A Novel Fully Automated Artificial Pancreas for Type 1 Diabetes

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Abstract

Artificial pancreas systems reduce glycemic variability and improve glucose control compared to conventional pump therapy, yet users are still required to count and enter the carbohydrate content of meals. The objective of this thesis is to develop and test a novel fully automated multi-hormone artificial pancreas that does not require any user input.

First, an insulin-pramlintide-glucagon artificial pancreas was iteratively enhanced until convergence through pilot experiments with nine adults (age 37±13 years, HbA1c 7.7±0.7%) with type 1 diabetes. The details of the optimization process are outlined in Manuscript 1.

Second, the final version of the dosing algorithm resulted in an insulin-plus-pramlintide artificial pancreas that was subsequently tested on 24 adults (age 35±14 years, HbA1c 8.1±1.3%) with type 1 diabetes using a randomized controlled trial (Manuscript 2). The fully automated system resulted in comparable time in target range (3.9-10.0 mmol/L) (74% [62-83%] vs. 78% [68-88%]; non-inferiority p=0.28), time spent below 3.9 mmol/L (0% [0.0-2.3] vs. 1.8% [0.0-6.3]; p=0.058), and time spent above 10 mmol/L (24% [15-36] vs. 20% [5.2-33]; p=0.093) to the insulin alone artificial pancreas with full carbohydrate counting. The results of this study warrant a longer outpatient study with the fully automated system.

Résumé

Les systèmes de pancréas artificiels réduisent la variabilité glycémique et améliorent le contrôle glycémique comparativement à la thérapie par pompe conventionnelle, cependant les utilisateurs doivent tout de même compter et entrer la teneur en glucides de leurs repas. L'objectif de cette thèse est de développer et tester un nouveau pancréas artificiel à multi-hormone entièrement automatisé qui ne nécessite aucune entrée de l'utilisateur.

En premier lieu, un pancréas artificiel à insuline, pramlintide et glucagon a été amélioré itérativement jusqu'à convergence au moyen d'expérimentations pilotes avec neuf adultes (âge 37 ±13 ans, HbA1c 7,7 ± 0,7%) atteints de diabète de type 1. Les détails du processus d'optimisation sont décrits dans le Manuscrit 1.

En second lieu, la version finale de l'algorithme de dosage a entrainé un pancréas artificiel à insuline et pramlintide qui a ensuite été testé sur 24 adultes (âge 35 ±14 ans, HbA1c 8,1 ± 1,3%) atteints de diabète de type 1 à l'aide d'un essai clinique randomisé contrôlé, (Manuscrit 2). Le système entièrement automatisé a donné un temps comparable d'intervalle (3,9-10,0 mmol/L) (74% [62-83%] vs. 78% [68-88%]; non-infériorité p=0,28), des temps passé en dessous de 3,9 mmol/L (0% [0,0-2,3] vs. 1.8% [0,0-6,3]; p=0,058), et le temps passé au-dessus de 10 mmol/L (24% [15-36] vs. 20% [5,2-33]; p=0.093) dans un pancréas artificiel à insuline seulement avec calcul complet des glucides. Les résultats de cette étude justifient une étude ambulatoire plus longue avec le système entièrement automatisé.

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Additionally, I would like to thank Jennifer Rene, Sarah Bernier-Twardy, Nikita Gouchie-Provencher, Joanna Rutkowski, and Anas El Fathi for your collaboration. You all played an instrumental part in the coordination of the trial and analysis of the results.

Finally, I would like to thank Diabetes Canada for funding this research project, and all the research participants who made this thesis possible.

Contribution of Authors

In the following thesis, a multi-hormone fully automated artificial pancreas was developed and tested through a series of experiments. First, the dosing algorithm for an insulin-pramlintide-glucagon artificial pancreas was optimized on nine adults with type 1 diabetes. Second, the final version of the dosing algorithm, an insulin-plus-pramlintide artificial pancreas, was tested on 24 adults with type 1 diabetes using a randomized control trial.

My contributions to this thesis was design and optimize the dosing algorithm for the artificial pancreas, write the protocol and consent form for the randomized controlled clinical trial, recruit patients, coordinate daily logistics of the study, manage medication and regulatory communication, analyze the data, close the study, and write both manuscripts.

Dr. Ahmad Haidar was my supervisor and developed the algorithm with the aid of Anas El Fathi's mathematical meal detection model. Dr. Haidar contributed to all aspects of my research, from study design to writing of the manuscripts. The randomized controlled trial was conducted in collaboration with Dr. Michael A. Tsoukas, the principal investigator, and Dr Laurent Legault, Dr. Natasha Garfield, and Dr. Jean-François Yale. Dr. Michael A. Tsoukas, a first co-author for the second manuscript oversaw the study, admitted patients, reviewed adverse events, helped with algorithm optimization, analyzed and interpreted results, and reviewed the manuscript. Joanna Rutkowski and Anas El Fathi carried out data analysis including statistical analysis.

Chapter 1: Introduction

1.1 Diabetes Mellitus

Diabetes mellitus is a group of chronic metabolic disorders characterized by elevated blood sugar (glucose) levels due to defects in insulin secretion, action, or both. Different classifications of diabetes mellitus are based on the different etiological and pathological processes of the disorder. Type 1 diabetes is characterized by the body's inability to produce insulin, while type 2 diabetes is characterized by the body's resistance to insulin [13]. Gestational diabetes mellitus is a glucose intolerance triggered by onset of pregnancy and can be reversible after termination of pregnancy [14]. Other less common types of diabetes are linked to genetic mutations, diseases of exocrine pancreas, and drug use [15].

Despite the different pathophysiological processes, diabetes mellitus results in deficient insulin action or secretion. Insulin is a primary anabolic hormone that regulates blood glucose levels. Glucose is the body's main energy source and in normal physiology, the pancreas maintains blood glucose levels within a narrow range (4.0 – 6.0 mmol/L) through a glucose homeostatic process regulated primarily by insulin and glucagon (Figure 1.1) [16]. In diabetes mellitus, glucose homeostasis is no longer functional and results in sustained high blood glucose levels known as hyperglycemia.

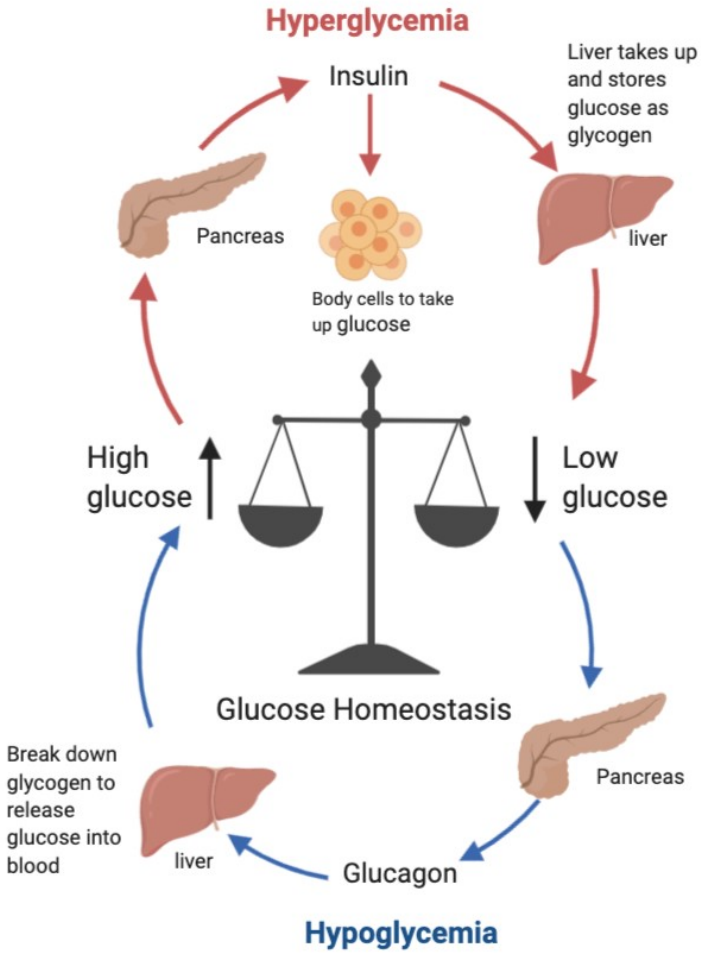

Figure 1.1: Normal glucose homeostasis

When glucose levels rise after consuming a carbohydrate-rich meal, pancreatic beta-cells release insulin into the blood stream. Insulin reduces the production and release of glucose in the liver and promotes glucose uptake from insulin-receptive tissues, such as adipose and muscle cells shown in Figure 1.1. Glucose is the dominant stimulus for insulin secretion, displaying a classic negative feedback loop that keeps glycemia within a tightly controlled range.

While fasting or exercising, blood glucose levels are low which stimulates pancreatic alpha-cells to release glucagon into the blood stream. Glucagon stimulates the production and secretion of glucose from the liver through the breakdown of glycogen (glucose stores) to increase blood

glucose levels back to the homeostatic set point. Glucagon is inhibited by the ingestion of carbohydrates and hormones such as amylin and insulin.

Common diagnostic tests for diabetes mellitus include measuring fasting plasma glucose (FPG), oral glucose tolerance test (OGTT), and glycosylated hemoglobin A1C (HbA1c) [15]. HbA1c is a blood test that measures the level of glycated hemoglobin in the serum. Hemoglobin is a component of red blood cells that carries oxygen in tissues. When there is elevated glucose in blood, it attaches to the hemoglobin and forms a substance known as glycated hemoglobin. HbA1c is a main indicator of glycemic controls, providing an average blood glucose measurement over the past 6- to 12-weeks.

1.2 Type 1 Diabetes

Type 1 diabetes (T1D) results from a T-cell mediated autoimmune destruction of insulin-producing pancreatic beta-cells, resulting in a deficiency of insulin production and secretion [14].

The exact cause of type 1 diabetes is unknown but there is some evidence suggesting a genetic predisposition and strong evidence suggesting environmental factors that trigger the autoimmune reaction. Variations in the human leukocyte antigen (HLA) gene has been linked with increased risk of developing T1D [17]. HLA aids in the production of proteins that are important in the immune system. Although genetic variations may contribute to the cause of the disease, studies have found only a 50% concordance rate of the disease among identical monozygotic twins [18,19]. When comparing monozygotic and dizygotic twin-pairs in North America, studies revealed up to 79% of the twin liability to type 1 diabetes was due to a shared environment [20]. These studies indicate a strong contribution of non-genetic factors in the etiology of the disease.

An ecological analysis of incidence data of type 1 diabetes worldwide indicates an inverse correlation with mean annual temperature, with the highest rates reported in Scandinavia and the lowest in Africa and Japan [18]. Epidemiological studies suggest that accelerated growth rate during puberty is linked to incidence of type 1 diabetes, as growth is known to increase peripheral insulin resistance through action of growth hormone [18]. Epidemiological studies have also suggested that infections and psychological stress can initiate the onset of type 1 diabetes. However, the most compelling evidence for non-genetic risk factor is complications due to viral infections. There is a high prevalence of diabetes in children with perinatal virus exposure, but the mechanism by which this exposure induces type 1 diabetes is still unclear [21].

Roughly 86,000 children worldwide develop type 1 diabetes each year, with higher prevalence in Europe and North America [22,23]. More than 300,000 Canadians have type 1 diabetes and the national average incidence rate has been growing at an estimated 5.1% per year, which is higher than the global average [23,24]. The rapid increase in incidence of type 1 diabetes is unlikely due to an increase in genetic predisposition in the population, but rather by the increase of non-genetic risk factors [18].

1.2.1 Social and Economic Impacts

Type 1 diabetes is a major burden to both patients and the healthcare system. Each year, type 1 diabetes costs the United States $14.4 billion in medical costs and lost income [25]. Type 1 diabetes requires daily insulin injections, constant monitoring, and leads to long-term complications that construct a major lifelong financial burden for patients and the healthcare system. Additionally, there are indirect costs due to missed school, employment, educational attainment, and loss of productivity as a result of early mortality [25].

Studies have shown that people with childhood-onset diabetes are less likely to be employed than the general population, more likely to be absent from school, and more likely to miss work due to sickness [26]. People with diabetes are shown to have lower household income than control subjects due to work disability associated with diabetic complications [26]. Moreover, poor glycemic control can lead to substantial psychological distress, irritable behavior, and self-image problems that directly impact quality of life of patients [27].

1.2.2 Complications

There are both acute (short-term) and chronic (long-term) complications associated with type 1 diabetes. Acute complications include hypoglycemia, hyperglycemia, and diabetic ketoacidosis. These complications result from imprecise insulin replacement therapy.

Hypoglycemia is characterized by glucose levels below 3.9 mmol/L [28] and can occur daily due to excessive insulin delivery or extreme physical exercise. Symptoms of hypoglycemia include fatigue, shakiness, hunger, and sweating [28]. In type 1 diabetes, the counterregulatory mechanism that protects against hypoglycemia is defective, a phenomenon referred to as hypoglycemia-associated autonomic failure (HAAF). The pancreas fails to appropriately secrete glucagon and adrenal glands fail to increase epinephrine production when blood glucose levels drop [29,30]. Based on severity, hypoglycemia can result in cognitive impairment [31,32], cardiovascular disease, seizure, coma and even death [30].

Hyperglycemia, characterized by high glucose level above 10.0 mmol/L [33], can generally occur after meals or due to insufficient insulin management. Symptoms of hyperglycemia include increased thirst, increased urination, fatigue, and blurry vision [34]. Untreated hyperglycemia can lead to diabetic ketoacidosis or hyperosmolar hyperglycemic syndrome. Hyperosmolar

hyperglycemia occurs when there is high blood glucose that results in high osmolarity without the presence of ketones in the blood.

Diabetic Ketoacidosis is life-threatening and occurs when organs can no longer use glucose as an energy source. The liver starts processing and breaking down free fatty acids into fuel, known as ketone bodies [35]. Ketone bodies are strong organic acids and when they are produced too rapidly for the body to process, they make the blood acidic, known as ketoacidosis. Common symptoms include frequent urination, fruity-smelling breath, headache, muscle stiffness, nausea, and vomiting [36]. Diabetic ketoacidosis is treated with immediate exogenous insulin delivery, fluids, and electrolytes. Diabetic Ketoacidosis usually occurs with improper insulin self-management or underlying illness or infection that causes the body to produce higher levels of adrenaline and cortisol that counter the effect of insulin [36]. Thus, the best preventative measures are frequent blood sugar monitoring, frequent ketone monitoring, and appropriate insulin dosage adjustments.

Long-term chronic complications of type 1 diabetes, generally attributed to chronic hyperglycemia, include macrovascular and microvascular disease, outlined in Figure 1.2. Macrovascular complications lead to accelerated cardiovascular disease, cerebrovascular disease, and peripheral vascular disease. Microvascular complications can lead to retinopathy, nephropathy, and neuropathy.

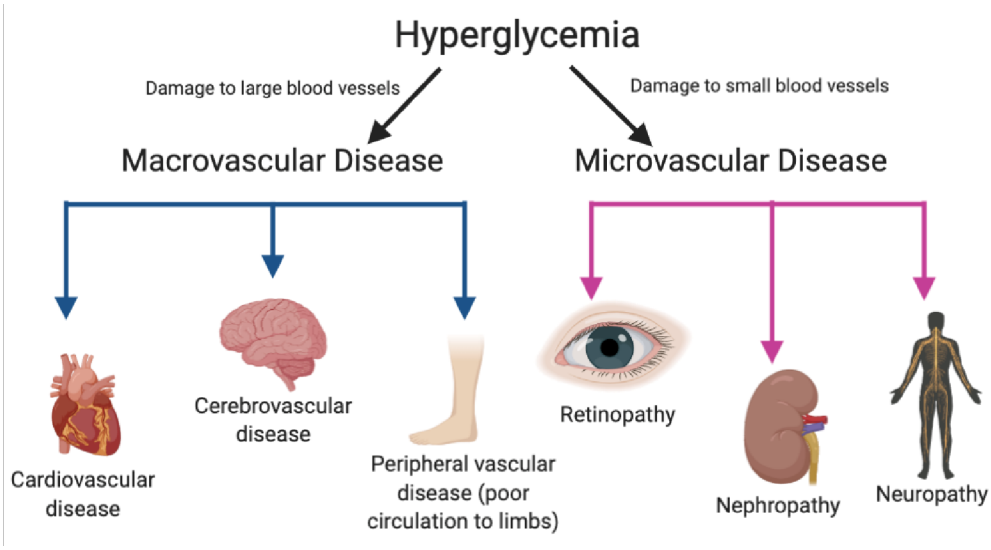

Figure 1.2: Long-term complications of diabetes

A major long-term trial known as the Diabetes Control and Complications Trial demonstrated that intensive glycemic management reduces the frequency and severity of long-term diabetic complications [3]. 1441 participants with type 1 diabetes were randomized to intensive insulin therapy or conventional insulin therapy. Intensive insulin therapy consisted of an insulin pump or 3+ daily injections guided by frequent blood glucose monitoring of at least 4-times a day and conventional therapy consisted of 1-2 daily insulin injections with daily self-monitoring. Intensive insulin therapy resulted in a significant reduction in HbA1c, which correlated with a significant reduction in the development of and progression of retinopathy, nephropathy, and neuropathy [3] (Figure 1.3).

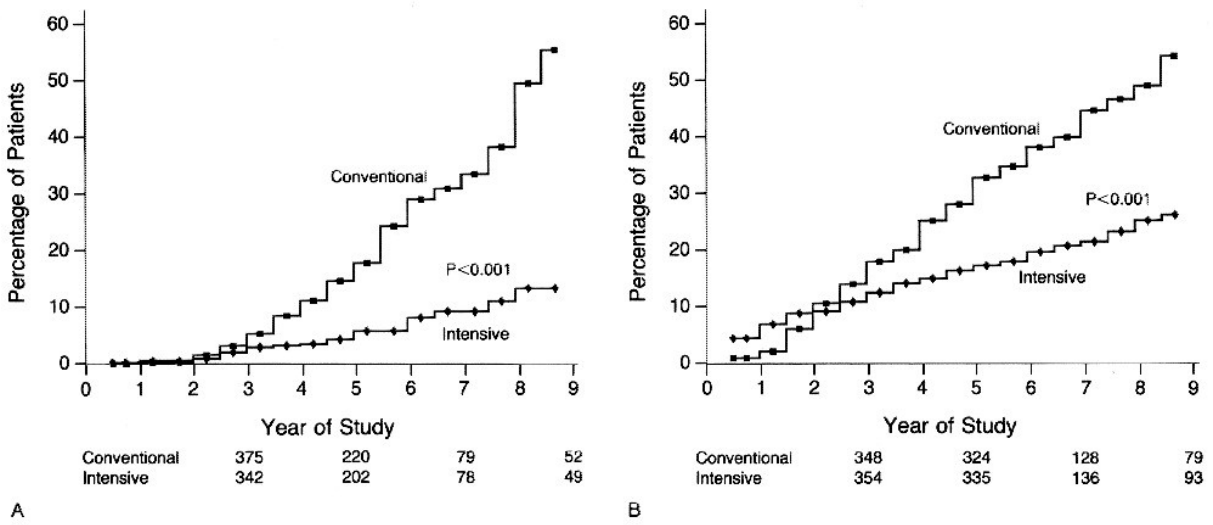

Figure 1.3: Incidence of change in retinopathy in patients who received conventional or intensive therapy during the diabetes control and complications trial [3]. Panel A is the cohort that had no retinopathy at baseline. Panel B is the cohort that had mild retinopathy at baseline

The results from this study highlight the importance and clinical significance of intensive insulin therapy and the relationship between HbA1c and risk of developing retinopathy and other long-term diabetes complications. These findings have redirected patient care strategies with the American Diabetes Association (ADA) setting general target HbA1c values of <7.5% for youths and <7.0% for adults in 1995 [37].

1.2.3 Insulin

Insulin promotes absorption of carbohydrates from the blood into the liver, fat cells, and muscle tissue [38] (Figure 1.4). Absorbed glucose is converted into glucose stores known as glycogen through a process called glycogenesis or into fat through a process called lipogenesis. Insulin also inhibits glucose production and secretion from the liver.

