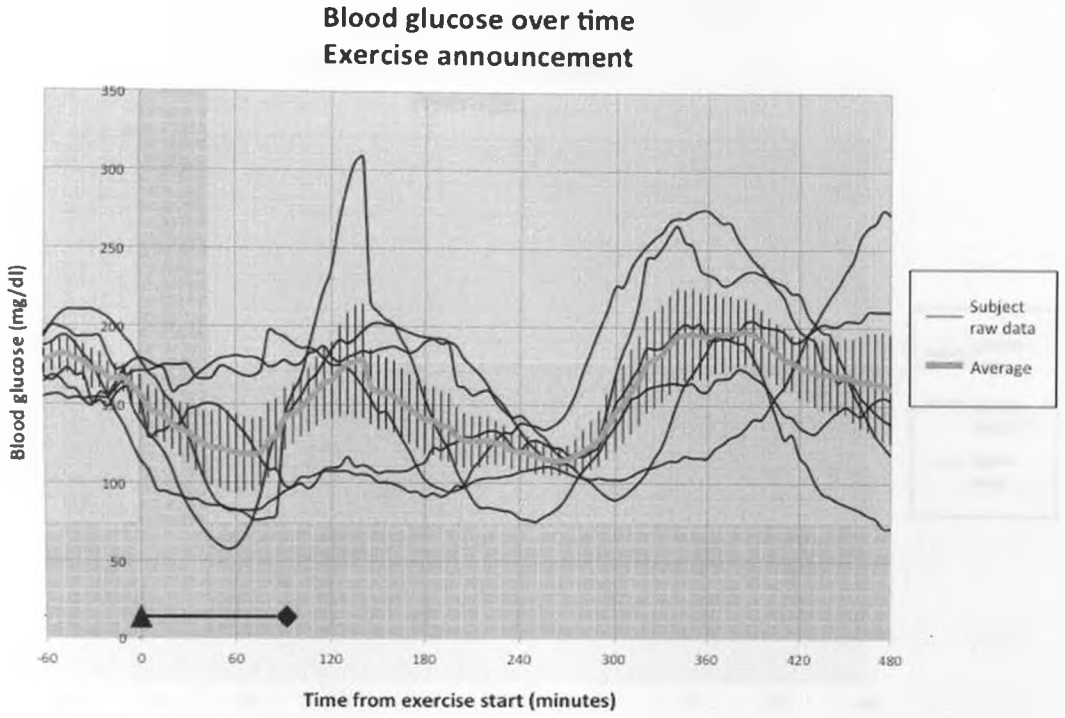

Figure 5: Closed loop with exercise announcement graph

This graph is the compiled data from the closed loop with exercise announcement portion of the study. Each black line represents the raw data of a study participant; the blue line represents the average blood glucose readings of each five-minute increment. The red portion of the graph represents hypoglycemia, the green portion represents target blood glucose, and the orange portion represents hyperglycemia. The purple portion of the graph represents the time the subject was exercising. The line enclosed by a triangle and diamond represents the portion of time that the exercise announcement algorithm changes were in effect.

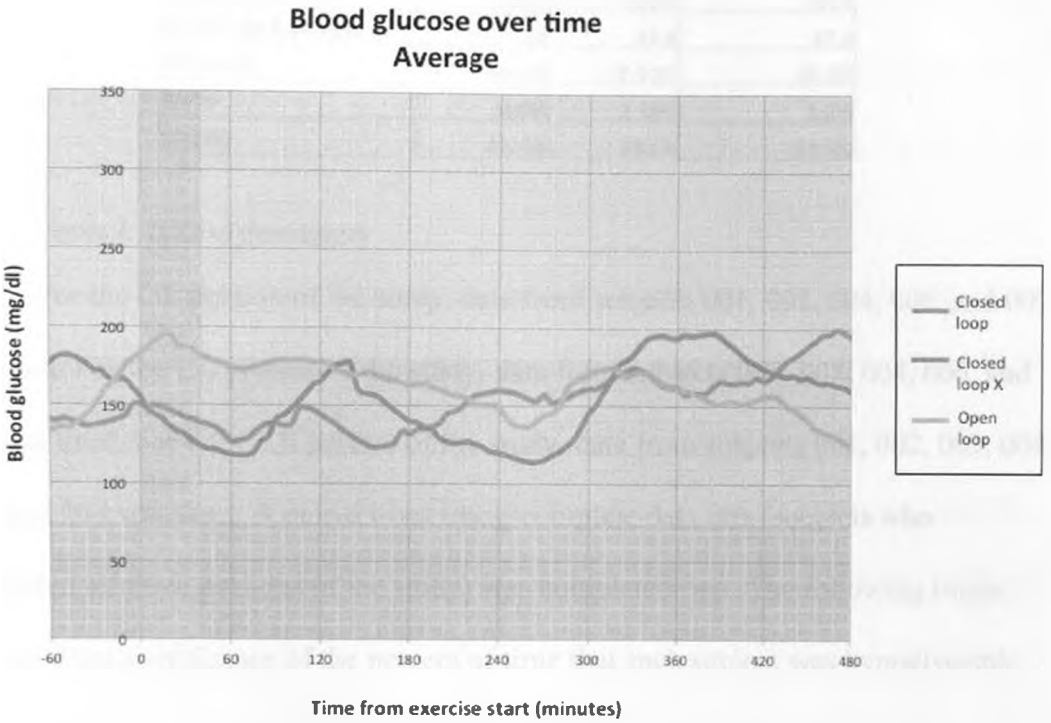

Figure 6: Average blood glucose over time

This graph shows the average blood glucose of each time increment, for each separate study condition.

The parameters for evaluation of the success of this study were the percent of time in target range (75-180 mg/dl), the percent of time spent in hypoglycemia (below 75 mg/dl), and the percent of time spent in hyperglycemia (above 180 mg/dl). These measurements were taken from the raw data, not the average trends. The following table shows these percentages for each component of the study, as well as overall average blood glucose reading and the standard deviation from that average.

	Open Loop	Closed Loop	Closed Loop with announcement
Average BG	161.6	152.4	154.6
Standard deviation	54	47.8	47.8
% 75-180	53.6%	78.50%	69.3%
%<75	4.0%	2.38%	1.2%
%>180	42.4%	19.1%	29.5%

Figure 7: Table of percentages

For the OL portion of the study, data from subjects 001, 002, 004, 006, and 007 was used. For the CL portion of the study, data from subjects 002, 003, 004, 006, and 007 was used. For the CLX portion of the study, data from subjects 001, 002, 003, 004, 006, and 007 was used. A paired t-test using complete data sets (subjects who completed all three portions of the study) was completed first. The following t-tests measured the significance of the percent of time that each subject was hypoglycemic (figure 8).

Subject	Open Loop	Closed Loop	Closed loop with exercise announcement
1	0.0183		0
2	0.101	0	0
3		0.0458	0
4	0	0	0
6	0.083	0.0769	0
7	0	0	0.073

Figure 8: Fraction of time spent in hypoglycemia per subject

This table represents the fraction of time that each subject spent in hypoglycemia. Subject 001 did not complete the closed loop portion of the study, and subject 003 did not complete the open loop portion of the study.

The p-value of a paired, two-tailed t-test comparing the OL and CL portions of the study was 0.36. The p-value of a paired t-test comparing the OL and CLX portions of the study was 0.54. The p-value of a paired t-test comparing the CL and CLX was

0.98. Because there were only four subjects with complete data sets, unpaired t-tests were also completed. An unpaired t-test comparing the OL and CL portion of the study resulted in a p-value of 0.57. An unpaired t-test comparing the OL and CLX portion of the study resulted in a p-value of 0.57. An unpaired t-test comparing the CL and CLX resulted in a p-value of 0.55.

The secondary parameters used to measure the success of this study included the standard deviation of each subject, and the percent of time spent in target range (75-180 mg/dl) for each subject.

The p-value for an unpaired t-test comparing the standard deviations from the OL and CL portions of the study was 0.73. The p-value for an unpaired t-test comparing the standard deviations from the CL and CLX portions of the study was 0.84. The p-value for an unpaired t-test comparing the standard deviations from the OL and CLX portions of the study was 0.84.

The percent of time spent in target range for each subject was measured as well.

Subject	Open Loop	Closed Loop	Closed Loop with exercise announcement
1	0.651		0.615
2	0.615	0.872	0.512
3		0.569	0.734
4	0.66	0.716	0.817
6	0.55	0.771	0.817
7	0.202	1	0.633

Figure 9: Percent of time spent in target (75-180 mg/dl) range

The p-value for an unpaired t-test comparing the fraction of time spent in target range between the OL and CL portions of the study was 0.06. The p-value comparing the same measurements between the CL and CLX portions of the study was 0.30. The p-value comparing the OL and CLX portions of the study was 0.17.