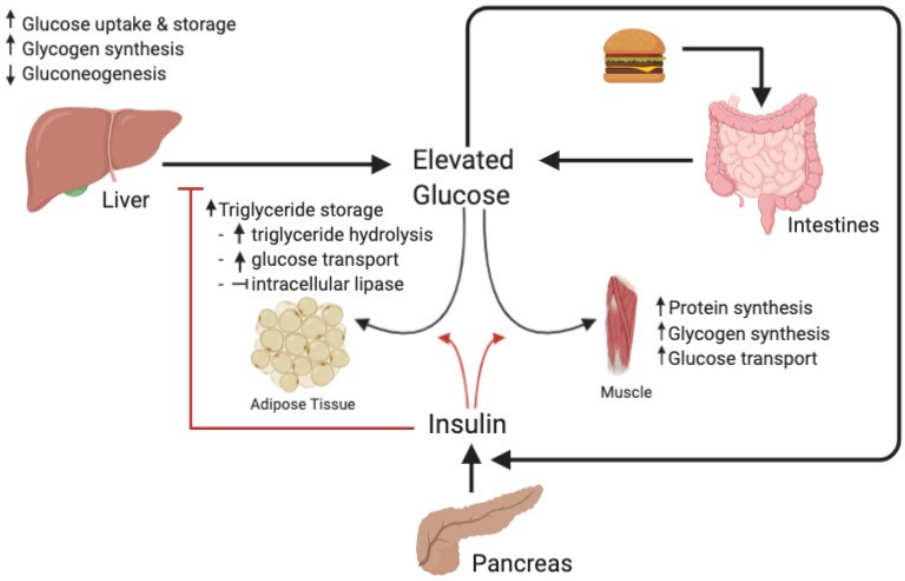

Figure 1.4: Insulin action

Insulin was first discovered in the pancreas of dogs in 1921 by the physician Frederick Banting and his assistant Charles Best [39]. With the help of J.B. Collip and John Maclead, insulin was refined and purified further from the pancreases of cattle and soon after, in 1922, Leonard Thompson became the first human patient to be treated with insulin [40].

Large scale production of insulin from cattle and pig extracts was used to save millions of lives around the world, but these types of insulin varied in efficacy and caused allergic reactions in many people. In 1978, the first genetically engineered, synthetic “human” insulin was produced using E. Coli bacteria. Human insulin produced by recombinant DNA technology reduced the severity and frequency of immune responses, and in 1982, Eli Lilly sold the first commercially available biosynthetic human insulin under the brand name, Humulin [40].

There are different types of insulin analogs that vary in the onset time and duration of action to accommodate different needs and lifestyles of people with diabetes (Figure 1.5).

i. **Rapid-acting insulin** starts working approximately 15 minutes after injection and peaks after 1 hour, with a duration of action of up to 2-4 hours. This type of insulin is usually taken before a meal in addition to a long-acting insulin.

ii. **Short-acting insulin** starts working approximately 30 minutes after injection and peaks after 2-3 hours, with a duration of action up to 6 hours. Short-acting insulin is usually delivered as boluses, single large doses, prior to meal consumption

iii. **Intermediate-acting insulin** starts working 2-4 hours after injection and the time to peak is between 4 to 12 hours. It lasts up until 18 hours after delivery and is usually taken twice a day in addition to short- or rapid-acting insulin.

iv. **Long-acting insulin** can work up to 24 hours after delivery and is usually delivered once a day in order to mimic physiological basal levels of insulin. This type of insulin is long acting without a large action peak to cover times of fasting. The acidic pH of long-acting insulin can result in a slight burning sensation when administered.

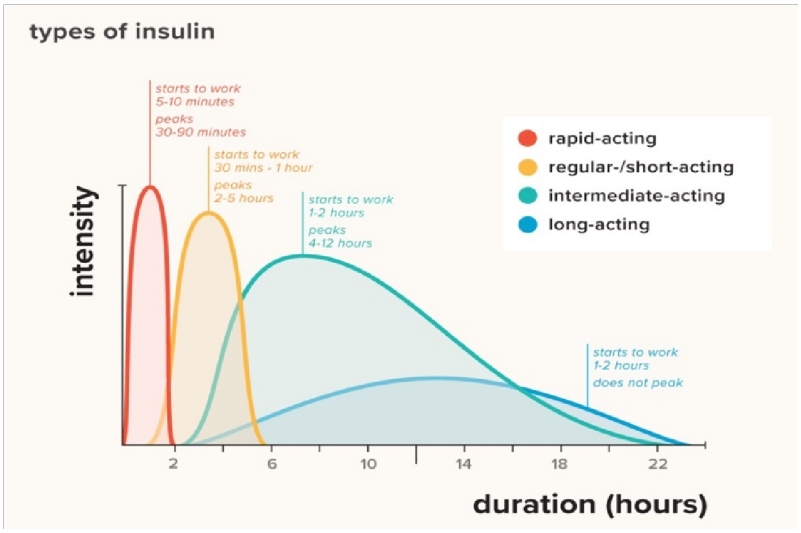

Figure 1.5: Duration and Intensity of different types of insulin [7]

Recent efforts have been made to develop ultra-rapid insulins with faster onset and shorter duration of action. Fast-acting insulin aspart (Fiasp) is an ultra-rapid insulin analog that has a faster onset and shorter duration of action than insulin aspart, a rapid-insulin analog. Fiasp has been shown to achieve lower postprandial glucose concentrations compared to insulin aspart [41,42].

1.2.4 Insulin Replacement Therapies

Current therapies for type 1 diabetes require exogenous insulin replacement therapies through multiple daily injections or continuous subcutaneous insulin infusion.

Multiple daily injections are the most common type of insulin therapy for type 1 diabetes. Multiple Daily Injections involves using an insulin pen or syringe to inject a long-acting insulin daily to cover fasting insulin needs and rapid or intermediate-acting insulin before each meal (Figure 1.6). Long-acting insulin is sometimes divided into two injections, with half a dose administered in the morning and the other half in the evening.

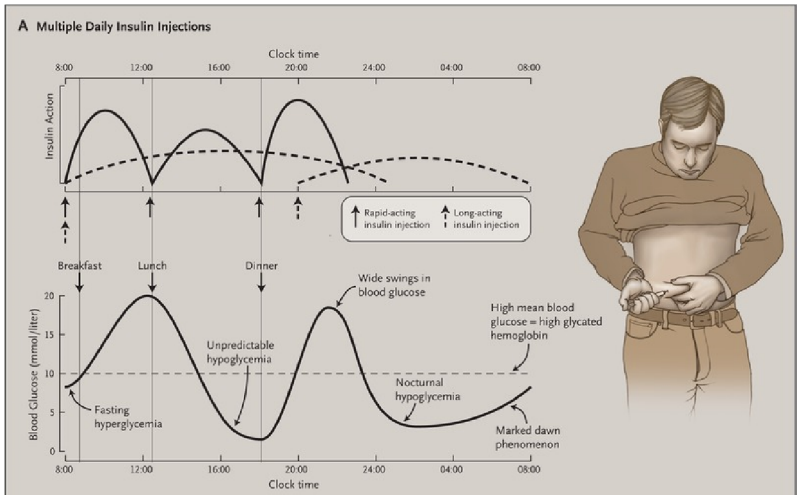

Figure 1.6: A sample glycemic profile for multiple daily injection therapy [11]

An alternative to multiple daily injections is continuous subcutaneous insulin infusion, known as pump therapy. This treatment strategy mimics the function of a normal pancreas more closely and replaces frequent insulin injections by delivering precise doses of rapid-acting insulin. An insulin pump is made up of several main components: an insulin reservoir, a delivery motor which is linked to a control mechanism, and a subcutaneous insulin infusion set (Figure 8). A catheter is manually inserted into a desirable injection site that has a layer of fat beneath the skin to absorb the insulin with few nerve endings such as the abdomen, upper thighs, upper outer arms, and buttocks. The insulin pump infuses the rapid acting insulin throughout the day (Figure 1.7). Due to the precise dosing capability, insulin-pump therapy can reduce inter- and intra-daily glycemic variability seen with insulin injections [43]. According to the Advanced Technologies & Treatments for Diabetes panel, the target glucose range for type 1 diabetes is 3.9 – 10.0 mmol/L [5].

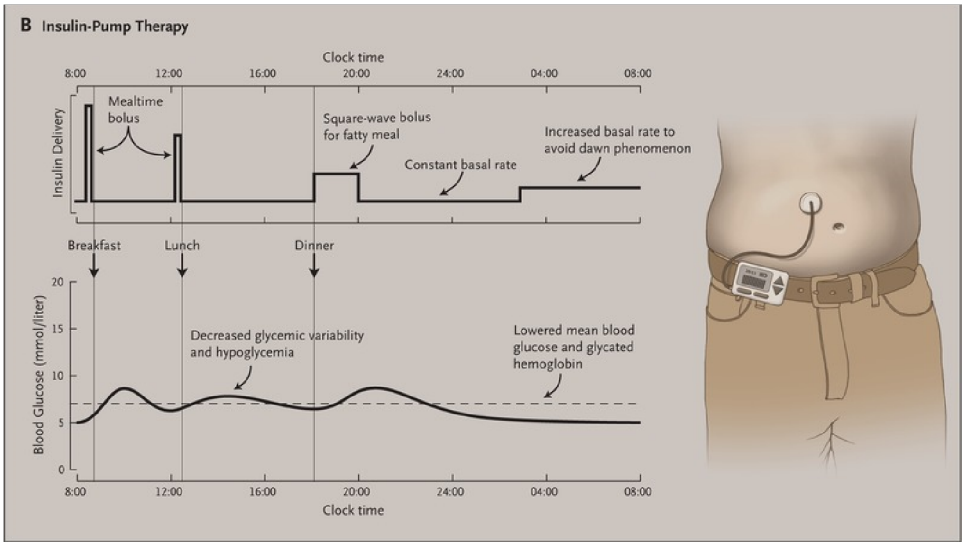

Figure 1.7: Sample glycemic profile and insulin action of conventional pump therapy [11]

1.2.5 Pharmacological Adjunctive Therapies

Glucose homeostasis is multifaceted, and insulin alone only corrects part of the underlying pathophysiology of diabetes. Additional hormones that are also dysregulated in type 1 diabetes are being recognized to play a vital role in glucose regulation.

1.2.5.1 Amylin

Amylin is a 37-amino acid neuropeptide that is produced and co-secreted with insulin from the pancreatic beta-cells in response to nutrient stimuli. Amylin signals to the brain and plays several important physiological functions in the body (Figure 1.8): it slows down gastric emptying, decreases glucagon secretion from the pancreas, and increases satiety [44]. Amylin appears to be secreted in high frequency pulsatile manner with a 24-hour profile similar to insulin [45]. People with type 1 diabetes are deficient in amylin due to the destruction of pancreatic beta-cells. Furthermore, amylin analogues have been explored as a potential adjunctive therapy with insulin to improve glycemic control and help with weight management [46].

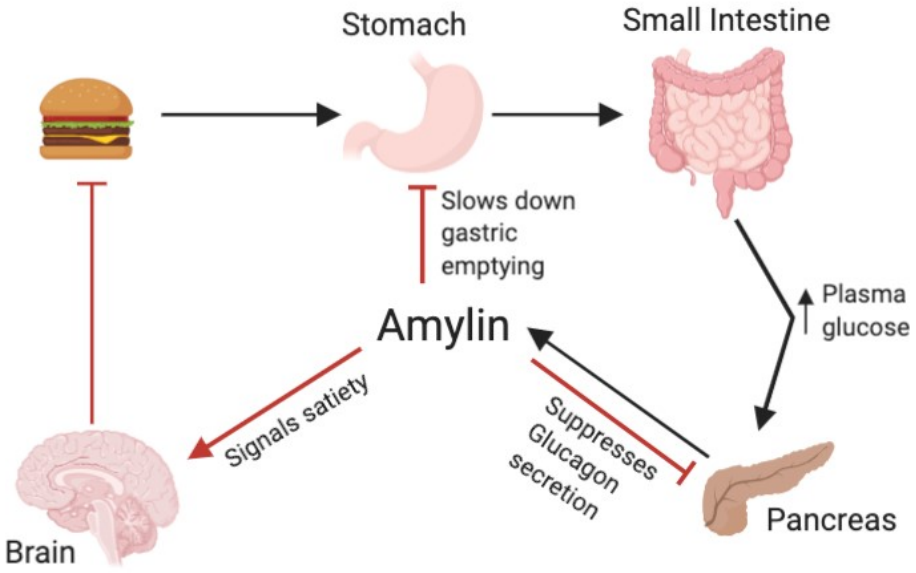

Figure 1.8: Amylin mechanism of action

Pramlintide is a synthetic analogue of amylin and was approved by the US Food and Drug Administration (FDA) in 2004 for use with mealtime insulin for type 1 and type 2 diabetes. Pramlintide is injected subcutaneously prior to each meal at fixed doses and has been shown to improve glycemic excursions after meals and reduce body weight [46,47].

There have been several clinical trials that have assessed the safety and efficacy of different doses of pramlintide administered prior to meals in participants with type 1 diabetes. In a 52-week multicenter trial, 480 subjects with type 1 diabetes received either pramlintide or placebo in addition to their usual insulin therapy. Pramlintide resulted in a 0.67% reduction in HbA1c from baseline to week 13 and a significant placebo-corrected treatment difference was sustained through week 52 [48].

Another study looked at benefits of 60 µg pramlintide as an adjunctive to insulin therapy over the course of 52-weeks in type 1 diabetes [46]. Pramlintide led to a reduction of 0.29% in HbA1c from baseline when administered three-times a day and a reduction of 0.34% when administered four-times a day. In both studies, the most common adverse effect of pramlintide was nausea, which appeared to be transient and dissipated within the first 2 weeks of treatment [46,48,49].

1.2.6 Carbohydrate counting

In order to achieve tight glycemic control, people with type 1 diabetes need a regimen composed of proper diet, exercise, and accurate carbohydrate counting. Carbohydrates are sugars, starches, and fibers that make up 45-65% of daily caloric intake. Carbohydrates are a major nutritional determinant of postprandial glucose levels [50,51] and accurate carbohydrate counting is recommended and associated with improved glycemic control [52]. Accurate carbohydrate

counting allows for proper dosing of insulin based on individual insulin-to-carbohydrate ratios that determine the amount of insulin needed to cover a specific amount of carbohydrate. Insulin-to-carbohydrate ratios vary between individuals and may vary by time of day.

Among the pediatric population, studies have shown that parents tend to overestimate the carbohydrate content of their children's meal by 20% [53]. In contrast, adults with type 1 diabetes tend to underestimate the carbohydrate content of their meals by 20%, independent of age, time since diagnosis, or physical activity level [54].

Carbohydrate counting is a burdensome and error-prone task that has been linked to poor dietary choices. The ease of nutrition labels has led to some preferring prepackaged processed foods over whole foods including whole grains, fruits, and legumes [55]. Additionally, an emphasis on carbohydrate counting and focus on food's effect on glycemia has caused some to base dietary choices on perceived postprandial glycemic effect rather than nutritional content of the food.

1.2.7 Measure of Glycemic Control

There are several measures of glycemic control that are used among patients and clinicians. HbA1c is a good indicator of effectiveness of treatment and should be measured every 6 months if glycemic targets are achieved and every 3 months if they are not met or if there is a change in therapy. Mean glucose level indicates short-term efficacy of artificial pancreas performance, yet like HbA1c only captures an average glycemia and does not provide information regarding frequency of hypoglycemic or hyperglycemic events. A lower mean glucose level may indicate better performance; however, it is important to ensure that the lower mean glucose is not achieved at the cost of increased hypoglycemia (Figure 1.9). Glucose variability is captured more

accurately by looking at time spent in target range, which is a relatively newly accepted analytical endpoint for short-term studies.

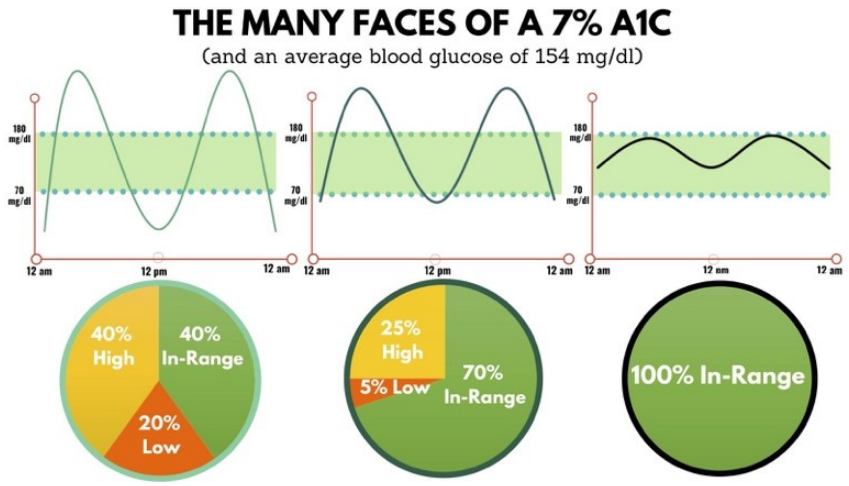

Figure 1.9: Three glycemic profiles with the same mean glucose level of 7% [5]

The need for closer glucose monitoring resulted in the development of continuous glucose monitors in 1999 [56]. A continuous glucose monitor has a subcutaneously inserted sensor and an attached transmitter that wirelessly transmits real-time data to a monitor or smartphone application. The inserted sensor contains an enzyme electrode that catalyzes the glucose oxidation reaction to hydrogen peroxide, which is then detected and converted into an electric current (Figure 1.10).

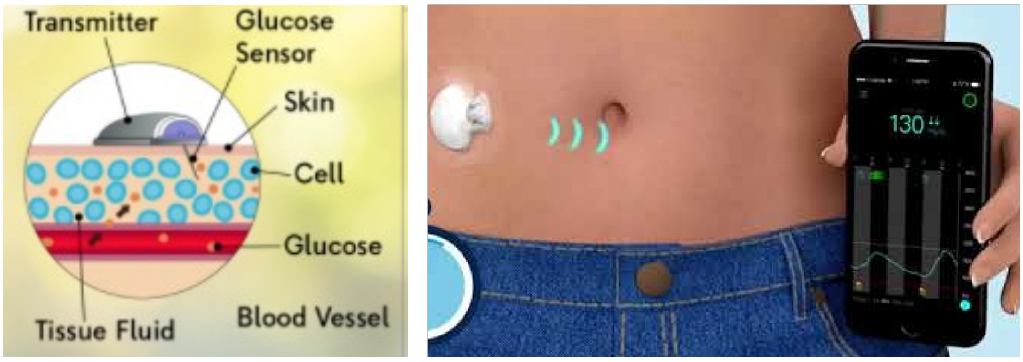

Figure 1.10: A continuous glucose sensor is inserted subcutaneously and wirelessly communicates with a monitor or smartphone displaying glucose levels and trends [9,10]

Continuous glucose monitors measure glucose concentrations in interstitial fluid every 5 to 15 minutes, and provide information about direction, magnitude, duration, and frequency of changes in glucose levels that are important to ensure proper diabetes management [57]. An advantage of this technology is that it can detect postprandial hyperglycemia and asymptomatic nocturnal hypoglycemia, which commonly occur and are left unnoticed even in well-controlled individuals with type 1 diabetes [58]. Successful adherence and longer duration of usage has shown to improve HbA1c when compared to fingerstick testing [59].

The introduction of continuous glucose monitors led to improvement in pump therapy known as sensor-augmented pump therapy. Sensor-augmented insulin pump (SAP) combines the technology of an insulin pump with continuous glucose monitoring sensor that transmits glucose readings to the person wearing the device, with an alarm function for hypo- and hyperglycemia and a mealtime bolus advisor. Sensor-augmented pump therapy improves glycemic control and reduces HbA1c compared to intensive multiple daily injection therapy and pump therapy alone [60-62].

First generation sensor-augmented pump therapy on the market used an insulin dosing software that functioned independently of continuous glucose values. The user would get alarms indicating low blood glucose values and need to manually adjust basal rates accordingly. Advancements led to a second-generation sensor-augmented pump therapy that have an insulin dosing software that incorporated continuous glucose monitors to automatically suspend basal insulin delivery in response to predicted or detected low glucose levels [63]. However, for both generations, correction boluses need to be manually entered and basal rates are not constantly

fine-tuned according to metabolic needs of the patient each day. To overcome these limitations, researchers have developed an automated insulin-delivery system known as the artificial pancreas.

1.3 Artificial Pancreas

The artificial pancreas, also referred to as closed-loop control, is a bioengineering management system that uses a mathematical dosing algorithm that takes real-time data from a continuous glucose monitor to titrate the infusion of insulin through an insulin pump. The artificial pancreas consists of three main components: a continuous glucose monitor, a control algorithm, and an insulin pump (Figure 1.11).