Discussion

These results are preliminary results of the Artificial Pancreas Control study that is in progress at Oregon Health and Sciences University. None of the results are so far significant ($p>0.05$)[22], but there is good direction for the remainder of the APC study. Both the closed loop (CL) system and the closed loop with exercise announcement (CLX) system seem to be efficient at avoiding hypoglycemia during exercise. However, after exercise there were a few more hypoglycemic instances in the CL portion of the study than the CLX portion of the study. This wasn't proved to be significant by the data, but it does show that the decrease of insulin and increase of glucagon by the exercise announcement has a long-term effect for the hours after exercise. During exercise, there is insulin- and noninsulin- mediated glucose uptake into cells for energy use. If insulin is present in a DM1 patient in the bloodstream, it will be used to facilitate glucose transport into cells, regardless of falling blood glucose levels (Briscow, *et. al.*, 2007). The exercise announcement algorithm decreases the amount of insulin (basal and extra) given during the programmed duration, and thus lowers the amount of insulin available for cells to use to transport glucose.

By increasing the maximum amount of glucagon dosage allowed during the exercise announcement program, hypoglycemia was avoided. In DM1 patients, the typical response to falling blood glucose levels are blunted; glucagon, epinephrine, norepinephrine, growth hormones, and lipolysis all occur in non-diabetics. Many of these hormones fail to respond, or respond weakly, when a DM1 patient becomes hypoglycemic. It was found, however, that the hormone response for a single episode of

[22] Reasons for insignificance will follow this section

hypoglycemia was much greater when there were no hypoglycemic episodes in the twenty-four hours prior. When multiple hypoglycemic episodes occurred, the hormone response was significantly lower (Briscow, *et. al.*, 2007). Preventing hypoglycemia in the APC study gives the body a chance to reserve its strong hypoglycemic response for a later episode, and by increasing the maximum amount of glucagon allowed, hypoglycemia during exercise is less likely to happen.

It was also expected that both closed loop systems would allow for tighter control (i.e. a smaller standard deviation and a higher percentage of time spent in target range, 75-180 mg/dl) when compared to the open loop system. While neither of these parameters showed statistical significance ($p>0.05$), it is important to explore why control may be different across systems.

Open loop control is typically predictive or reactive, especially when a patient is able to view their blood glucose levels constantly[23]. Many DM1 patients are used to experiencing hypoglycemia during and after exercise, so they consciously make changes so that their blood glucose levels run higher than normal. This will result in higher average blood glucose and less time spent in target range. Open loop control essentially puts a human (the subject) in control of the system. While DM1 patients have many ratios[24] calculated specifically for their own insulin needs, there is always room for error and miscalculations. Human error in the open loop systems can result in large fluctuations in blood glucose, or extended period of time out of target range.

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[23] As with the CGM used in the APC study

[24] Such as insulin to carb, correction factors, and set basal rates

Closed loop systems, however, have minimal human input. Calculations for insulin dosing are taken directly from the algorithm, and are all numerically based; the only human input occurs when announcements (such as the exercise announcement) are made to the algorithm. This is a much more precise way of calculating insulin dosing, and requires no outside thought. The closed loop system is reactive as well, but in a different way than the open loop system. In an open loop system, a DM1 patient may see that their blood glucose levels are falling, and decide to temporarily decrease the amount of basal insulin they receive by a large amount to avoid potential hypoglycemia. However, a closed loop algorithm would detect a decrease in blood glucose levels, would gradually decrease the insulin infusion rate as the blood glucose levels change, and then begin to gradually increase the insulin infusion rate as the blood glucose levels become steady. In the open loop scenario, the DM1 patient has the danger of rebounding with hyperglycemia due to too little insulin from the decreased basal rate. In the closed loop scenario, the system is able to adjust as the blood glucose levels change. This would result in a greater percent of time spent in target range, and less blood glucose fluctuations.