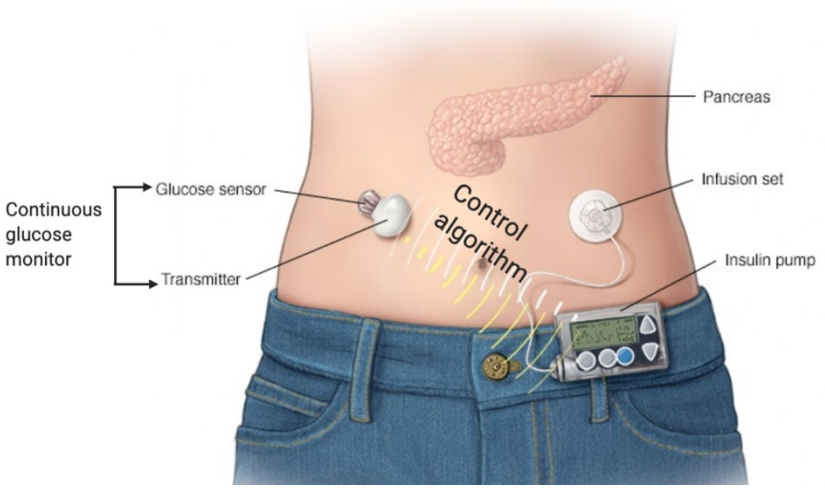

Figure 1.11: Artificial pancreas: Continuous glucose monitor data is communicated to a control algorithm that adjusts the insulin dosing of an insulin pump [6]

The main components of a control system are (i) insulin-bolus calculator to compensate for carbohydrates of meals, and (ii) basal-insulin algorithm [64].

i. **Bolus algorithm:** This is a feedforward algorithm that calculates insulin boluses based on announced grams of carbohydrate, insulin-to-carbohydrate ratios, and glycemic targets to compensate for expected blood glucose excursion due to a meal intake.

ii. **Basal algorithm:** Basal insulin is the constant level of insulin infusion provided to mimic fasting level of insulin released by a healthy pancreas. Basal insulin continuously adapts to glucose levels measured by continuous glucose monitor.

1.3.1 Control Algorithms

Although these main components are present in all artificial pancreas systems, the algorithms differ. Proportional-integral-derivative controllers adjust insulin delivery based on deviation from target glucose level, area under the curve between measured and target glucose, and rate of change of glucose level [65]. Model predictive controllers accommodate delays in insulin absorption and account for meals, manual insulin boluses, and other events that influence glucose levels [65]. Additionally, a fuzzy-logic approach may be used which relies on expert human knowledge to set glucose management parameters [66].

In September 2016, the US food and drug administration approved the first commercial hybrid closed-loop system, Medtronic MiniMed 670G. Two years later, in 2018, Medtronic MiniMed 670G received Health Canada approval and entered the Canadian market. The system uses a novel proportional-integral derivative controller with insulin feedback from a continuous glucose monitor to calculate insulin dosing. Hybrid closed-loop systems still require users input for meals and exercise and are not fully closed-loop. Although the MiniMed 670G system looks promising, it is not completely automated, or “fully closed-loop”, and still requires users to manually enter the carbohydrate content of their meals to receive appropriate insulin boluses.

1.4 Thesis Objective

A major limitation of current artificial pancreas systems is that they still require users to manually enter carbohydrate content of each meal. In this thesis, we aim to address this limitation by developing and testing a novel fully automated multi-hormone artificial pancreas system that no longer requires user input. The objective of this thesis was to design and optimize an insulin, pramlintide, and glucagon artificial pancreas through a pilot study with 9 participants. The optimized final algorithm was then tested through a randomized controlled trial with 24 adults with type 1 diabetes in an inpatient setting.

1.5 Hypothesis

We hypothesized that the fully automated artificial pancreas with insulin and pramlintide, will alleviate the burden of carbohydrate-counting without degrading glucose control compared to an insulin-alone artificial pancreas with carbohydrate-matched boluses. The efficacy of the system was assessed through a non-inferiority inpatient randomized crossover trial comparing time spent in target glucose range (3.9 – 10.0 mmol/L) with the fully-automated artificial pancreas compared to insulin-alone hybrid closed loop during a 24-hour period.

Chapter 2: Literature Review

2.1 Pump Therapy in Canada

A meta-analysis was conducted examining the metabolic and psychosocial impact of pump therapy on adults, adolescents, and children [67] with type 1 diabetes. Study findings show that pump therapy was associated with a significant decrease in HbA1c, mean glucose, and frequency in hypoglycemic episodes compared to conventional therapy and multiple daily injections [67]. Majority of the advantages of pump therapy listed by people with type 1 diabetes were improved flexibility, ease with scheduling meals, decreased physical restrictions, and improved glycemic control [67].

A few years later, a multinational randomized control crossover trial was conducted to assess effects on glycemic control and quality of life with pump therapy compared to multiple daily injections with intermediate-acting insulin [2]. Pump therapy lowered HbA1c by 0.22% ($p<0.001$) (Figure 2.1) and mean glucose by 0.7 mmol/l ($p<0.001$) [2]. The quality-of-life assessment was higher for pump therapy ($p<0.001$) with a marked improvement in perception of mental health ($p<0.05$) [2].

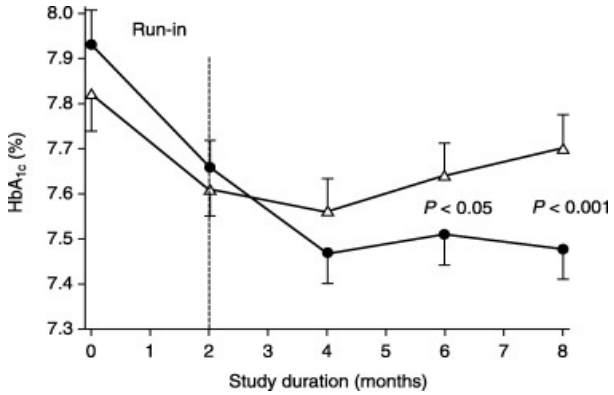

Figure 2.1: HbA1c values by type of treatment.
(▵) MDI, (•) CSII [2]

In 2009, about 10% of Canadians with type 1 diabetes reported being on pump therapy [68]. In order to assess the prevalence of insulin pump in older patients with type 1 diabetes in whom the benefits may be amplified, a Canadian Study of Longevity in Type 1 Diabetes was conducted [69]. The study looked at 305 Canadians living with diabetes for at least 50 years to determine factors associated with complications [69]. Prevalence of pump use was 44%, with a median duration of use of 8 years. Pump users had a lower risk of nephropathy (29% vs 45%), significantly higher physical activity level ($p=0.02$), and a non-significant higher self-assessment for quality-of-life (44% vs 35%) compared to non-pump users [69]. These findings show that technology and self-management play important roles in managing glycemic and long-term outcomes of type 1 diabetes.

2.2 Artificial Pancreas

In order to further enhance glucose control in type 1 diabetes, automated artificial pancreas systems have been developed. A systemic review and meta-analysis of artificial pancreas systems in type 1 diabetes was conducted in 2018 to look at effect of artificial pancreas compared to its control group during 24-hour periods [70]. The control groups were either conventional pump therapy or sensor augmented pump therapy. The studies found that the artificial pancreas maintained better mean glucose level ($p<0.001$) and significantly reduced time spent in hypoglycemia ($p<0.001$) compared to its control group (n=354 participants).

Another meta-analysis reviewed 40 studies with the artificial pancreas systems in outpatient settings with 1027 participants with type 1 diabetes [71]. The meta-analysis found that time spent between 3.9-10.0 mmol/L was significantly higher with the artificial pancreas system, both overnight and over a 24-hour period, compared to the control treatment. The control treatments were either conventional insulin pump therapy or sensor-augmented pump therapy.

In conclusion, artificial pancreas systems improve glycemic control and reduce incidences of hypoglycemia, yet still require users to input carbohydrate content of meals.

2.2.1 Fully Closed-Loop Systems

The early fully closed-loop artificial pancreas systems omitted mealtime boluses and relied solely on glucose sensor readings to cover mealtime insulin needs. This approach was tested on adolescents during a 34-hour intervention, compared to a hybrid closed-loop control with a simple-meal announcement in which the user presses a button to announce to the algorithm the consumption of a meal in order to receive a premeal "priming" bolus [72]. Mean glucose in the fully closed-loop arm was higher than in the hybrid closed loop arm ($p=0.09$) with a peak postprandial glucose level of 12.5 mmol/L vs. 10.8 mmol/L ($p=0.04$) [72]. The fully closed loop system did not begin to respond to the meal until 15-20 minutes after the participant started eating, which resulted in an observed insulin peak concentration occurring 120 minutes after the meal [72]. The fully reactive system responded only to changes in glucose levels and was hindered by the delayed subcutaneous absorption of insulin [73]. A strategy to provide priming insulin boluses before meals outperformed a fully automated system, however, it still requires users to announce meals to the system.

An integrated closed loop therapy that applied a similar premeal priming bolus was tested in a multicenter randomized study in an outpatient setting with 18 participants with type 1 diabetes [74]. The control arm was sensor-augmented pump therapy [74]. Results from this study showed that closed-loop therapy significantly reduced the risk of hypoglycemia ($p=0.003$), however, the reduction in hypoglycemia was accompanied by a 4.6% decrease in percentage of time spent in target range (3.9-10.0 mmol/L) and an increase in mean glucose by 0.5 mmol/L ($p=0.04$).

2.2.2 Insulin-Plus-Glucagon Artificial Pancreas

Additional efforts to fully automate artificial pancreas systems were attempted by using glucagon to prevent or treat hypoglycemia. Fear of hypoglycemia is a major barrier in tight glycemic management, leading to suboptimal HbA1c levels.

A bihormonal artificial pancreas with insulin and glucagon was tested in 20 adults and 32 adolescents in crossover outpatient setting for 5-days [4]. Insulin and glucagon were administered subcutaneously through insulin pumps and the dosing algorithm was run wirelessly on an iPhone. Users announced meal type and size rather than carbohydrate content. Meal types included "breakfast," "lunch," or "dinner," and meal-sizes included "typical," "more than usual," "less than typical," or "a small bite." Announcing the meal triggered a partial meal-priming bolus based on participant's weight. The control arm was participant's usual pump therapy. In adults, mean glucose level on days 2-5 was 7.4 mmol/L on the bihormonal system compared to 8.8 mmol/L in the control arm ($p<0.001$) [4]. Participants spent 79.5% in target (3.9- 10 mmol/L) in the bihormonal arm compared to 58.8% in the control arm (<0.001) [4] (Figure 2.2). Additionally, there was a significant reduction in number of hypoglycemic episodes in the bihormonal arm. In adolescents, mean glucose was 7.9 mmol/L in the bihormonal arm compared to 8.8 mmol/L in the control arm ($p=0.004$) [4]. Percentage of time in target was also zigher in the bihormonal arm (75.9% vs 64.5%, $p<0.001$) [4].

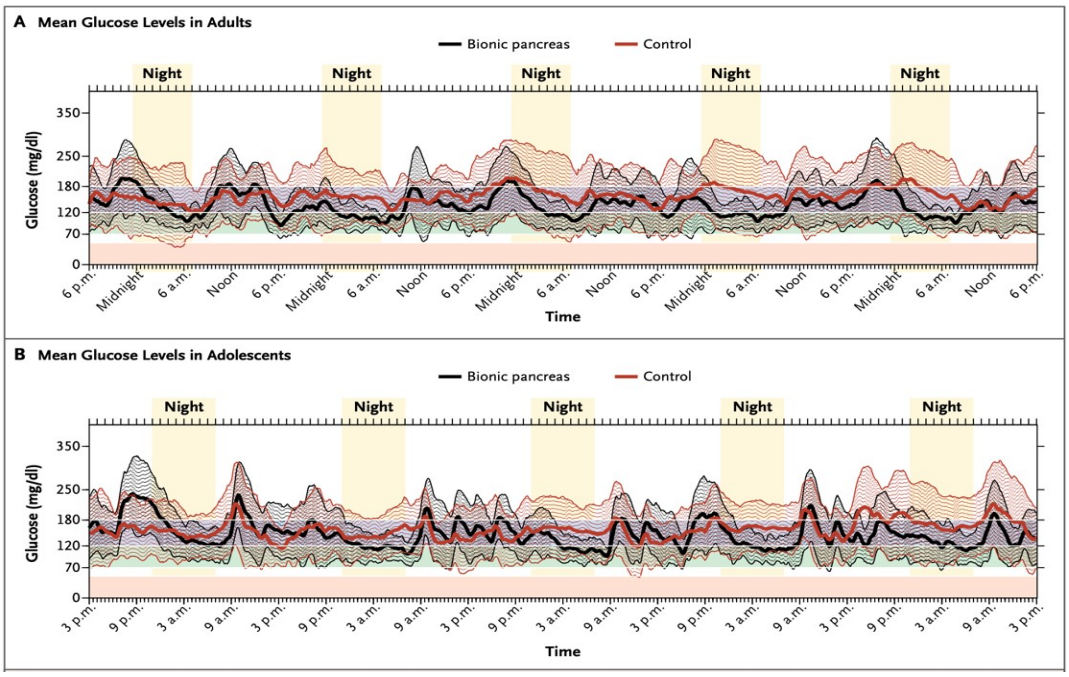

Figure 2.2: Mean glucose (SD) levels during the 5-day period in 20 adult patients (panel A) and 32 adolescent participants (panel B). Black lines indicate the bihormonal artificial pancreas arm and the red line indicates the conventional insulin pump control arm [4]

Haidar et al. looked at the effects an insulin-and-glucagon artificial pancreas has on glycemic control compared to an insulin-alone artificial pancreas and conventional insulin pump therapy in adolescents and adults with type 1 diabetes [75]. The dual-hormone system still required full carbohydrate counting input for the calculation of prandial boluses. The average time spent between 4.0-10.0 mmol/L over a 24-hour period was 62% for the insulin-alone artificial pancreas arm, 63% for the insulin-and-glucagon artificial pancreas arm, and 51% for conventional pump therapy arm [75]. The difference between time spent in range for the dual-hormone artificial pancreas arm and conventional insulin pump therapy was 12% (p=0.00011), however, there was no significant difference between the insulin-and-glucagon vs insulin-alone arm [75]. There were fewer hypoglycemic events with the insulin-and-glucagon artificial pancreas arm compared to both the insulin-alone artificial pancreas arm and conventional pump therapy arm. The study shows

promising glycemic control with both the insulin-alone and insulin-and-glucagon artificial pancreas compared to conventional pump therapy.

2.2.3 Insulin-Plus-Pramlintide Artificial Pancreas

Researchers have also attempted to improve postprandial glycemic control and develop a fully closed-loop system with pramlintide. A study was conducted comparing insulin-alone closed-loop with an insulin-and-pramlintide closed loop system [1]. 60µg of pramlintide was administered 15-minutes before each meal. The time and content of meals were identical during the closed-loop visits and meals were not announced to the system. Pramlintide delayed time to peak of meal-stimulated glucose excursion (1.6 vs 2.6h, $p<0.001$) and reduced peak increment in postprandial glucose level by 39% [1] (Figure 2.3). Additionally, time in range (3.9-10.0 mmol/L) was greater during the day with pramlintide compared to insulin-alone closed-loop ($p=0.004$) [1].

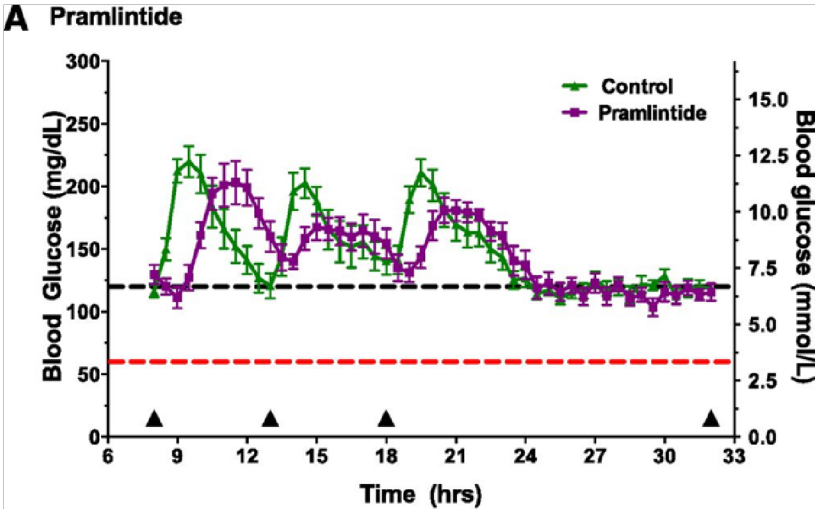

Figure 2.3: Glucose profile of participants on closed-loop alone (green) and closed-loop with pramlintide (purple) during a 24-hour visit. The red line denotes 60 mg/dL (3.3 mmol/L) which is the threshold of hypoglycemia. Black line is the systems target and meals are indicated by triangles on the x-axis [1].

Since the first use of insulin in treatment of diabetes in 1922, diabetes management has come a long way in improving the lives of people with type 1 diabetes. Automated insulin delivery systems improve the quality of life and reduced both short- and long-term complications for people with type 1 diabetes. Future trends within diabetes technology are towards developing a fully automated insulin delivery system that closely mimics a healthy pancreas and alleviates the burden of constant insulin adjustments and meal carbohydrate counting. A fully automated system is a "holy grail" in diabetes management but is limited by the slow pharmacokinetics of insulin analogs on the market and the complexity of mimicking the normal human endocrine pancreas. In recent years, the notion of using adjunctive therapies with closed-loop systems to address these limitations has gained increased popularity.

In this thesis, I develop and test a novel fully automated artificial pancreas that does not require meal announcement. The approach to our fully automated system was to administer multiple hormones that are dysregulated in type 1 diabetes yet play important roles in glucose homeostasis. Fully automated insulin-alone closed-loop control systems result in prolonged postprandial hyperglycemia due to the slow insulin absorption and time to peak [73] relative to meal absorption [76]. Pramlintide administered in a basal-bolus manner mimics normal physiology and delays gastric emptying and meal absorption, which helps match the pharmacokinetics of insulin absorption to meal absorption. A fully reactive insulin and pramlintide system may be effective in improving postprandial glycemic control but may result in increased risk of hypoglycemia. Therefore, exogenous glucagon may be needed to protect against hypoglycemia as the counterregulatory defense mechanism is defective in type 1 diabetes. A fully automated multihormone system was developed, optimized, then tested through a randomized control trial.

Chapter 3: Manuscript #1

Fully Automated Artificial Pancreas for Adults with Type 1 Diabetes using Multiple Hormones: Exploratory Experiments

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Short running title: Optimizing a fully automated artificial pancreas

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ABSTRACT

Objective: A fully automated insulin-pramlintide-glucagon artificial pancreas that alleviates the burden of carbohydrate counting without degrading glycemic control was iteratively enhanced until convergence through pilot experiments on adults with type 1 diabetes.

Methods: Nine participants (age 37±13 years, HbA1c 7.7±0.7%) completed two 27-hour interventions: a fully automated multi-hormone artificial pancreas and a comparator insulin-alone artificial pancreas with carbohydrate counting. The baseline algorithm was a model-predictive controller that administered insulin and pramlintide in a fixed ratio, with boluses triggered by a glucose threshold, and administered glucagon in response to low glucose levels.

Results: The baseline multi-hormone dosing algorithm resulted in non-inferior time in target range (3.9-10.0 mmol/L) (71%) compared to the insulin-alone arm (70%) in two participants, with minimal glucagon delivery. The algorithm was modified to deliver insulin and pramlintide more aggressively to increase time in range and maximize the benefits of glucagon. The modified algorithm displayed a similar time in range for the multi-hormone arm (79%) compared to the insulin-alone arm (83%) in two participants, but with undesired glycemic fluctuations. Subsequently, we reduced the glucose threshold that triggers glucagon boluses. This resulted in inferior glycemic control for the multi-hormone arm (81% vs 91%) in two participants. Thereafter, a model-based meal detection algorithm to deliver insulin and pramlintide boluses closer to mealtimes was added and glucagon was removed. The final dual-hormone system had comparable time in range (81% vs 83%) in the last three participants.

Conclusion: The final version of the fully automated system that delivered insulin and pramlintide warrants a randomized control trial.

INTRODUCTION

Type 1 diabetes mellitus is a chronic disease caused by an autoimmune destruction of the insulin producing pancreatic beta cells [1]. The cause of type 1 diabetes is still not well understood but it is known to be due to interactions of genetic and environmental factors [1]. Insulin regulates blood glucose levels, hence, its deficiency results in dysregulated glycemic control characterized by high glucose levels (hyperglycemia). As a result, people with type 1 diabetes require insulin replacement therapy.

The two methods for insulin-replacement therapy are multiple daily injections and continuous subcutaneous infusion via a portable pump. Intensive insulin therapy is necessary to avoid excessive hyperglycemia that can lead to long-term microvascular and macrovascular complications such as retinopathy, nephropathy, neuropathy, coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Randomized trials have shown that reducing glycated hemoglobin (HbA1c), an index of glycemic control, minimizes these long-term complications [2]. Currently, people with type 1 diabetes are required to frequently monitor their blood glucose levels, accurately count the carbohydrate content of their meals [3,4], and decide upon their insulin doses. Despite this laborious regimen, most people still fail to achieve their target HbA1c [5].

In recent years, the development of continuous glucose sensors has made it possible to build automated insulin delivery systems, known as the artificial pancreas. The artificial pancreas uses a mathematical dosing algorithm that relies on sensor readings to titrate the infusion of an insulin pump [6]. Randomized trials have shown that the artificial pancreas reduces HbA1c compared to a stand-alone sensor and pump [7]; however, current systems still requires people

with type 1 diabetes to count the carbohydrate content of each meal to determine prandial insulin boluses.

Carbohydrate counting is an imprecise and burdensome task, with estimation errors around 20% [8,9]. Additionally, having to count the carbohydrate content of meals can negatively influence dietary choices as the relative ease provided by nutrition labels encourage the selection of prepackaged processed foods over whole foods, such as whole grains and fruits [8]. Therefore, early artificial pancreas studies attempted to eliminate carbohydrate counting by omitting mealtime insulin boluses and relying solely on glucose sensor readings to cover meal-related insulin needs. This approach resulted in prolonged hyperglycemia [10,11] due to insulin's slow subcutaneous absorption [12]. Consequently, artificial pancreas systems that outperformed conventional pump therapy required either carbohydrate counting [7] or meal size categorization [13].

We aimed to create a novel artificial pancreas that is fully automated and no longer requires carbohydrate counting by delivering three hormones: insulin, pramlintide, and glucagon. Glucagon is a hormone produced by pancreatic alpha-cells and is dysregulated in type 1 diabetes. Glucagon increases circulating blood glucose levels by stimulating glucose production in the liver [10]. Pramlintide is an analog of a hormone called amylin, a hormone that is produced by pancreatic beta-cells and absent in people with type 1 diabetes. Pramlintide delays gastric emptying, suppresses nutrient-stimulated glucagon secretion, and increases satiety [14,15]. Studies that tested insulin-plus-pramlintide and insulin-plus-glucagon artificial pancreas systems with carbohydrate counting have shown that they improve glycemic control compared to insulin alone systems [16-21]. Here, we report a series of experiments to design and optimize a novel fully automated insulin-pramlintide-glucagon artificial pancreas system that alleviates the burden of

carbohydrate counting while maintaining comparable glycemic control to first-generation insulin alone hybrid artificial pancreas systems.

METHODS

Study design

We optimized the system on nine adults with type 1 diabetes at the Research Institute of McGill University Health Center, Montreal, Canada from December 2018 to March 2019. Each participant underwent two 27-hour interventions: (i) an insulin-alone artificial pancreas with full carbohydrate counting and (ii) a fully automated multi-hormone artificial pancreas. The order of the interventions was randomized. The data of each participant were analyzed, and the dosing algorithm was iteratively enhanced until convergence to desirable performance.

Participants

Participants were required to be above 18 years old, have an HbA1c ≤ 12% (108 mmol/mol), and be on an insulin pump for at least 6 months (Table 3.1). Exclusion criteria included gastroparesis, significant diabetes complications (nephropathy, neuropathy, or retinopathy), recent acute macrovascular event, pregnancy, and use of anti-hyperglycemic agents. Participants provided written informed consent and the study was approved by the local ethics committee.

Study procedures

During the admission visit, inclusion and exclusion criteria were assessed, and participant's weight, height, and insulin therapy (total daily dose, basal rates, and carbohydrate ratios) were recorded. The order of the two interventions was then randomized.

Prior to the insulin-alone intervention, participants installed a glucose sensor (Dexcom G5®) and underwent a brief run-in period at home with faster-acting insulin (Fiasp®, Novo Nordisk,

Denmark) for 3-6 days, while remaining on open loop therapy. Prior to the multi-hormone intervention, participants installed a glucose sensor (Dexcom G5®) and an additional pump (Minimed® 630G or Veo, Medtronic, USA) for pramlintide. Participants underwent a brief-run-in at home with Fiasp and pramlintide for 3-6 days, while remaining on open loop therapy. Pramlintide was delivered at 3µg of pramlintide per unit of insulin in the first 0-2 days then 6µg per unit for the remaining 3-6 days. The reason for the run-in was to avoid the acute effect of pramlintide during the interventions which may not be representative of chronic use. During the run-in, a research member was in contact with the participants and at times adjusted insulin therapy parameters based on glucose levels to ensure safety while at home with the medications, however, any adjustments made were not used to initialize the artificial pancreas.

Participants arrived at the research facility at 19h00, started the artificial pancreas interventions at 19h30, and were discharged at 22h00 the following evening. Analysis was made for the period from 22h00 to 22h00. For the triple-hormone interventions, a third pump (Minimed® 630G or Veo, Medtronic, USA) was installed to deliver freshly reconstituted glucagon (Eli Lily and Company, Indianapolis, USA). The glucose sensor was calibrated prior to meals using capillary glucose levels. During the interventions, participants ate a self-selected snack (22g ±6g) at 22h30 on the first evening and three meals during the following day at 08h00 (44g ±14g), 12h00 (62g ±16g) and 17h00 (60g ±12g). Meals were standardized between visits of each participant but were different between participants. The carbohydrate counting of the meals was performed by the research team. Participants could choose to go on walks; the time and duration of walks were standardized between visits.

Plasma glucose was measured every 10-30 minutes by venous blood samples that were tested on a YSI2300 STAT Plus Analyser (Yellow Springs, Ohio, USA). If plasma glucose fell below

3.3 mmol/L, participants self-administered oral carbohydrates (16g). The same protocol was applied during the two artificial pancreas interventions. Participants were asked if they experienced any nausea, vomiting, bloating, or heartburn at the start of the intervention, after the snack, and after each meal. Symptoms were ranked as mild, moderate, moderate-to-severe, or severe.

The artificial pancreas

The dosing algorithms used in both artificial pancreas systems were based on an adaptive model predictive control. The algorithm adapts by using multiple linear models, switching, and tuning [22]. Controllers adopting this approach have been shown to improve the transient responses compared to conventional controllers when faced with complex systems and environments, and rigorous stability proofs have been reported for the linear case [22].

The algorithm's models were parametric, compartmental, and physiologically-based, and had an identical structure but different parameter values. The models' structure included two insulin absorption compartments, two glucagon absorption compartments, two meal absorption compartments, two plasma glucose compartments, and one interstitial glucose compartment [6,23,24]. The various models' parameters represented four insulin absorption profiles, three meal absorption profiles, and four insulin sensitivity factors (total number of models 48). These models accommodate different pharmacokinetics of insulin [12], the pramlintide's effect on meal absorption [14], different meal types (low/high glycemic loads [25,26]), and diurnal variation in insulin sensitivity [27]. The models were accompanied with states that were continuously tuned using distinct, parallel Kalman filters.

At every control cycle, the models were compared using a performance index based on weighted least squares of residuals (models' predictions minus glucose measurements) over the previous 150-minute data [22]. The residuals were weighted to be decayed exponentially the further they are in the past [22]. The model with the smallest performance index is chosen, and subsequently used in the model predictive controller.

The model predictive algorithm used a quadratic objective function, with control and prediction horizons set to 4.5 hours. The objective function included a term that penalizes the mismatch between the predicted glucose profile and the glucose target, and a second term that penalizes the deviation of insulin delivery from the participant's usual basal rates. The nominal glucose target was set to 6.0 mmol/L.

For the insulin-alone artificial pancreas, the algorithm was initialized with the total daily dose, basal rates, and carbohydrate ratios at the time of the admission visit. The mealtime insulin boluses were delivered as single boluses at the onset of the meals and were calculated using the carbohydrate content of the meals, the carbohydrate-to-insulin ratios, and pre-meal glucose levels.

For the triple-hormone artificial pancreas, the algorithm was initialized with the total daily dose and basal rates at the time of the admission visit. Pramlintide and insulin were administered in a basal-bolus manner with a fixed ratio to mimic a co-formulation and the normal physiology of the pancreas. Glucagon was administered as mini boluses based on heuristic logical rules that used glucose levels and their trends as provided by the Kalman filters, and mimicked a proportional derivative controller [28]. These heuristic rules were previously used [29,30], and were shown to be minimal enough to avoid gastrointestinal symptoms and rebound hyperglycemia yet sufficient

to avoid hypoglycemia. This triple-hormone algorithm was iteratively enhanced between participants while the insulin-alone algorithm remained unchanged and served as a comparator.

Every 10 minutes, the available glucose sensor reading was entered manually into a laptop, which ran the hormonal dosing algorithms. Following the algorithms' recommendations, a study personnel adjusted the temporary basal rates on the pumps and delivered manual boluses. For this system to be used in outpatient settings, an automated system needs to be developed to automatically adjust the basal rates and administer boluses on multiple pumps. Participants were masked to hormonal infusions and glucose data during the interventions.

RESULTS

Participants 1 & 2: baseline algorithm

The baseline algorithm for the triple-hormone artificial pancreas administered pramlintide and insulin boluses when glucose levels crossed 9.0 mmol/L. The size of the boluses were determined so glucose levels reach a target of 4.0 mmol/L based on the algorithms' mathematical model predictions. Boluses were delivered every 30 minutes as long as glucose level remained above 9.0 mmol/L. The algorithm considered the previously delivered insulin (insulin-on-board) and would not recommend boluses if the insulin-on-board is predicted to bring glucose levels below 4.0 mmol/L.

Pramlintide was administered in a basal-bolus manner with a fixed ratio of 10µg per unit of insulin. We have previously done studies with pramlintide at a fixed-ratio of 6µg per unit of insulin [31]; however, in those studies full-meal boluses were administered. Since this new triple-hormone artificial pancreas is giving smaller insulin correction boluses rather than full-meal insulin boluses, a higher pramlintide co-delivery ratio was used in order to provide pharmacologically

effective doses of pramlintide. Glucagon was administered as mini boluses in order to avoid potential hypoglycemia due to the insulin and pramlintide boluses.

This algorithm was tested on two participants (Figure 3.1). Participant 1 spent 85% time in target range (3.9–10.0 mmol/L) on the multi-hormone system compared to 77% with the Fiasp-alone system. Participant 1 spent no time < 3.9 mmol/L in either arm (0%, 0%) and spent less time >10.0 mmol/L in the multi-hormone arm compared to the insulin-alone arm (15%, 23%; respectively). Participant 2 spent 57% time in target range on the multi-hormone artificial pancreas system compared to 63% on the insulin-alone artificial pancreas. Participant 2 spent no time < 3.9 mmol/L (0%, 0%) and spent comparable time >10.0 mmol/L on the multi-hormone system compared to the insulin-alone arm (43%, 37%; respectively).

Participant 1 received 36u of insulin in the insulin-alone arm and 40u of insulin, 400µg of pramlintide, and 62µg of glucagon in the triple-hormone arm. Participant 2 received 35u of insulin in the insulin-alone arm but only 31u of insulin and 310µg of pramlintide in the triple-hormone arm. Promising glycemic outcomes were obtained despite glucagon being minimally delivered for Participant 1 and not delivered at all for Participant 2. Neither participant experienced any gastrointestinal side-effects.

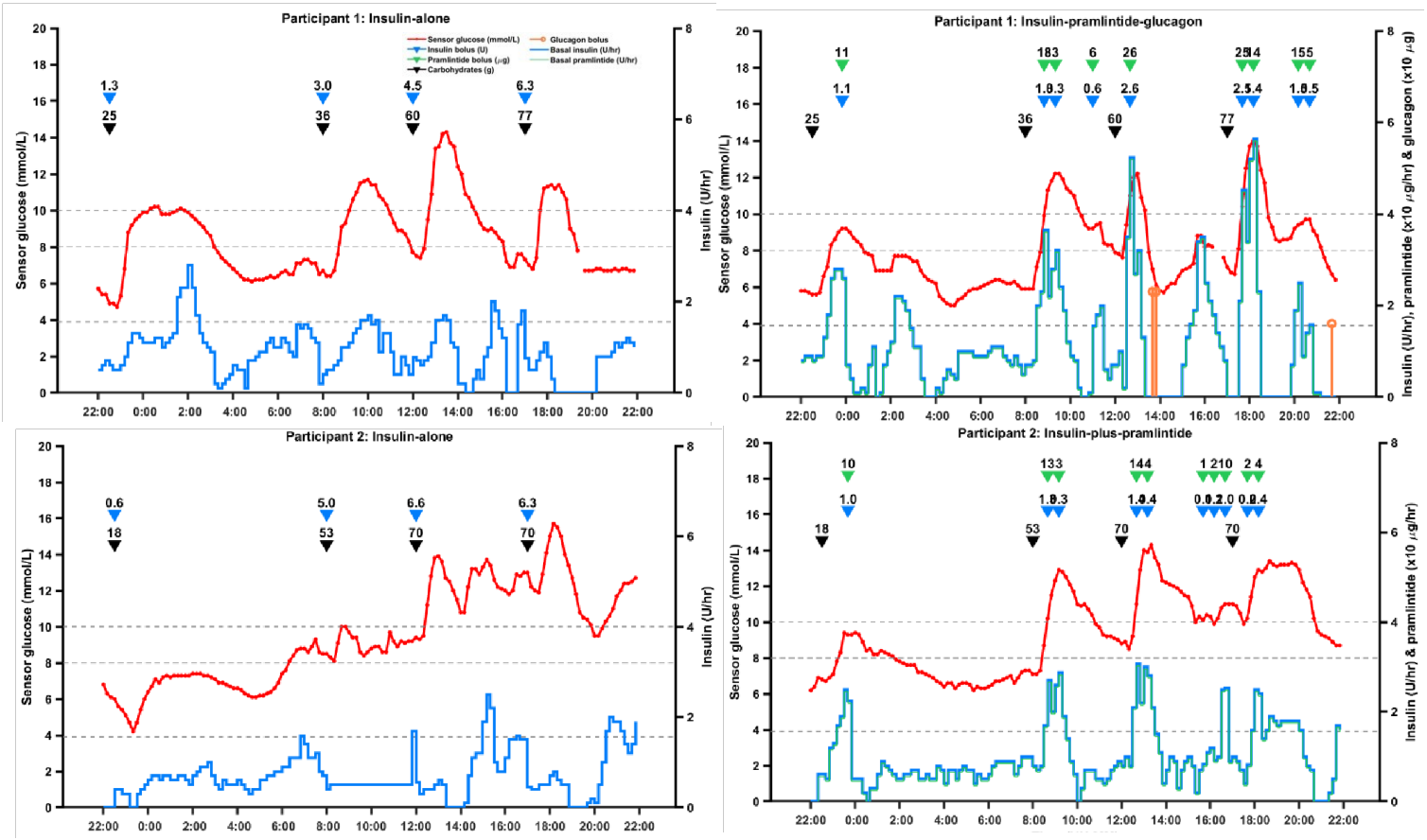

Figure 3.1: Glucose levels and hormonal deliveries with the baseline algorithm. During the multi-hormone intervention, participant 1 (age 24 years, HbA1c 7.4%) had 85% time in range, 0% time <3.9 mmol/L, and 15% time >10.0 mmol/L. During the insulin alone intervention, participant 1 had 77% time in range, 0% time <3.9 mmol/L, and 23% time >10.0 mmol/L. During the multi-hormone intervention, participant 2 (age 54 years, HbA1c (8.8%) had 57% time in range, 0% time <3.9 mmol/L, and 43% time >10.0 mmol/L. During the insulin alone intervention, participant 2 had 63% time in range, 0% time <3.9 mmol/L, and 37% time >10.0 mmol/L.

Participants 3 & 4: more aggressive insulin and pramlintide delivery

The algorithm was modified to deliver insulin and pramlintide more aggressively in order to maximize the benefits of glucagon and to achieve a lower mean glucose level without increasing risk of hypoglycemia [17]. The modified algorithm was tested on two participants (Figure 3.2). Participant 3 spent 76% time in target range on the multi-hormone artificial pancreas system compared to 70% on the insulin-alone artificial pancreas, with less time < 3.9 mmol/L (2.1%, 5.6%), and comparable time >10.0 mmol/L (22%, 24%). Participant 4 spent 81% time in target range on

the multi-hormone artificial pancreas system compared to 92% on the insulin-alone artificial pancreas with more time < 3.9 mmol/L (6.3%, 0%) and more time >10.0 mmol/L (13%, 8%).

Participant 3 received 97u of insulin in the insulin-alone arm and 108u of insulin, 108µg of pramlintide and 197µg glucagon in the triple-hormone arm. Participant 4 received 56u of insulin in the insulin-alone arm and 59u of insulin, 590µg of pramlintide and 227µg glucagon in the triple-hormone arm. Despite delivering higher doses of insulin and pramlintide, this strategy did not increase the time spent in the target range, rather it was accompanied by undesirable glucose fluctuations (Figure 3.2).

Moreover, unlike the first two participants, both participants with the modified aggressive algorithm experienced different degrees of nausea throughout the intervention. Participant 3 experienced mild nausea after breakfast, severe nausea after lunch, and moderate-to-severe nausea after dinner. Patient 4 experienced mild nausea after lunch and dinner, but the nausea was transient and subsided before the end of the intervention.

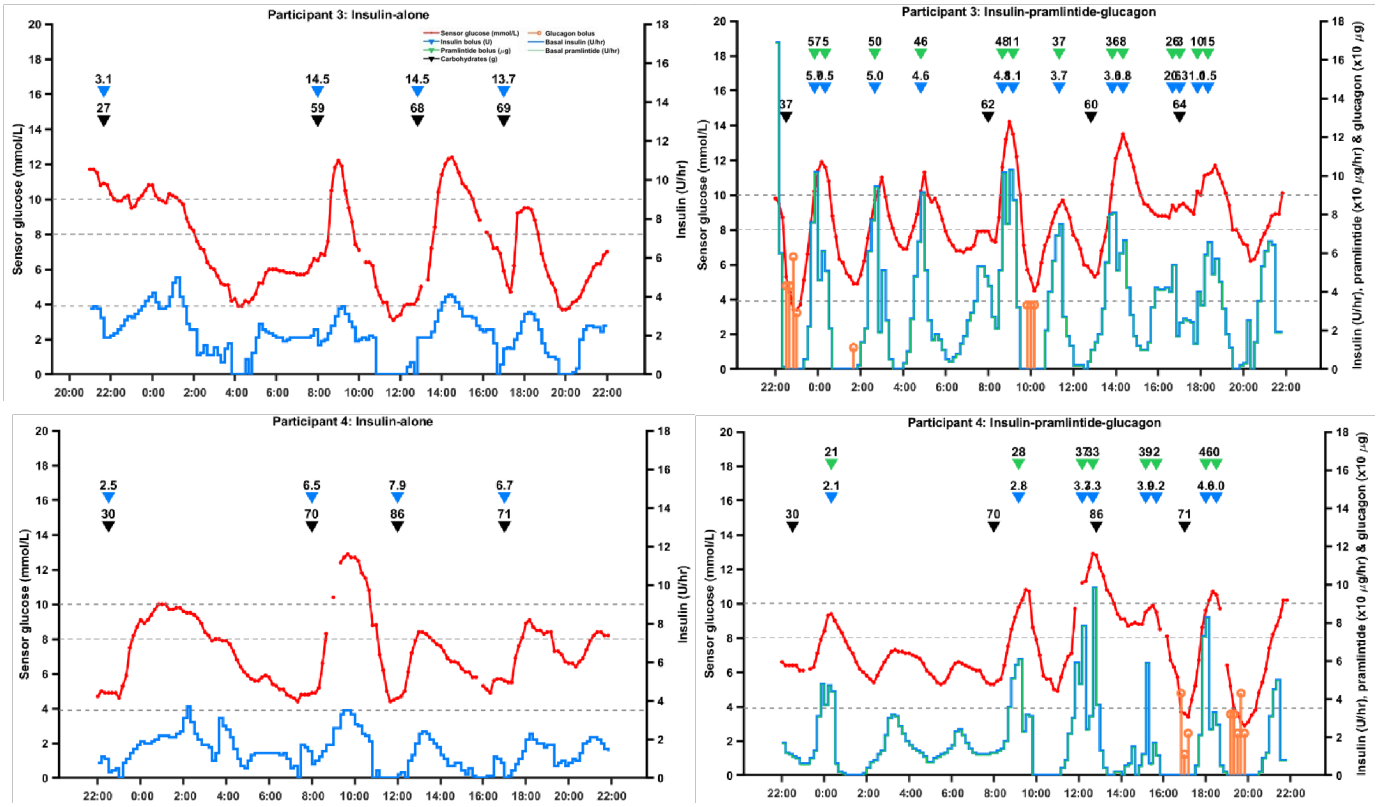

Figure 3.2: Glucose levels and hormonal deliveries for two participants with more-aggressive insulin and pramlintide delivery. During the multi-hormone intervention, participant 3 (age 52 years, HbA1c 8.1%) had 76% time in range, 2.1% time <3.9 mmol/L, and 22% time >10.0 mmol/L. During the insulin alone intervention, participant 3 had 70% time in range, 5.6% time <3.9 mmol/L, and 24% time >10.0 mmol/L. During the multi-hormone intervention, participant 4 (age 39 years, HbA1c 7.6%) had 81% time in range, 6.3% time <3.9 mmol/L, and 13% time >10.0 mmol/L. During the insulin alone intervention, participant 4 had 92% time in range, 0% time <3.9 mmol/L, and 8% time >10.0 mmol/L.