The tendency of open loop control to result in higher average blood glucose levels can become dangerous after a while. Because hypoglycemia is an immediate danger, some DM1 patients prefer to maintain a higher average blood glucose. High blood glucose, along with large fluctuations that are common in open loop systems, presents the danger for complications in later life. Nephropathy, retinopathy, and other nerve problems are common in older patients who have been dealing with DM1 for a number of years. Non-diabetic patients have protection at a cellular level against

hyperglycemia. When blood glucose levels become high, cells that are exposed to the blood stream are able to reduce the rate of glucose transport, so that cellular glucose levels remain at a normal level. In a DM1 patient, this mechanism to protect the cells is damaged. Hyperglycemia does not cause a change in glucose transport into the cells. In fact, because DM1 patients tend to have a large amount of insulin circulating when their blood glucose levels are high, it is likely that cellular glucose levels are high as well. Long-term exposure to high cellular glucose levels leads to cell damage, and the regular mechanisms are unable to function (Brownlee, 2005). This is why it is important to avoid hyperglycemia, as well as hypoglycemia. In the APC study, hyperglycemia was not prevented, and occurred throughout each condition. The closed loop systems presented a lower average blood glucose reading, but still had some incidences of hyperglycemia. This could be due to the meals; the insulin used in the study can take up to thirty minutes to work. While the system was calculating the amount of insulin needed for a meal, the subjects' bodies were reacting to the meal before the insulin. This could also be due to glucagon infusion. While glucagon was being infused in very small rates, there is a variance across the population to glucagon sensitivity. Some subjects were very sensitive to glucagon, and experienced hyperglycemia after a few doses. Others required a larger amount of glucagon to prevent hypoglycemia.

There were a number of limitations during the first subject studies that could affect results. First was a hardware problem. If the controller happened to run out of battery power, it was unable to recover the study after crashing. This happened with two

subjects (005[25] and 001), which caused a gap in the raw data. One other subject experienced a failed pump infusion site, and received no insulin for an extended amount of time. This would result in extreme hyperglycemia. Finally, disruptions could occur at any communication point (controller, Dexcom, or pump), and could skew data.

[25] The hardware problem occurred at subject 005's first visit, so none of the data was used from subject 005.

Conclusion and Future Research Directions

The challenge with closed-loop systems is that the final product must be able to replicate the mechanisms of a working organ. A pancreas in a non-diabetic is able to immediately detect small changes in blood glucose, and release the exact amount of insulin (or glucagon) required to maintain a homeostatic level. These hormones work quickly, since they are released directly into the blood stream. At any given time, a blood glucose reading from a non-diabetic is likely to read between 80 and 100 mg/dl. This is an extremely small window for error, and the human body is well practiced at maintaining blood glucose levels within this range.

It is the perfection of the human body that makes it so difficult to duplicate with machines. A working continuous glucose monitor is very good at recognizing trends, but can lag behind quick blood glucose level changes by up to half-an-hour. A CGM that isn't working great may still display readings, but can be 100 mg/dl off from the actual level. The action time of synthetic insulin has become quicker since the invention of insulin, but it can still take up to thirty minutes to show an effect on blood glucose.

Outside effects on blood glucose are variable as well. Stress and adrenaline may cause one DM1 patient to experience hypoglycemia, and another DM1 patient to experience hyperglycemia. The insulin sensitivity of DM1 patients can change over time with age and weight. While 15 grams of carbohydrates may raise one individual's blood glucose by 50 mg/dl, it could raise another individual by 100 mg/dl. The effects of everyday life have extremely variable effects on blood glucose by patient, and even over time in a single patient. A non-diabetic pancreas can easily manage all the biological differences between patients, but a machine will have much more difficulty.

These systems have proven to be successful in maintaining a target blood glucose reading for long periods of time, preventing hypoglycemia after an overdose of insulin, preventing nocturnal hypoglycemia, preventing hyperglycemia after meal announcements, and detecting and estimating meals after failure to bolus (Lee, *et. al.*, 2009; Bakhtiani, *et. al.*, 2013; Buckingham, *et. al.*, 2009; Jacobs, *et. al.*, 2011; Peyser, *et. al.*, 2014). However, there is still a long way to go. A quicker-acting form of insulin must be developed before closed-loop systems are able to replicate the pancreas. The current form of synthetic glucagon decays at an exponential rate after being reconstituted. This is not stable enough to be used in a closed-loop system for a long period of time. Algorithms for such systems must be able to take into account all the variance that a DM1 patient may experience and adjust for major changes.