Participants 5 & 6: reduce glucagon threshold

The algorithm was modified again to reduce the aggressiveness of insulin and pramlintide back to the baseline algorithm used with participants 1 and 2. However, in the baseline algorithm used in the first two participants, glucagon was minimally administered, which made us question the need for it. As a result, the glucose threshold for when glucagon is administered was lowered for participants 5 and 6 (Figure 3.3). Participant 5 spent 72% time in target range on the multihormone artificial pancreas system compared to 96% on the insulin-alone artificial pancreas

with comparable time < 3.9 mmol/L (6.9%, 7.2%) but higher time >10.0 mmol/L (22%, 0%). Participant 6 spent comparable time in target during the multi-hormone artificial pancreas arm compared to the insulin-alone arm (89%, 86%), with less time < 3.9 mmol/L (2.8%, 4.2%), and comparable time >10.0 mmol/L (8%, 10%).

Participant 5 received 30u of insulin in the insulin-alone arm and 24u of insulin, 240µg of pramlintide, and 121µg of glucagon. Participant 6 received 34u of insulin in the insulin-alone arm and 28u of insulin, 280µg of pramlintide, and 161µg of glucagon in the triple-hormone arm.

Neither of the participants experienced nausea and only one participant experienced transient mild bloating after lunch. The results of these participants, combined with the previous participants, suggest that reducing the aggressiveness of insulin and pramlintide results in fewer glycemic fluctuations and reduced undesirable gastrointestinal side-effects. Participant 5 and 6 received correction boluses 1-2 hours after the meals, which resulted in poor postprandial glucose excursions. Participants may benefit from administering pramlintide and insulin closer to mealtimes.

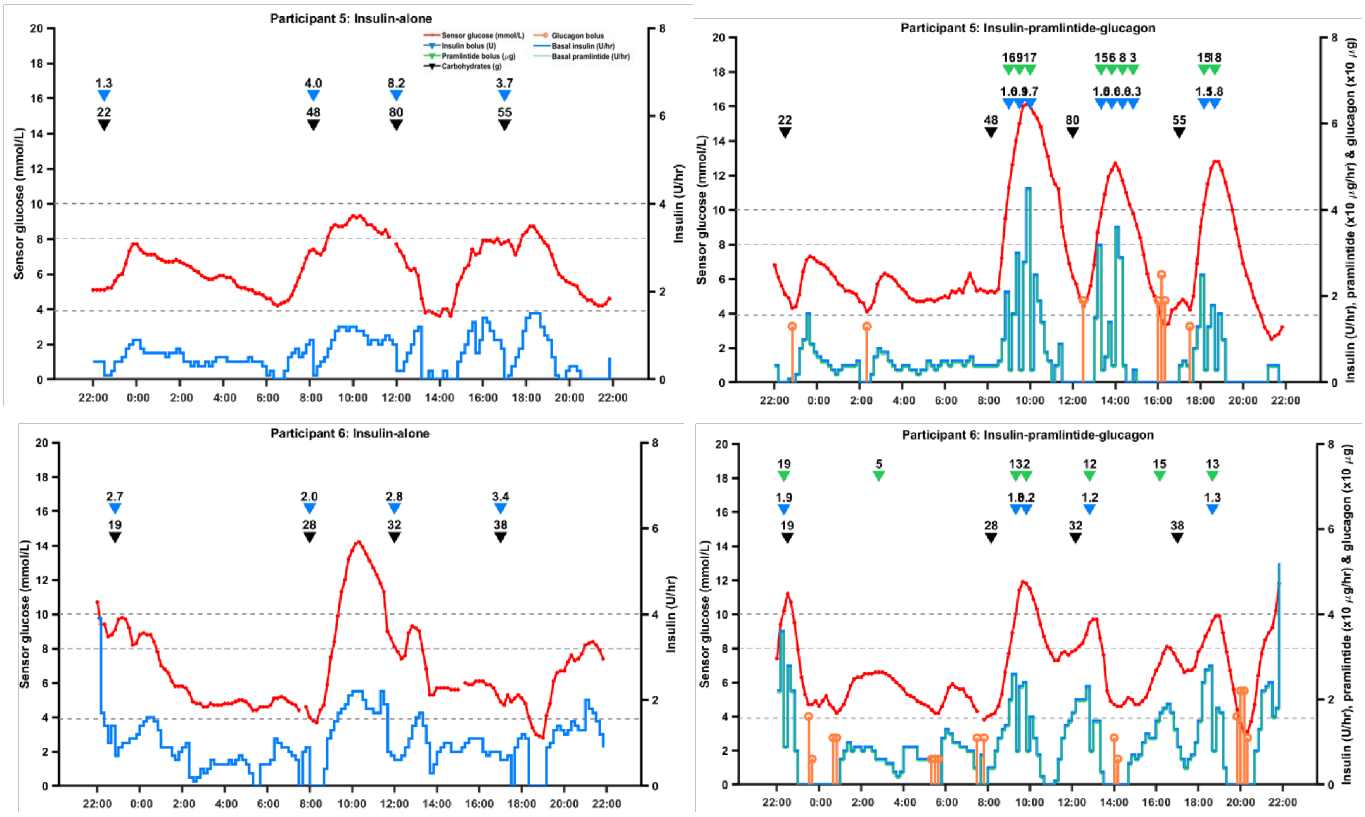

Figure 3.3: Glucose levels and hormonal deliveries for two participants with reduced glucagon threshold. During the multi-hormone intervention, participant 5 (age 41 years, HbA1c 6.5%) had 72% time in range,6.9% time <3.9 mmol/L, and 22% time >10.0 mmol/L. During the insulin-alone intervention, participant 5 had 96% time in range, 4.2% time <3.9 mmol/L, and 0% time >10.0 mmol/L. During the multi-hormone intervention, participant 6 (age 51 years, HbA1c 8.5%) had 89% time in range, 2.8% time <3.9 mmol/L, and 8% time >10.0 mmol/L. During the insulin-alone intervention, participant 6 had 86% time in range, 4.2% time <3.9 mmol/L, and 10% time >10.0 mmol/L.

Participant 7-9: meal detection algorithm and removal of glucagon

The fully-automated algorithm was administering correction boluses 1–2 hours after meals, yet studies show that approximately 25-50% of meal carbohydrates are already absorbed within the first hour after meal consumption [25,26]. Therefore, administering pramlintide more than one hour after the meal may not be effective in slowing gastric emptying and reducing postprandial hyperglycemia. Additionally, administering late insulin boluses may also increase the risk of post-meal hypoglycemia [31]. Rather than giving correction boluses when glucose levels exceed 9.0 mmol/L, we added a model-based meal detection algorithm to detect meals 30-40

minutes following ingestion [32] and trigger insulin and pramlintide boluses. Subsequently, we modified the algorithm to no longer deliver glucagon as the results from Participants 5 and 6 suggest that glucagon was only needed to prevent impending hypoglycemia that resulted from late insulin and pramlintide boluses.

The meal detection algorithm uses a Kalman filter to estimate glucose levels and employs a generalized likelihood ratio test [33] to evaluate the consistency of the filter under the null hypothesis that all previous consumed meals were announced [32]. A threshold criterion is applied on the likelihood ratio to test for the alternative hypothesis that observed glucose levels are due to an unannounced meal.

At first, the pramlintide ratio was increased from 10µg/unit insulin to 15µg/unit insulin in order to improve the time spent in the target range. This was tested on Participant 7 but the increased pramlintide ratio led to undesirable gastrointestinal side-effects. Participant 7 experienced mild nausea on the first night, mild nausea at breakfast, and moderate nausea at lunch. As a result, pramlintide ratio was reduced to 12µg/unit insulin for Participants 8 and 9, which decreased but not eliminated the gastrointestinal side-effects. The last two participants experienced transient mild nausea after lunch, so the algorithm was tuned again to lower the pramlintide ratio down to 10µg/unit insulin.

Participant 7 spent less time in the target range on the multi-hormone artificial pancreas system (68%) compared to the insulin-alone artificial pancreas (90%), with less time <3.9 mmol/L (0%, 2.1%) but more time >10.0 mmol/L (32%, 8%). Participant 8 spent more time in target during the multi-hormone artificial pancreas arm (97%) compared to the insulin-alone arm (81%), with more time < 3.9 mmol/L (2.8%, 0%), and less time >10.0 mmol/L (0%, 19%). Participant 9 spent comparable time in range on the multi-hormone arm (78%) compared to the insulin-alone arm

(79%), with less time < 3.9 mmol/L (0%, 11.8%), but more time >10.0 mmol/L (22%, 9%) (Figure 3.4).

Participant 7 received 56u of insulin in the insulin-alone arm and 52u of insulin and 780µg of pramlintide in the multi-hormone arm. Participant 8 received 57u of insulin in the insulin-alone arm and 49u of insulin and 588µg pramlintide in the multi-hormone arm. Participant 9 received 38u of insulin in the insulin-alone arm and 37u of insulin and 444µg pramlintide in the multihormone arm.

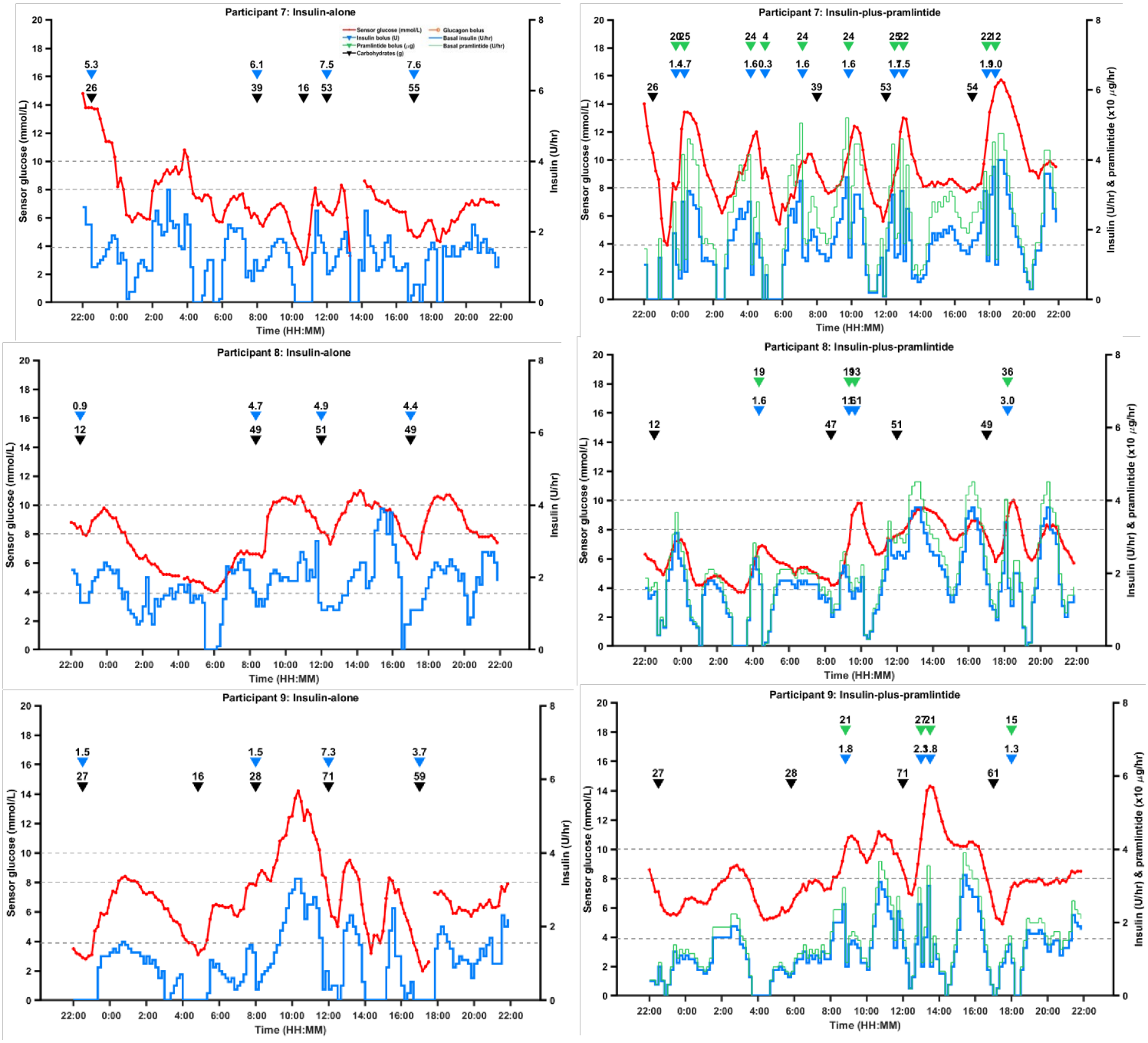

Figure 3.4: Glucose levels and hormonal deliveries for 3 participants with meal-detection algorithm. During the multi-hormone intervention, participant 7 (age 26 years, HbA1c 7.5%) had 68% time in range, 0% time <3.9 mmol/L, and 32% time >10.0 mmol/L. During the insulin-alone intervention, participant 7 had 90% time in range,2.1% time <3.9 mmol/L, and 8% time >10.0 mmol/L. During the multi-hormone intervention, participant 8 (age 21 years, HbA1c 7.1%) had 97% time in range, 2.8% time <3.9 mmol/L, and 0% time >10.0 mmol/L. During the insulin-alone intervention, participant 8 had 81% time in range, 0% time <3.9 mmol/L, and 19% time >10.0mmol/L. During the multi-hormone intervention, participant 9 (age 27 years, HbA1c 7.7%) had 78% time in range, 0% time <3.9 mmol/L, and 22% time >10.0 mmol/L. During the insulin-alone intervention, participant 9 had 79% time in range,11.8% time <3.9 mmol/L, and 9% time >10.0mmol/L.

DISCUSSION

We attempted to develop a fully automated artificial pancreas that delivers insulin, pramlintide, and glucagon via a novel dosing algorithm. The system was iteratively enhanced between nine participants in order to reduce postprandial hyperglycemia, reduce gastrointestinal symptoms, and avoid hypoglycemia. The changes resulted in a final system that administers insulin and pramlintide at a fixed ratio of 10μg/unit with a meal-detection algorithm to trigger post-meal boluses. Preliminary testing of the fully automated system indicates comparable performance to the hybrid insulin-alone artificial pancreas with carbohydrate-matched meal boluses.

Although glucagon and insulin artificial pancreas system have shown to reduce time spent in hypoglycemia and improve time spent in target range [34], these systems require manual entry of carbohydrate content of meals. The objective of the experiments outlined in this paper was to optimize a novel artificial pancreas system that alleviates the burden of carbohydrate counting while maintaining non-inferior glycemic control to an insulin-alone artificial pancreas with carbohydrate counting. By removing carbohydrate counting and adding pramlintide, the benefits of glucagon were not seen in the first six participants. Subsequently, glucagon was removed from the system. Removing glucagon did not increase the amount of time participants spent in hypoglycemia (Table 3.2).

Data from the first six participants indicate that threshold-triggered insulin-and-pramlintide boluses appear to achieve suboptimal post-meal glucose excursions. Insulin and pramlintide boluses were administered one to two hours after meals, which not only resulted in prolonged post meal hyperglycemia but also increased the risk of late postprandial hypoglycemia. This may be attributable to the pharmacokinetics of insulin and pramlintide compared to meal absorption profiles. Studies have shown that 25-50% of a high-glycemic carbohydrate meal is

absorbed within the first hour of meal consumption [25,26]. Since pramlintide boluses were administered one to two hours after meals [35], the potential effects of pramlintide may be wasted as a large portion of the meal carbohydrate content has already been absorbed at that time. In addition, 75% of a meal is absorbed between 1.5 to 2.5 hours after its consumption, yet Fiasp, despite being the fastest rapid acting insulin on the market, has a duration of action lasting up to five hours [36]. This appeared to result in an increased risk of late postprandial hypoglycemia. When the meal detection algorithm was added, insulin and pramlintide were administered closer to mealtimes, which made the system more effective in improving postprandial glucose levels.

Currently, pramlintide and insulin cannot be mixed in a single-chamber pump because they are stable at different pH levels; however, a dual-chamber pump and a co-formulation of insulin and pramlintide are underdevelopment [37,38]. An advantage of a co-formulation of insulin and pramlintide is that it would eliminate the need for two separate infusion sites and allow the use of conventional single-chamber insulin pumps that are already on the market to deliver both hormones. An advantage of a dual-chamber pump is that it provides the flexibility to adjust the dosing of the two hormones. For example, pramlintide appears to have no effect during fasting hours [21], and with dual-chamber pump users have the flexibility to limit pramlintide administration to certain hours of the day when it is most effective. Another advantage of a dual chamber pump is that it enables personalized tailoring of the system to deliver different pramlintide to insulin ratios based on individual tolerance to gastrointestinal side-effects of pramlintide.

Other hormones such as glucagon-like peptide-1 (GLP-1) may also be explored for developing a fully automated artificial pancreas. GLP-1 is a hormone that is released in the gut from nutrient stimulation and, like pramlintide, it inhibits gastric emptying, induces satiety, and

inhibits glucagon secretion [39]. GLP-1 agonists have been developed and approved for type 2 diabetes in the form of daily oral pills and daily or weekly injections [40]. A drawback of using GLP1 is that the current mode of delivery does not allow adjustments to be made continuously in a glucose responsive manner, the way delivering pramlintide through a pump can be, which may be less representative of natural physiology. Overall, the similarity between the pharmacodynamics of GLP-1 and pramlintide warrants a comparison between a fully automated GLP-1 agonist-plus-insulin system and a fully automated pramlintide-plus-insulin system.

The approach we used to optimize the fully automated artificial pancreas has several limitations. First, the study was conducted at an inpatient setting for only one day without vigorous exercise, which is not representative of real-life conditions. Second, the run-in period lasted on average 4 days, which may not have been long enough for the transient acute gastrointestinal side-effects to dissipate. The algorithm was iteratively tuned during the inpatient visits based on the observed gastrointestinal symptoms, which may thus not have been representative of prolonged pramlintide use. Third, each change to the algorithm was driven by the results of two to three participants which may not be generalizable to the general population. Although only a few participants were used to drive the changes, each change was small, incremental, and justified by the data and clinical judgment. Otherwise, each small change made would warrant a randomized control trial, which would not be practical. Fourth, the system required the manual control of pumps to change basal rates and administer boluses. This was unlikely to have affected glucose control as the hormonal deliveries would have been the same if we had used an automated system. A flexible automated system to support three pumps and various algorithms would have required significant developmental efforts. An automated system will need to be developed before the system can be used in free-living outpatient conditions.

We proposed a novel fully automated Fiasp-and-pramlintide system that alleviates the burden of carbohydrate counting for type 1 diabetes and seem non-inferior to a Fiasp-alone hybrid system. The system design was iteratively enhanced over nine individuals resulting in a final insulin-plus-pramlintide fully automated system that appeared to be feasible, safe, and effective in controlling glucose levels without increasing the risk of hypoglycemia. These proof-of-concept experiments support the conduct of a randomized controlled clinical trial to assess the efficacy of the system. We are currently conducting such a clinical trial with the fully automated algorithm in 24 adult participants.

CONTRIBUTION

AH and MT supervised the study. DM, AH, LL, JFY, and MT designed the study. DM, JFY, MT, NG, AH, JR, and LL conducted the study. JR and AEF carried out the data analysis including the statistical analyses. AH and AEF designed the dosing algorithm. AH had full access to the data and takes responsibility for the integrity of the data analysis. All authors read and approved the final version of the manuscript.

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Patient	Age	HbA1c (%)	Body Mass Index (kg/m^2)	Total daily dose (u)	Duration of diabetes (years)
1	24	7.4	24.6	38.5	6
2	54	8.8	24.2	22.8	21
3	52	8.1	30.2	66.7	14
4	39	7.6	22.8	53.0	25
5	41	6.5	23.5	30.5	11
6	51	8.5	19.9	26.7	25
7	26	7.5	23.9	40.4	15
8	21	7.1	34.1	56.1	13
9	27	7.7	25.4	38.4	14

Table 3.1: Participant demographics taken during admission visit

Time spent at glucose level (%) during a 24-hour period (22h00-22h00)

	Insulin-alone intervention					Multi-hormone intervention				
Pt	3.9 – 10.0 mmol/L	<3.9 mmol/L	>10.0 mmol/L	>13.9 mmol/L	>16.7 mmol/L	3.9 – 10.0 mmol/L	<3.9 mmol/L	>10.0 mmol/L	>13.9 mmol/L	>16.7 mmol/L
1	77	0.0	23	1.4	0.0	85	0.0	15	0.0	0.0
2	63	0.0	37	4.2	0.0	57	0.0	43	1.4	0.0
3	70	5.6	24	0.0	0.0	76	2.1	22	0.7	0.0
4	92	0.0	8	0.0	0.0	81	6.3	13	0.0	0.0
5	96	4.2	0	0.0	0.0	72	6.9	22	4.9	0.0
6	86	4.2	10	1.4	0.0	89	2.8	8	0.0	0.0
7	90	2.1	8	1.4	0.0	68	0.0	32	5.6	0.0
8	81	0.0	19	0.0	0.0	97	2.8	0.0	0.0	0.0
9	79	12	9	0.0	0.0	78	0.0	22	1.4	0.0

Table 3.2: Pt, participant number. Participants 1 and 2 were on the baseline algorithm that administered insulin and pramlintide at a fixed ratio (1u:10ug), with boluses triggered by a glucose threshold and glucagon as mini boluses. Participants 3 and 4 received a modified algorithm that administered insulin and pramlintide more aggressively. Participants 5 and 6 received the baseline algorithm with a reduced glucose threshold for glucagon delivery. A meal detection algorithm was added, and glucagon was removed from the system for participants 7, 8 and 9. Insulin and pramlintide were delivered at a fixed ratio of 1u:15ug for participant 7 and 1u:12ug for participants 8 and 9.

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Chapter 4: Manuscript #2

A Fully Closed-loop Fiasp-plus-Pramlintide System (Artificial Pancreas) for Type 1 Diabetes: a Randomized Controlled Trial

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Table count: 4; Figure count: 2

Keywords: Type 1 diabetes, artificial pancreas, fully closed-loop system, pramlintide, Fiasp, carbohydrate counting

ABSTRACT

There is currently no fully automated insulin delivery system on the market that does not require meal-input for people with type 1 diabetes. We propose a novel Fiasp-plus-pramlintide fully closed-loop system. We conducted a randomized, crossover, non-inferiority clinical trial (NCT03800875) in 24 adults with type 1 diabetes (age 35±14 years, HbA1c 8.1±1.3%) comparing (i) Fiasp-plus-pramlintide closed-loop system with no meal input and (ii) Fiasp-alone closed-loop system with full carbohydrate counting. Time spent in target range (3.9-10.0 mmol/L) with the Fiasp-plus-pramlintide closed-loop system (74% [62–83%]) was comparable but not non-inferior to the Fiasp-alone closed-loop system (78% [68–88%]), with an estimated difference of 2.6% ([-2.4 to 12%] CI; non-inferiority p=0.28). 8 (33%) participants experienced at least one hypoglycemia event (<3.3 mmol/L) during the Fiasp-plus-pramlintide intervention compared to 14 (58%) participants during the Fiasp-alone intervention. Non-mild nausea was reported by three participants (13%) and non-mild bloating was reported by one participant (4%) during the Fiasp-plus-pramlintide intervention compared to zero (0%) during the Fiasp-alone intervention. The fully closed-loop Fiasp-plus-pramlintide system achieved comparable glycemic control to the Fiasp-alone closed-loop system, though non-inferiority was not confirmed.

INTRODUCTION

Type 1 diabetes is a chronic metabolic disorder caused by an autoimmune destruction of insulin-producing pancreatic ß-cells[1]. People with type 1 diabetes need life-long insulin replacement therapy through multiple daily injections or continuous subcutaneous insulin infusion, guided by blood and/or interstitial glucose measurements.

Intensive insulin therapy is a comprehensive management system that comprises of frequent glucose monitoring, insulin adjustments, and carbohydrate counting. Intensive insulin therapy aimed at tight glycemic control reduces long-term microvascular and macrovascular complications[2]; however, more than 70% of people with type 1 diabetes still do not achieve glycemic targets[3]. Moreover, the demands of diabetes management and the fear of long-term complications worsen the quality of life for people with type 1 diabetes[4].

The development of continuous glucose monitors has led to the introduction of automated insulin delivery systems, known as the artificial pancreas or closed-loop insulin delivery systems. Closed-loop insulin delivery uses a mathematical dosing algorithm that takes real-time data from a continuous glucose monitor to titrate the infusion of an insulin pump[5]. Randomized trials have shown that closed-loop systems improve glycemic control compared to conventional pump therapy and sensor-augmented pump therapy[6,7]; however, these systems still require users to manually count and enter carbohydrate content of meals to determine prandial insulin boluses. These systems are described as “hybrid” closed-loop systems rather than fully closed-loop systems due to manual entry of premeal boluses.

Meal carbohydrate content is the major nutritional determinant of postprandial glucose levels in type 1 diabetes[8,9], and accurate carbohydrate counting is recommended and associated with improved glycemic control[10]. However, accurate carbohydrate counting is a burdensome and error-prone task, with an estimation error of around 20% in adults[10,11]. Having to count the carbohydrate content of meals affects quality of life of people with type 1 diabetes by making them feel restrained, anxious, and less confident, especially when interacting with peers around food[12]. Additionally, people with type 1 diabetes tend to turn to standardized food choices[12] to facilitate carbohydrate counting which may negatively influence dietary choices. The relative ease provided by Nutrition Facts labels encourage the selection of prepackaged processed foods over whole foods, such as whole grains and fruits[13]. Therefore, a fully automated closed-loop system has become a 'holy grail' for type 1 diabetes.

Amylin is a hormone that is physiologically co-secreted with insulin and is deficient in people with type 1 diabetes. Amylin delays gastric emptying, suppresses nutrient-stimulated glucagon secretion, and increases satiety[14,15]. Pramlintide is an analog of amylin and is an FDA approved adjunctive therapy for type 1 and type 2 diabetes[16]. Studies have shown that pramlintide administered at a fixed dose[17] and in a basal-bolus manner[18] with insulin in a closed-loop system improves postprandial glucose excursions compared to an insulin-alone closed-loop system.

Here, we aimed to assess the efficacy of a novel fully automated insulin-plus-pramlintide closed-loop system without meal announcement. We used a faster-acting insulin aspart analog (Fiasp®), which has a faster onset and shorter duration of action compared to insulin aspart[19,20]. We conducted a randomized, crossover, non-inferiority trial comparing the fully automated Fiasp-plus-pramlintide closed-loop system without carbohydrate counting or meal announcement to a Fiasp-alone closed-loop system with full carbohydrate counting in 24 adults with type 1 diabetes.

METHODS

Study design

We conducted a randomized, crossover study with 24 adults with type 1 diabetes at the Research Institute of McGill University Health Center, Montreal, Canada. Each participant underwent two 27-hour interventions: (i) a Fiasp-alone hybrid closed-loop system with full-carbohydrate counting and (ii) a Fiasp-plus-pramlintide fully closed-loop system with no meal announcement.

Participants

Adults (≥ 18 years) with an HbA1c of ≤12% who had been on insulin pump therapy for at least 6 months were enrolled. Participants who had gastroparesis, significant diabetes complications, a recent acute macrovascular event, a recent severe diabetic ketoacidosis episode, a recent severe hypoglycemia episode, or were on non-insulin antihyperglycemic agents were excluded (Supplementary Table 1). Participants provided written informed consent and the study was approved by the local ethics committee.

Randomization and masking

A computer-generator allocated the randomization sequence of the interventions during the admission visit. Participants and investigators were not blinded to the allocation. Participants were masked to hormonal infusions and glucose data during intervention visits. For safety reasons, investigators had access to glucose levels.

Study procedures

During the admission visit, the participant's weight, height, and usual insulin therapy (e.g. total daily dose, basal rates, and carbohydrate ratios) were recorded. Prior to the hybrid closed-loop intervention, participants installed a glucose sensor (Dexcom G5 or G6®) and underwent a brief run-in period at home with faster-acting insulin aspart (Fiasp®, Novo Nordisk, Denmark) for up to nine days, while remaining on open-loop therapy. If participants were not on a Medtronic pump, participants were asked to switch to a study pump (Minimed® 630G or Veo, Medtronic, USA) at least one day prior to the intervention. If participants were on Medtronic 670G pump, they were asked to remain on manual mode throughout the duration of the study.

Prior to the fully closed-loop intervention, participants installed a glucose sensor (Dexcom G5 or G6®) and an additional pump (Minimed® 630G or Veo, Medtronic, USA) for pramlintide. Participants underwent a brief run-in at home with Fiasp and pramlintide for up to nine days, while remaining on open-loop therapy. 3µg of pramlintide per unit of insulin (µg/u) were administered in a basal-bolus manner for the first one to three days of the run-in period. Participants were then asked to increase the pramlintide dose to 6µg/u for an additional one to three days. Lastly, basal pramlintide rates were escalated to 10µg/u while boluses were kept at 6µg/u for the remaining run-in period prior to the intervention. If participants were not on a Medtronic pump, participants were asked to switch to a study pump (Minimed® 630G or Veo, Medtronic, USA) at least one day prior to the intervention. The reason for the run-in was to avoid the acute gastrointestinal effects of pramlintide during the interventions which may not be representative of chronic use.

During the run-in period for both arms, a research member was in contact with the participants and could adjust insulin therapy parameters based on glucose levels to ensure safety while at home with the study medications. However, any adjustments made were not used to

initialize the closed-loop systems. We did not optimize the dosing algorithm based on adjustments made during the run-in period because we wanted to assess how the system would perform with suboptimal insulin parameters that resemble usual care.

Participants arrived at the research facility at 19h00, started the closed-loop interventions at 19h30, and were discharged at 22h00 the following evening. If participants were on the Dexcom G5, the glucose sensor was calibrated prior to meals using capillary glucose levels. Calibrations were not performed for the Dexcom G6 sensor. Each participant used the same sensor model (G5 or G6) in both interventions. During the interventions, participants ate a self-selected snack (30g±8g) at 22h30 on the first evening and ate breakfast (51g±21g) at 08h00, lunch (74g±21g) at 12h00, and dinner (77g±21g) at 17h00 the following day. Meals were standardized between visits but were different between participants. Participants were asked if they experienced any nausea, vomiting, bloating, or heartburn after each meal and at discharge. Symptoms were ranked as mild or non-mild (moderate, moderate-to-severe, or severe). A research staff counted the carbohydrate content of meals based on the labeled packages. Participants were recommended to go on walks, with the time and duration of walks standardized between visits. 18 participants (75%) went on walks for a median duration of 30 minutes [30–50 minutes].

Exercise

The last 11 participants underwent 40 minutes of moderate aerobic exercise at 40–60% heart rate reserve. At 15h00, participants used a cycle ergometer and completed two 20-minute cycling sessions with a 5-minute rest in between. If participants were ≤ 12 mmol/L 10 minutes prior to the start of exercise session, they were given a self-selected 20–40g snack without an insulin

bolus. Participants only started the exercise sessions when their glucose level was above 5.0 mmol/L.

Hypoglycemia protocol

If plasma glucose fell below 3.3 mmol/L, participants were treated with standardized 16g of oral carbohydrates. If glucose levels fell below 3.7 mmol/L during the exercise period, the participant stopped the exercise and were treated with standardized 16g of oral carbohydrates. Exercise was resumed and completed after glucose levels were above 5.0 mmol/L. The same protocol was applied during both closed-loop interventions.

The closed-loop systems

The basal dosing algorithms used in both artificial pancreas systems were based on an adaptive model predictive control. The algorithm switches between models of various insulin and meal absorption profiles, automatically accommodating the kinetics of insulin and pramlintide, and pramlintide's effect on meal absorption[21].

For the hybrid closed-loop system, the algorithm was initialized with the participant's total daily dose, basal rates, and insulin-to-carbohydrate ratios at the time of the admission visit. The mealtime insulin bolus was delivered as a single bolus at the onset of the meal and was calculated using carbohydrate content of the meal, insulin-to-carbohydrate ratio, and pre-meal glucose levels.

For the fully closed-loop system, the algorithm was initialized with the participant's total daily dose and basal rates at the time of the admission visit. Pramlintide and insulin were administered in a basal-bolus manner with a fixed ratio of 10µg/u to mimic a co-formulation and

normal physiology of the pancreas. In our previous study, we have dosed pramlintide in a basal-bolus manner at a fixed ratio of 6µg/u, which proved to be safe and effective[18]. This fully automated dosing algorithm does not calculate insulin and pramlintide boluses based on carbohydrate content of meals. As a result, insulin boluses are smaller and subsequently the pramlintide-to-insulin ratio was increased in order to deliver comparable doses of pramlintide to our previous study.

In addition to basal adjustments, the fully closed-loop system recommended insulin and pramlintide boluses which were triggered by a model-based meal-detection algorithm[22]. Once a meal was detected, the algorithm delivered one to three insulin and pramlintide boluses, separated by at least 30 minutes, depending on glucose levels and rate of change of glucose.

Every 10 minutes, the available glucose sensor reading was entered manually into a laptop, which ran the hormonal dosing algorithms. Following the algorithms' recommendations, the study personnel adjusted the temporary basal rates on the pump and delivered manual boluses. A phone-based automated system that adjusts basal rates and administers boluses in two pumps is currently under development and will be needed to test this system in outpatient settings.

Study outcomes

The primary outcome was time spent in target range (3.9–10.0 mmol/L) for a 24-hour period (22h00–22h00) during the interventions. Secondary outcomes included mean glucose level, time spent 3.9–7.8 mmol/L, <3.9 mmol/L, <3.3 mmol/L, <2.8 mmol/L, >7.8 mmol/L, >10 mmol/L, >13.9 mmol/L, and >16.7 mmol/L during the 24-hour period (22h00–22h00) and at night (24h00–08h00). Additional outcomes included incremental area under the curve 4 hours after meals, standard deviation (SD) and coefficient of variation (CV) of glucose levels, and total pramlintide and insulin

deliveries. Safety outcomes included number of participants experiencing hypoglycemia requiring oral treatment during the 24-hour study period (22h00–22h00), at night (24h00–08h00), and during the day (08h00–22h00). Gastrointestinal symptoms during the 27-hour interventions were assessed.

Statistical analysis

We anticipated that the fully closed-loop system would be within 6% time in target range to the hybrid closed-loop system. Therefore, we did a power analysis using the formula for the two-sided paired t-test with 5% significance level and standard deviation of 10%[17,23]. We calculated that 23 participants would provide 80% power. Participants who did not complete both interventions were excluded from analysis and replaced in the enrollment process.

Our analysis was on a modified intention-to-treat basis. Participants who did not complete both interventions were not included in the analysis and were replaced in the enrollment process. A liner mixed model was fitted to the data while adjusting for the type and order of interventions. Residual values from the regression model were examined for an approximate normal distribution. If values were highly skewed, a transformation or nonparametric analyses was used. The hypothesis of no sequence effect was tested to assess for carry-over effects. A 5% significance threshold was used to declare statistical significance. Results reported as median [IQR], mean (SD), or median confidence interval [95% CI]. Unless otherwise stated, p-value is reported for a superiority test.

Role of funding

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between February 2019 and September 2020, 28 participants were randomized, of which 24 completed both interventions (Figure 1). One participant dropped-out due to scheduling conflicts, two participants dropped out due to gastrointestinal side effects of pramlintide during the dose escalation run-in period, and one participant was discontinued due to circumstances surrounding COVID-19. 24 participants who completed both interventions were included in the analysis (50% female; age, 35±14 years; HbA1c 8.1±1.3%, duration of diabetes 19±14 years, total daily insulin 0.68±0.23 units/kg; Table 1).

The fully closed-loop system had a comparable but not non-inferior median time spent in target range (3.9–10.0 mmol/L) compared to the hybrid system (fully 74% [62–83%] vs. hybrid 78% [68–88%], effect-size 2.6% CI [-2.4 to 12%], non-inferiority p=0.28, superiority p=0.36; Table 2). 12 participants (50%) had a higher time in target range with the hybrid system, ten participants (42%) had a higher time in target range with the fully closed-loop system, and two participants (8%) had equal time in range in both interventions. 14 participants (58%) had a difference of less than 6% in time in range between interventions. There was no difference in the coefficient of variance (p=0.95) and standard deviation (p=0.44) between interventions. Participants spent median 24% of time above 10.0 mmol/L with the fully closed-loop system compared to 20% with the hybrid system (p=0.11), and median 2.4% time above 13.9 mmol/L with the fully closed-loop system

compared to 0.35% with the hybrid system (p=0.69). Eight participants (33%) experienced at least one hypoglycemia event with the fully closed-loop system compared to 14 participants (58%) with the hybrid system (p=0.15). No treatment by period interaction was found, and no difference was observed due to the order of interventions (data not shown).

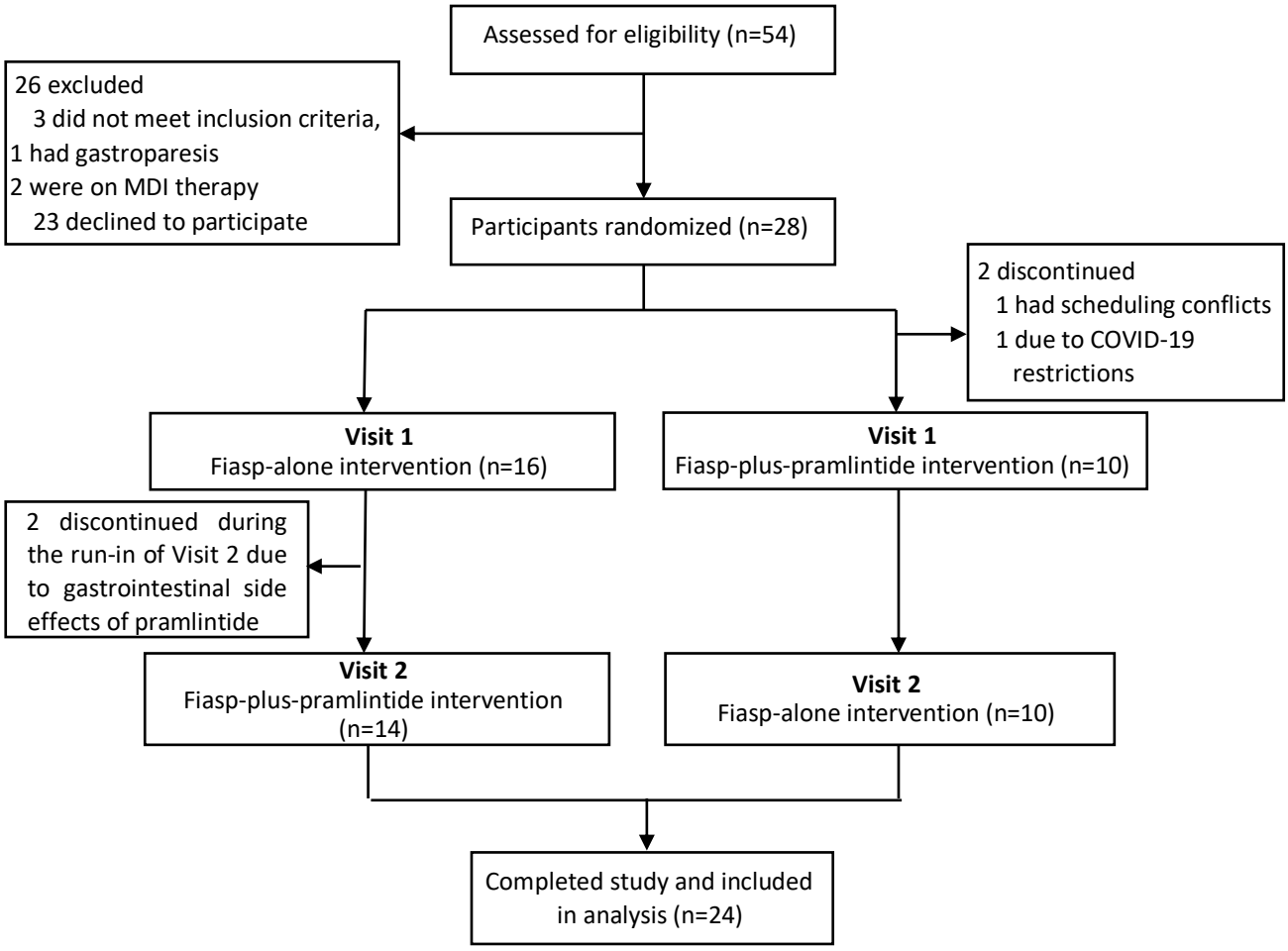

Figure 4.1: Study Profile

During the day (08h00–22h00), the fully closed-loop system had median 66% time in target range compared to 79% with the hybrid system (p=0.016; Table 3). Participants spent a median 33% time above 10.0 mmol/L with the fully closed-loop system compared to 21% with the hybrid system (p=0.0093), spent median 4.2% and 0%, respectively, above 13.9 mmol/L (p=0.3), and spent median

0% below 3.9 mmol/L with both systems (p=0.27). Six participants (25%) experienced at least one hypoglycemia event with the fully closed-loop system during the day compared to ten participants (42%) with the hybrid system (p=0.34). Out of the 11 participants who exercised, two participants experienced hypoglycemia during exercise with both systems. Exploratory analysis for the exercise period is presented in Supplementary Table 2. Postprandial glucose levels are shown in Figure 2, indicating higher transient glucose levels in the first two hours postprandially with the fully closed-loop system, which explains the higher time spent in mild hyperglycemia between 10.0 and 13.9 mmol/L during the day compared to the hybrid system. Supplementary Figure 1 shows the 24-hour glucose profiles for both systems.