Artificial pancreas studies are currently being completed at research hospitals throughout the United States. There are many different types of closed-loop systems that have varying levels of success. Some are unihormonal, and some are bi-hormonal. The first system to have success was created by a father of a type 1 diabetic son; other systems are being created at the hands of teams of engineers and doctors. There are closed loop systems that are popping up out of the woodwork; some are labeled as "do-it-yourself" closed-loop systems, and families are encouraged to test the efficacy of the system at their own risk (Hoskins, 2015). With the successful completion of each study, the world will be one step towards a complete artificial pancreas system. Every component of DM1 control must be taken into account and represented in the final closed-loop algorithm.

With the anticipated completion of the APC study at OHSU, researchers will have a better frame of reference and understanding of how a closed-loop algorithm can work to prevent expected hypoglycemia during and after exercise. Whether or not the final study results are significant, they will help future studies to fine-tune errors and work towards the end goal of a fully successful closed-loop system.

Current control methods are adequate for blood glucose control. Many DM1 patients have been surviving for years using blood glucose meters, continuous glucose monitors, insulin pumps, and even daily insulin injections. However, adequate does not mean easy. To maintain tight blood glucose control, DM1 patients must be constantly aware of how their blood glucose levels are changing and how their daily activities will—or could—affect these levels. Many patients who have been dealing with DM1 for a number of years also face a myriad of other complications such as nephropathy, neuropathy, retinopathy, and other nerve or organ diseases. While these complications can stem from poor control, most often they stem from the natural blood glucose swings that every DM1 patient experiences at some point in their life. The release of a closed-loop system to the medical market will help to decrease the amount of involvement that DM1 patients must have in their blood glucose control, and will also decrease the risk for complications that many DM1 patients face. While many DM1 patients are already adequately controlling their blood glucose levels, this system will help to free them from the constant worry and preoccupation that comes with type 1 diabetes management.

Appendix A

List of excluding criteria (Castle, 2014)

1. Female of childbearing potential who is pregnant or intending to become pregnant or breast-feeding, or is not using adequate contraceptive methods. Acceptable contraception includes birth control pill / patch / vaginal ring, Depo-Provera, Norplant, an IUD, the double barrier method (the woman uses a diaphragm and spermicide and the man uses a condom), or abstinence.
2. Any cardiovascular disease, defined as a clinically significant EKG abnormality at the time of screening or any history of: stroke, heart failure, myocardial infarction, angina pectoris, or coronary arterial bypass graft or angioplasty. Diagnosis of 2nd or 3rd degree heart block or any non-physiological arrhythmia judged by the investigator to be exclusionary.
3. Renal insufficiency (GFR < 60 ml/min, using the MDRD equation as report by the OHSU laboratory).
4. Impaired liver function, defined as AST or ALT ≥2.5 times upper limit of normal, according to OHSU laboratory reference ranges.
5. Hematocrit of less than or equal to 34%.
6. History of severe hypoglycemia during the past 12 months prior to screening visit or hypoglycemia unawareness as judged by the investigator.
7. Adrenal insufficiency.
8. Any active infection.
9. Known or suspected abuse of alcohol, narcotics, or illicit drugs.
10. Seizure disorder.
11. Active foot ulceration.
12. Severe peripheral arterial disease characterized by ischemic rest pain or severe claudication.
13. Major surgical operation within 30 days prior to screening.
14. Use of an investigational drug within 30 days prior to screening.
15. Chronic usage of any immunosuppressive medication (such as cyclosporine, azathioprine, sirolimus, or tacrolimus).
16. Bleeding disorder, treatment with warfarin, or platelet count below 50,000.
17. Allergy to aspart insulin.
18. Allergy to glucagon.
19. Insulin resistance requiring more than 200 units per day.
20. Need for uninterrupted treatment of acetaminophen.
21. Current administration of oral or parenteral corticosteroids.
22. Any life threatening disease, including malignant neoplasms and medical history of malignant neoplasms within the past 5 years prior to screening (except basal and squamous cell skin cancer).
23. C peptide level of ≥0.5 ng/ml

24. Any concurrent illness, other than diabetes, that is not controlled by a stable therapeutic regimen.
25. Beta blockers or non-dihydropyridine calcium channel blockers.
26. A positive response to any of the questions from the Physical Activity Readiness Questionnaire.
27. Any clinically significant disease or disorder which in the opinion of the Investigator may jeopardize the subject's safety or compliance with the protocol.

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