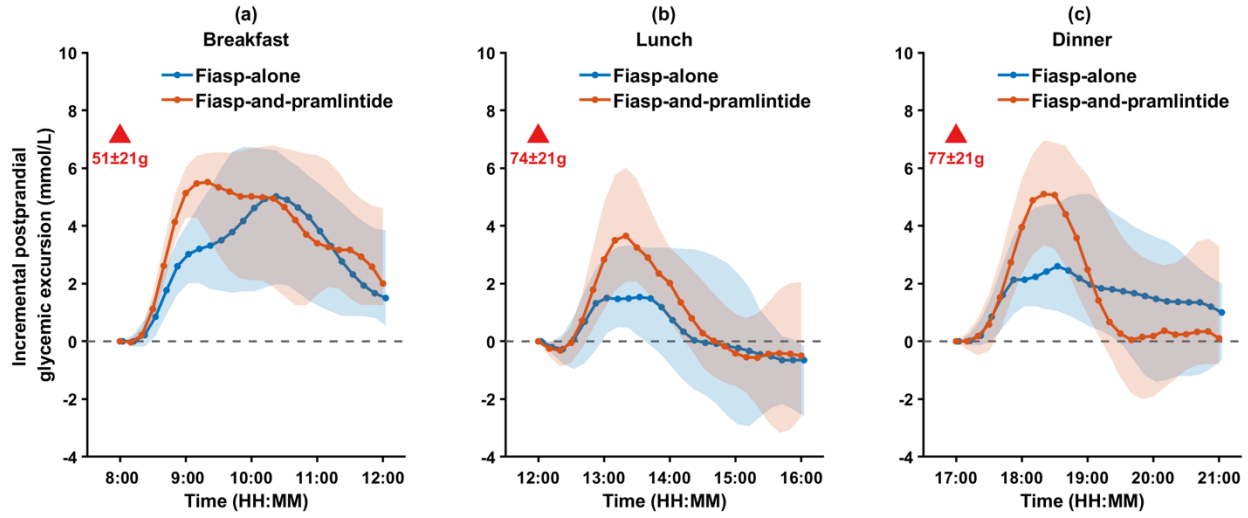

Figure 4.1: Incremental postprandial glucose profiles (median [IQR]) after breakfast (a), lunch (b), and dinner (c) during the closed-loop interventions. Shaded IQR areas indicate the upper and lower 25% of participants (n=24).

During the night (24h00–08h00), the fully closed-loop system had median 91% time in range compared to 86% with the hybrid system (p=0.26; Table 3). Participants spent median 4.2% time above 10.0 mmol/L with the fully closed-loop system compared to 8.4% with the hybrid system (p=0.5), and median 0% below 3.9 mmol/L with both systems (p=0.14). Six participants (25%)

experienced at least on hypoglycemia episode at night with the hybrid system compared to two (8%) with the fully closed-loop system (p=0.13).

The total daily basal insulin during the fully closed-loop intervention was 31u [20–40u] and during the hybrid closed-loop intervention was 31u [23–44u] (p=0.42; Table 2). The fully closed-loop system delivered 19u [13–24u] of bolus compared to 28u [19–33u] of bolus with the hybrid system (p=0.010; Table 2). Total pramlintide delivery during the fully closed-loop intervention was 518μg [408–601μg] (6.6μg/kg). In fully closed-loop intervention, the first insulin and pramlintide bolus after breakfast was administered 40 minutes [40–50 minutes] post-meal, after lunch was 50 minutes [48–60 minutes] post-meal, and after dinner was 40 minutes [20–60 minutes] post-meal. The average number of boluses administered with the fully closed-loop system was 10 [7.5–13] per day with an average bolus amount of 2.1U (1.0U).

During the fully closed-loop intervention, seven participants (29%) experienced gastrointestinal side effects compared to two participants (8%) during the hybrid closed-loop intervention (Table 4). During the fully closed-loop intervention, three participants (13%) experienced non-mild nausea and one participant (4%) experienced non-mild bloating. During the hybrid closed-loop intervention, no participants experienced non-mild gastrointestinal side effects. There were no elevated ketones (>1.0 mmol/L) in either of the closed-loop visits and no serious adverse events throughout the study. Treatment related adverse events that occurred during the study included site irritation at pramlintide infusion site experienced by one participant and vasovagal episode due to IV insertion experienced by one participant.

DISCUSSION

We developed a Fiasp-plus-pramlintide fully closed-loop system that does not require meal announcement. The fully closed-loop system resulted in comparable yet not non-inferior time in range to a Fiasp-alone closed-loop system with full carbohydrate counting. Non-inferiority was likely not met due to large variability within the small sample size. Just under half of the participants had a higher time in target range with the fully closed-loop system and more than half the participants had a difference of less than 6% between interventions. The most common adverse event with the Fiasp-plus-pramlintide closed-loop system was mild nausea. There were no serious adverse events or safety concerns with either closed-loop systems.

Early closed-loop systems attempted to alleviate the burden of carbohydrate counting by relying solely on glucose sensor readings to cover meal-related insulin needs, while omitting mealtime insulin boluses. Due to delays in insulin absorption[24] compared to meal glucose absorption, this approach resulted in prolonged postprandial hyperglycemia[25,26]. Consequently, all current closed-loop systems that outperformed conventional pump therapy require users to input either meal carbohydrate content[27] or meal size[28,29]. Simple meal announcement strategies are less burdensome than full carbohydrate counting but still requires an intervention on the part of the user. Here, we proposed a novel approach to a fully closed-loop system by using pramlintide to delay meal glucose absorption in order to match the delays in insulin absorption. Our study is the first attempt to test and quantify the performance of this novel fully closed-loop system.

The participants in our study had suboptimal glycemic control (HbA1c 8.1±1.3%), which may be a result of frequent bolus omissions[30], imprecise carbohydrate counting[11,31], or inaccurate insulin-to-carbohydrate ratios. Although the fully closed-loop system resulted in a transient increase in hyperglycemia within the first two hours post-meal during the day, an overall high time

in target range was still achieved within a population with suboptimal glycemic control. Additionally, there were fewer hypoglycemia events with the fully closed-loop system compared to the hybrid system. This may be attributable to less total insulin delivered with the fully closed-loop system compared to the hybrid system due to the addition of pramlintide, which acts to suppress gastric emptying and inhibits nutrient-stimulating glucagon secretion[32].

In this study, we used a higher pramlintide to insulin ratio than in our previous insulin-plus-pramlintide hybrid closed-loop study[18]. The most common adverse event in the pramlintide-treated arm was nausea and majority of the nausea events were mild in intensity. Studies have shown that nausea is a transient side effect of pramlintide therapy that tends to dissipate within days to weeks of pramlintide regimen[33]. Participants were exposed to pramlintide for an average of 6 days prior to the intervention, which may have increased individual tolerance to pramlintide but might have not been enough time for the side effects to dissipate prior to the intervention. Chronic pramlintide administration may also result in weight loss due to its effects on appetite suppression. A longer outpatient study with the fully closed-loop system needs to be conducted to determine if gastrointestinal side effects seen during the interventions will be transient and if weight loss is observed. Studies with different pramlintide to insulin ratios may also be warranted.

Pramlintide was administered at a fixed ratio to insulin to mimic a co-formulation and healthy pancreatic physiology[32]. Insulin and pramlintide cannot be mixed in a single-chamber pump because they are stable at different pH levels[34]; thus, a co-formulation or a dual-chamber pump is needed for the system to become commercially available. Several co-formulations of insulin and pramlintide are under development[34-37] and would eliminate the need for two separate infusion sites and allow for the use of conventional insulin pumps to deliver both hormones.

Our study has several limitations. First, the system required the manual control of pumps to change basal rates and administer boluses. A wireless system that automatically adjusts basal and boluses in two pumps needs to be developed before using this system in an outpatient setting. Second, we did not assess treatment satisfaction to determine how the fully automated system may affect quality of life of participants. It is important to assess whether the burden of administering an additional hormone is outweighed by the benefits of alleviating carbohydrate counting. Third, the generalizability of the study findings is limited by the inpatient study design. Participants selected prepackaged meals that were scheduled at pre-designed times of day without snacks in between. In addition, the carbohydrate content of meals was calculated by a research staff and not the participants. In real-world settings, people with type 1 diabetes tend to omit insulin boluses and underestimate the carbohydrate content of meals by around 20%[11]. As a result, an outpatient study needs to be conducted comparing the fully closed-loop system with an Fiasp-alone hybrid closed-loop or sensor augmented pump therapy with little or no interference from the research staff.

Our study is the first to propose a fully closed-loop Fiasp-plus-pramlintide system. The objective of the study was to alleviate the demands of intensive diabetes management without compromising glycemic control. The Fiasp-plus-pramlintide system achieved comparable glycemic control to the Fiasp-alone hybrid closed-loop system, though non-inferiority was not confirmed. There were no serious adverse effects reported with the fully closed-loop system. Studies with the Fiasp-plus-pramlintide fully closed-loop system in free-living outpatient settings are warranted.

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CONTRIBUTION

AH and MT supervised the study. DM, AH, LL, JFY, and MT designed the study. DM, JFY, MT, NG, AH, JR, and LL conducted the study. JR and AEF carried out the data analysis including the statistical analyses. AH and AEF designed the dosing algorithm. AH had full access to the data and takes responsibility for the integrity of the data analysis. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

AH received research support/consulting fees from Eli Lilly, Medtronic, AgaMatrix, and Dexcom, and has pending patents in the artificial pancreas area. MAT received research support from AgaMatrix, and speaker honoraria from Eli Lilly, Novo Nordisk, Boeringher-Ingelheim, Janssen, and AstraZeneca. JFY received research support from Sanofi, Bayer, Novo Nordisk, and consulting fees and speaker honoraria from Sanofi, Eli Lilly, Novo Nordisk, Boehringer-Ingelheim, Janssen, Takeda, Abbott, Merck, and Astra Zeneca. LL has pending patents in the field of artificial pancreas, received consulting fees from Dexcom, and has received support for clinical trials from Merck, Astra-Zeneca and Sanofi. No other competing financial interests at the time of writing the manuscript were reported

DATA AVAILABILITY

The raw data (i.e. insulin delivery, glucose levels) could be shared by the corresponding author upon reasonable request for academic purposes, subject to Material Transfer Agreement and

approval of McGill University Health Center's Research Ethics Board. All data shared will be de-identified.

CODE AVAILABILITY

The code used for analysis is available from the corresponding author upon reasonable request. The mathematical dosing algorithm has been explained in detail in previous literature[21,22]. The source code cannot be shared due to proprietary reasons.

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	Mean (SD) or n (%)	Range
Age, years	35 (14)	19–62
HbA1c, %	8.1 (1.3)	6.3–11.8
HbA1c, mmol/mol	65 (15)	45–105
Sex		
Male	12 (50%)	-
Female	12 (50%)	-
Duration of diabetes, years	19 (14)	2–53
Total daily insulin dose, U/kg	0.68 (0.23)	0.35 –1.1
BMI, kg/m²	28 (6.1)	18–43

Table 4.1: Baseline characteristics (n=24)

	Fiasp-alone closed-loop system (n=24)	Fiasp-plus-pramlintide closed-loop system (n=24)	Paired comparisons[†], P-value
24H OUTCOMES (22:00-22:00)			
Time spent at glucose levels (%):			
3.9–10.0 mmol/L[¶]	78 [66–88]	74 [62–83]	2.6 (-2.4 to 12), 0.36 non-inferiority p=0.28[*]
3.9–7.8 mmol/L	53 (20)	45 (16)	7.8 (-1.7 to 17), 0.10
< 2.8 mmol/L	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 (0.0 to 0.0), 0.38
< 3.3 mmol/L	0.0 [0.0–1.4]	0.0 [0.0–0.69]	0.0 (0.0 to 0.69), 0.32
< 3.9 mmol/L	1.8 [0.0–6.3]	0.0 [0.0–2.3]	1.1 (0.0 to 2.8), 0.058
> 7.8 mmol/L	44 (23)	54 (17)	-9.4 (-19 to 0.54), 0.063
> 10.0 mmol/L	20 [5.2–33]	24 [15–36]	-4.9 (-14 to 0.69), 0.093
> 13.9 mmol/L	0.35 [0.0–9.55]	2.4 [0.0–9.2]	-1.2 (-5.9 to 2.5), 0.56
> 16.7 mmol/L	0.0 [0.0–0.0]	0.17 [0.0–0.17]	0.0 (-1.0 to 1.0), 0.92
Mean glucose (mmol/L)	7.9 [6.6–9.0]	8.2 [7.5–9.1]	-0.70 (-1.4 to 0.07), 0.06
SD of glucose (mmol/L)	2.5 (0.9)	2.7 (0.8)	-0.18 (-0.66 to 0.30), 0.44
CV of glucose (%)	31 (7.8)	31 (5.4)	-0.12 (-4.1 to 3.8), 0.95
Total Basal Insulin (U)	31 [23–44]	31 [20–40]	1.8 (-2.2 to 6.4), 0.42
Total Bolus Insulin (U)	28 [19–33]	19 [13–24]	6.9 (1.9 to 12), 0.010
Total Pramlintide (µg)	-	518 [408–601]	-

[¶]Primary outcome. [*]6% non-inferiority margin Data are mean (±SD) or median [IQR], unless otherwise specified. P-value of less than 0.05 is regarded as significant. [†]Median paired difference between the Fiasp-alone and the Fiasp-plus-pramlintide system (95% CI); SD= standard deviation; CV = coefficient of variance.

Table 4.2: 24-hour outcomes of (i) Fiasp-alone closed-loop system and (ii) Fiasp-plus-pramlintide closed-loop system

	Fiasp-alone closed-loop system (n=24)	Fiasp-plus-pramlintide closed-loop system (n=24)	Paired comparisons†, P-value
Day outcomes (08:00-22:00)			
Time spent at glucose levels (%):			
3.9–10.0 mmol/L	79 [58–84]	66 [46–75]	10 (2.4 to 20), 0.016
3.9–7.8 mmol/L	47 (22)	32 (19)	15 (5.1 to 26), 0.0051
< 2.8 mmol/L	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 (0.0 to 0.0), 0.75
< 3.3 mmol/L	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 (0.0 to 0.0), 0.25
< 3.9 mmol/L	0.0 [0.0–2.4]	0.0 [0.0–1.5]	0.0 (0.0 to 1.8), 0.27
> 7.8 mmol/L	51 (24)	68 (19)	-16 (-27 to -5.8), 0.0040
> 10.0 mmol/L	21 [6.3–41]	33 [18–54]	-12 (-23 to -4.2), 0.0093
> 13.9 mmol/L	0.0 [0.0–13]	4.2 [0.0–15]	-3.0 (-14 to 4.2), 0.30
> 16.7 mmol/L	0.0 [0.0–0.0]	0.0 [0.0–0.30]	0.0 (-2.4 to 0.0), 0.72
Mean glucose (mmol/L)	8.4 [6.9–9.8]	8.9 [8.5–10]	-1.2 (-1.9 to -0.29), 0.018
SD of glucose (mmol/L)	2.3 [1.8–3.1]	2.8 [2.1–3.1]	-0.14 (-0.63 to 0.29), 0.46
CV of glucose (%)	30 (9.3)	28 (6.9)	2.3 (-2.3 to 6.9), 0.31
Total Basal Insulin (U)	22 (11)	20 (11)	1.8 (-2.3 to 6.0), 0.38
Total Bolus Insulin (U)	24 [17–29]	15 [11–19]	6.7 (3.6 to 11), 0.0011
Total Pramlintide (µg)	-	345 [274–435]	-
Night outcomes (24:00-08:00)			
Time spent at glucose levels (%):			
3.9–10.0 mmol/L	86 [73–96]	91 [83–98]	-3.1 (-11 to 3.1), 0.26
3.9–7.8 mmol/L	66 (21)	67 (25)	-2.3 (-15 to 11), 0.72
< 2.8 mmol/L	0.0 [0.0–0.0]	0.0 [0.0-0.0]	0.0 (0.0 to 0.0), 1.0
< 3.3 mmol/L	0.0 [0.0–0.84]	0.0 [0.0–0.0]	0.0 (0.0 to 1.0), 0.56
< 3.9 mmol/L	0.0 [0.0–4.2]	0.0 [0.0–0.0]	1.6 (0.0 to 3.1), 0.14
> 7.8 mmol/L	32 (24)	32 (25)	0.22 (-13 to 14), 0.97
> 10.0 mmol/L	8.4 [0.0–23]	4.2 [0.0–17]	1.0 (-5.2 to 10), 0.50
> 13.9 mmol/L	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 (0.0 to 0.0), 0.31
> 16.7 mmol/L	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 (0.0 to 0.0), 1.0
Mean glucose (mmol/L)	7.1 [6.3–8.0]	7.0 [6.0–8.1]	-0.19 (-0.73 to 0.52), 0.64
SD of glucose (mmol/L)	1.7 [1.2–2.0]	1.6 [1.2–1.9]	0.12 (-0.16 to 0.43), 0.47
CV of glucose (%)	25 (8.4)	23 (7.3)	1.8 (-2.0 to 5.6), 0.33
Total Basal Insulin (U)	9.1 [8.2–14]	8.3 [7.4–12]	0.95 (-0.42 to 2.5), 0.13
Total Bolus Insulin (U)	0.0 [0.0-0.0]	0.17 [0.0–3.4]	-1.7 (-3.0 to -0.17), 0.00049
Total Pramlintide (µg)	-	108 [83–140]	-

Data are mean (±SD) or median [IQR], unless otherwise specified. P-value of less than 0.05 is regarded as significant. †Median paired difference between the Fiasp-alone and the Fiasp-plus-pramlintide system (95% CI); SD= standard deviation; CV = coefficient of variance.

Table 4.3: 24- Comparisons of (i) Fiasp-alone closed-loop system and (ii) Fiasp-plus-pramlintide closed-loop system during the daytime (08h00-22h00) and overnight (22h00-08h00) study period

	Fiasp-alone closed-loop(n=24)			Fiasp-plus-pramlintide closed-loop(n=24)			P-value
Number of participants with:							
At least one hypoglycemia event	14 (58%)			8 (33%)			0.15
At least one nocturnal hypoglycemia event	6 (25%)			2 (8%)			0.13
At least one daytime hypoglycemia event	10 (42%)			6 (25%)			0.34
Number of hypoglycemia events requiring treatment*							-
During a 24-hour period (22:00-22:00)	21			11			
Overnight (24:00-08:00)	7			3			-
During the day (08:00-22:00)	14			8			-
Exercise induced hypoglycemia events	2			2			-
Number of participants experiencing any gastrointestinal symptom	2 (8%)			7 (29%)			-
Number of participants who experienced non-mild gastrointestinal events:	**Moderate**	**Moderate to Severe**	**Severe**	**Moderate**	**Moderate to Severe**	**Severe**	
Nausea	0 (0%)	0 (0%)	0 (0%)	3 (13%)†	1 (4%)†	13(13%)†	
Bloating	0 (0%)	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	
Heartburn	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

Data are number (%) or numbers. *Hypoglycemia events are defined as a glucose concentration below 3.3 mmol/L and treated with 16g oral carbohydrate. †The same participant experienced moderate, moderate-to-severe, and severe nausea during the intervention.

Table 4.4: Hypoglycemia events and gastrointestinal side effects during closed-loop interventions

Chapter 5: Discussion

Current artificial pancreas systems that improve glucose control still require users to input either meal carbohydrate content or meal size. We aimed to develop a novel fully automated closed loop system that does not require meal announcement through the use of multiple hormones. An insulin-pramlintide-glucagon system was first optimized through a series of experiments on nine adult participants with type 1 diabetes. Insulin lowers blood glucose levels, pramlintide suppresses glucagon secretion and slows down gastric emptying, and glucagon increases blood glucose levels to protect against hypoglycemia.

Based on the data of each participant, the dosing algorithm was iteratively enhanced until convergence. First, the aggressiveness of insulin and pramlintide were increased and subsequently reduced. Second, the glucose threshold that triggers glucagon boluses was lowered. Third, a meal-detection algorithm was added and consequently glucagon was removed. A final fully automated Fiasp-plus-pramlintide artificial pancreas was developed and tested on 24 adult participants through two 27-hour interventions.

Results from the randomized, controlled, crossover trial showed that the insulin-alone hybrid closed-loop control system marginally outperformed the insulin-plus-pramlintide closed-loop system during the day but achieved overall comparable time in range (78% vs. 74%; p=0.36 and non-inferiority p=0.28).

5.1 Research in Context

Our lab has previously assessed the benefits of amylin with insulin in an artificial pancreas through a randomized crossover trial comparing [12]:

I. Rapid insulin-alone artificial pancreas

II. Rapid insulin-and-pramlintide artificial pancreas

III. Regular insulin-and-pramlintide artificial pancreas

The study included three 24-hour inpatient visits with the three different systems. The primary outcome was time in target range (3.9-10.0 mmol/L). Pramlintide was administered at a fixed ratio of 6µg/u. Participants spent 74% time in range during the rapid insulin-alone intervention (n=28), 84% during the rapid insulin-and-pramlintide intervention (n=27), and 69% during the regular insulin-and-pramlintide intervention (n=26) (Figure 5.1) [12]. The increased time in range with the rapid insulin-and-pramlintide system was due to an improvement in daytime control, with an increased time in range from 63% to 78% (p=0.0004). There were comparable hypoglycemic events between the rapid insulin alone arm (11) and rapid insulin-and-pramlintide arm (12), but higher hypoglycemic events with the regular insulin-and-pramlintide arm (18).

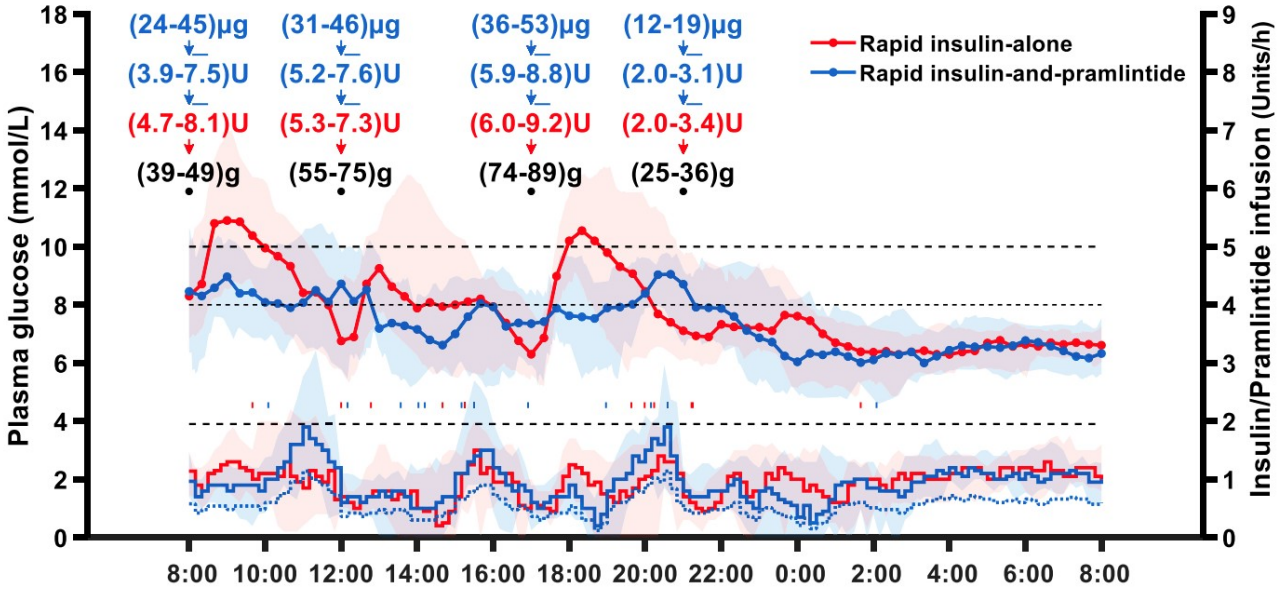

Figure 5.1: Median (IQR) glycemic profiles and hormonal deliveries during the artificial pancreas visits. Meal and hormonal boluses (IQR). Solid lines indicate glucose levels and basal insulin. Dotted lines indicate basal pramlintide [12]

The results from this study highlight the potential benefits of pramlintide in an artificial pancreas system, however, this system was not fully automated. The dual-hormone system still required users to announce meals. In the fully automated system developed and outlined in this thesis, boluses were administered independent of meal size and without any user input. Insulin and pramlintide boluses were administered based on a model-based meal-detection algorithm that used predictive glycemic trends.

The meal-detection portion of the dosing algorithm used in the fully automated system outlined in the thesis was first developed by Dr. Anas El Fathi, a former PhD student in the lab. The meal detection algorithm was first tested on 11 adolescents through a randomized crossover trial comparing glycemic levels after an unannounced meal [77]:

I. Conventional pump therapy
II. Artificial pancreas therapy
III. Artificial pancreas therapy with a meal-detection algorithm

During the arm with the meal-detection algorithm, a meal was detected around 40 minutes after meal consumption and an insulin bolus was subsequently triggered. The meal detection and artificial pancreas system decreased postprandial incremental area under the curve from 24.1±9.5 h.mmol/L in conventional pump therapy to 15.4±8.0 h.mmol/L ($p=0.03$) (Figure 5.2). Time spent above 10 mmol/L did not differ between conventional pump and artificial pancreas alone ($p=0.52$), but it was higher for conventional therapy (79.6±27.5%, $p=0.02$) and artificial pancreas alone (74.2±20.6%, $p=0.047$) compared to the artificial pancreas and meal detection (58.0±26.6%).

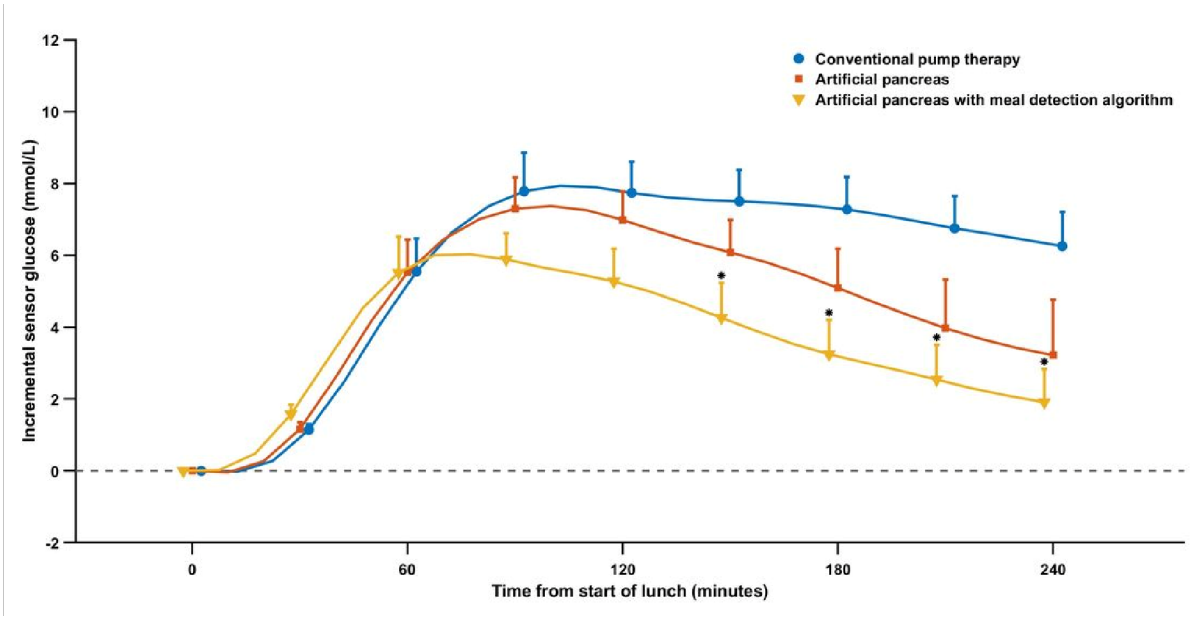

Figure 5.2: Mean (SD) glucose levels from start of lunch without a bolus to 4-hours post-lunch between the three interventions (n=11)

Based on preliminary results from the first insulin-and-pramlintide artificial pancreas study and the meal-detection missed bolus study, we hypothesized that a novel dosing algorithm with a meal detection and pramlintide administered in a basal-bolus manner with insulin may alleviate the burden of carbohydrate counting and be fully reactive without meal announcement.

5.2 Alternative Methods

Alternative methods to alleviate the burden of carbohydrate counting with the artificial pancreas are being explored in our lab. One method is replacing carbohydrate counting with qualitative meal categorization based on size of the meal. Another method is replacing carbohydrate counting with simply pressing a button in the algorithm to indicate consumption of a meal, known as simple meal announcement. Although these systems are not fully automated, they still reduce a major burden of people with type 1 diabetes.

5.2.1 Insulin and Amylin

A randomized crossover pilot study comparing Fiasp-alone hybrid closed-loop with full carbohydrate counting and Fiasp-plus-pramlintide closed-loop with a simple meal announcement system on 4 adults and 3 adolescents was recently conducted [8]. There was a 3-day run-in for both arms followed by a 24-hour inpatient intervention. Pramlintide was administered at a fixed ratio of 10µg/u of insulin. Participants self-selected their meals, with no restrictions on size and time of meal. The average time in target range (3.9-10 mmol/L) was 85.7% in the Fiasp-alone arm and 87.3% in the Fiasp-plus-pramlintide arm (p=0.21) (Figure 5.3). Participants on the Fiasp-plus-pramlintide system spent less time <3.9 mmol/L (2.1% vs. 4.1%, p=0.02) and comparable time >10 mmol/L (10.1% vs. 11.4%, p=0.38) to the Fiasp-alone system. There were no serious adverse events reported during the pilot study.

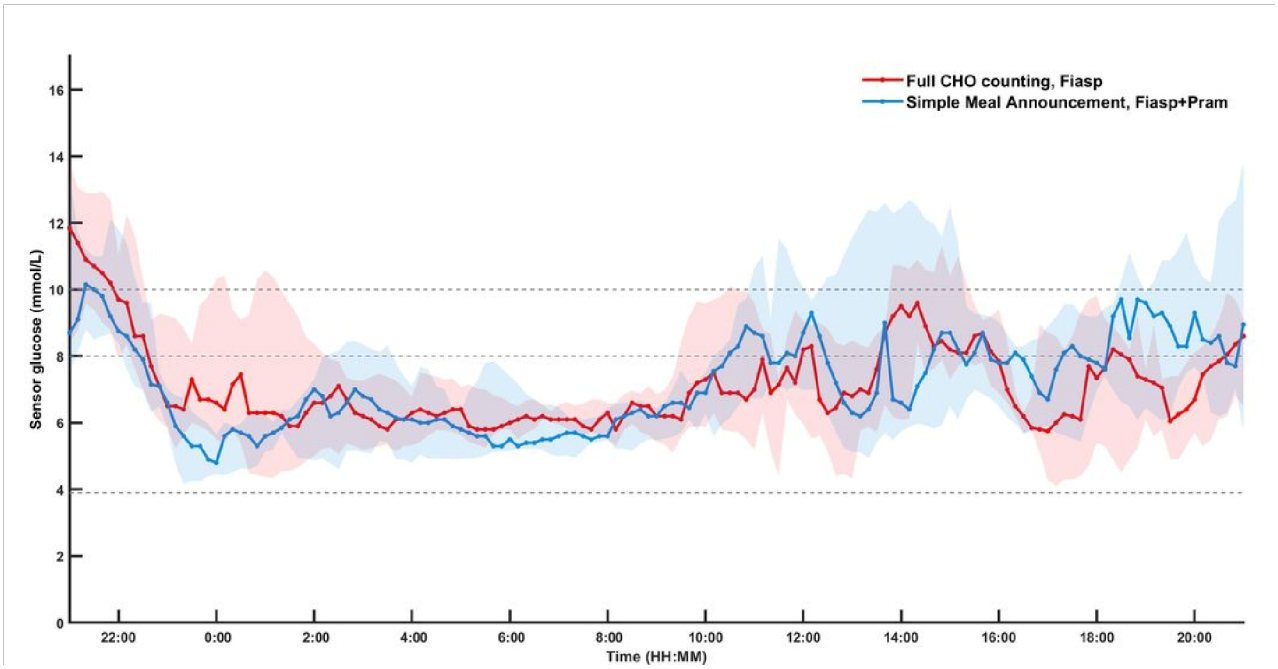

Figure 5.3: Mean (SD) glucose levels for Fiasp-alone closed-loop arm (red line) and the Fiasp-plus-pramlintide with simple meal announcement arm (blue line). N=7, HH=hour, MM=minute [8]

Based on the promising results from the pilot study, we decided to conduct an outpatient trial to assess whether a fiasp-plus-pramlintide closed-loop system with simple-meal announcement improves quality of life. A three-way, randomized, blinded, crossover trial is underway comparing:

I. Fiasp-plus-pramlintide closed-loop delivery with simple meal announcement
II. Fiasp-plus-placebo closed-loop delivery with conventional carbohydrate counting
III. Fiasp-plus-placebo closed-loop delivery with simple meal announcement

The McGill Artificial Pancreas (MAP) system is a phone-based system that runs the dosing algorithm on a smartphone (Figure 5.4). The phone (Nexus 5® Smartphone) receives continuous glucose data from the sensor (Dexcom®) and automatically communicates changes to the pumps (Tandem t:slim®) via Bluetooth.

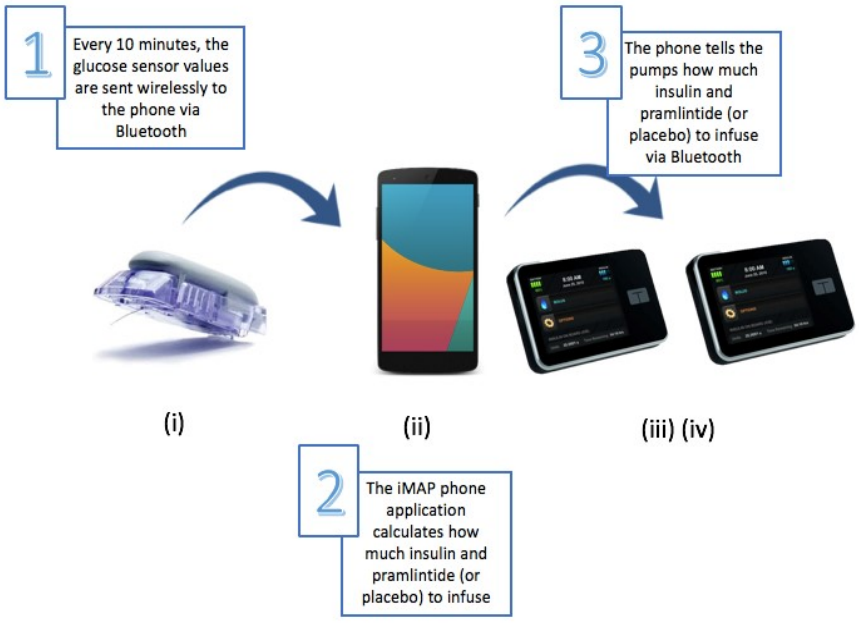

Figure 5.4: McGill Artificial Pancreas (MAP) System

A total of 15 adults and 15 adolescents with type 1 diabetes will be enrolled in the study. The trial design consists of an admission visit and training visit, where a questionnaire and an interview are conducted, followed by one-week on closed-loop. The participants then undergo the three interventions in random order. The interventions last a duration of 2-weeks each, with a questionnaire and interview conducted at the end of each intervention. Finally, at the end of the study, participants complete a final interview to assess what impact the system may have on quality of life. The questionnaires used in this study are: Type 1 Diabetes Distress Scale, Pictorial Representation of Illness and Self Measure, Hypoglycemia Fear Survey- II, INSPIRE questionnaire, Treatment Satisfaction Questionnaire, and Diabetes Bowel Symptoms Questionnaire.

Table 5.1 shows preliminary results from 4 adult participants who have completed the study. The time in target range (3.9-10 mmol/L) was 70% for the Fiasp-plus-placebo with full carbohydrate counting, 60% for the Fiasp-plus-placebo with simple meal announcement, and 70% for the Fiasp-plus-pramlintide with simple meal announcement. There was comparable time spent below 3.9 ($p=0.2$) and above 10 mmol/L ($p=0.8$) between the Fiasp-plus-placebo with full carbohydrate counting and the Fiasp-plus-pramlintide with simple meal announcement. Fiasp-plus-placebo with simple meal announcement reduced time spent <3.9 mmol/L but increased time spent >10 mmol/L compared to the other two interventions.

Outcome	Fiasp-plus-placebo with full carbohydrate counting (1)	Fiasp-plus-placebo with simple meal announcement (2)	Fiasp-plus-pramlintide with simple meal announcement (3)	P-values		
				(1) vs. (2)	(1) vs. (3)	(2) vs. (3)
Time spent at plasma glucose levels (%)						
3.9-10.0 mmol/L	70 ± 11	60 ± 13	70 ± 13	0.02	0.9	0.1
<3.9 mmol/L	1.2 ± 1.1	0.56 ± 0.37	1.8 ± 1.6	0.2	0.2	0.1
<3.3 mmol/L	0.34 ± 0.39	0.19 ± 0.22	0.67 ± 0.77	0.4	0.3	0.2
>10 mmol/L	28 ± 10	39 ± 12	28 ± 12	0.02	1.0	0.1
Mean glucose, mmol/L	8.68	9.77	8.76	0.07	0.8	0.1

Table 5.1: Comparison of Fiasp-plus-placebo with full carbohydrate counting, Fiasp-plus-placebo with simple meal announcement, and Fiasp-plus-pramlintide with simple meal announcement

5.2.2 Insulin and Sodium-Glucose Co-Transporter-2 (SGLT2) inhibitors

Alternatively, our lab has also been exploring the potential benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) with the artificial pancreas. Sodium-glucose co-transporter 2 inhibitors are a class of anti-diabetic agents that inhibit the glucose reabsorption in the kidney, causing an insulin-independent reduction of plasma glucose levels [78]. Sodium-glucose cotransporter 2 inhibitors have been shown to decrease blood pressure, reduce triglycerides, help with cardiovascular disease, and preserve renal function [78]. The benefits of empagliflozin, a sodium-glucose co-transporter 2 inhibitor, in combination with the artificial pancreas system was assessed through a randomized crossover trial.

30 Adults underwent a three-way crossover trial for 5-days at home with the artificial pancreas, on and off empagliflozin [79]. Three different prandial strategies were tested: no meal

announcement, simple meal announcement, and full carbohydrate counting. Mean glucose for the fully automated system with empagliflozin and the simple meal announcement with empagliflozin were compared to the carbohydrate counting control arm without empagliflozin.

The fully automated artificial pancreas with empagliflozin was inferior to the artificial pancreas with carbohydrate counting without empagliflozin (mean glucose 10.0 mmol/L vs 8.5 mmol/L; p=<0.001). However, the simple meal announcement with empagliflozin was non-inferior to the control artificial pancreas (8.5 mmol/L vs 8.5 mmol/L; p=0.003, non-inferiority p-value set at 0.75 mmol/L) (Figure 5.5). Empagliflozin with the artificial pancreas with carbohydrate counting resulted in lower mean glucose and higher time in range by 14% compared to the control. A sodium-glucose co-transporter 2 inhibitor and the artificial pancreas may be a suitable therapy to alleviate the need for carbohydrate counting, but it does not allow for a fully closed-loop system.

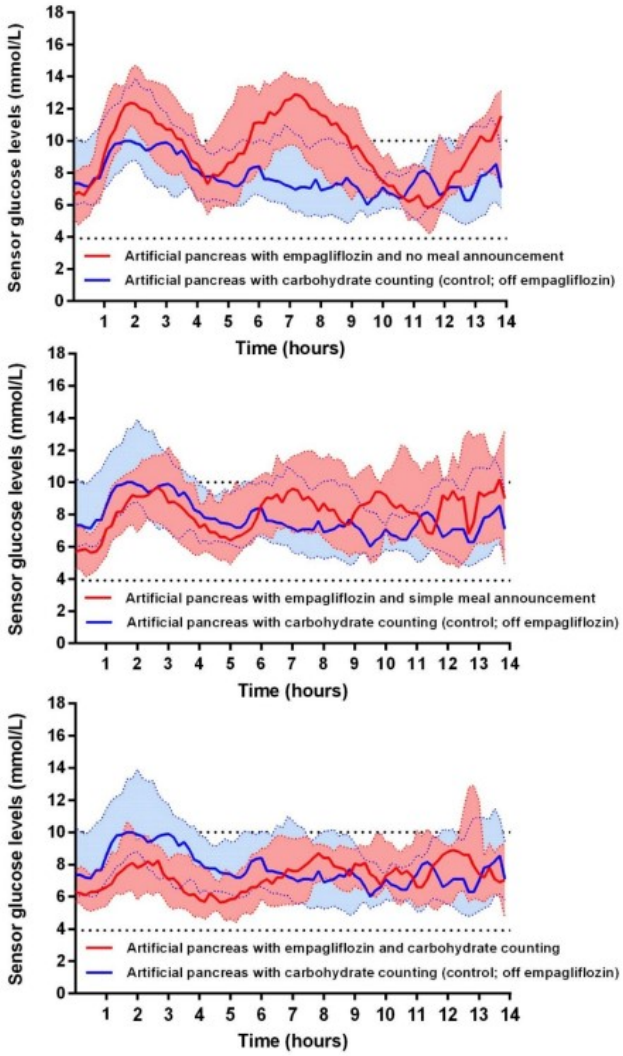

Figure 5.5: Median (IQR) profiles of glucose levels during the artificial pancreas visits, n=30

5.2.3 Insulin and Glucagon-Like Peptide-1 (GLP1)

Another future area of research is exploring glucagon-like peptide-1 (GLP1) in the context of the artificial pancreas. Glucagon-like peptide-1 agonists are an approved adjunctive therapy for the treatment of type 2 diabetes and share similar underlying pharmacological actions to amylin including delay gastric emptying, inhibit glucagon secretion, and increase satiety. In fact, some studies have shown that glucagon-like peptide-1 agonists inhibit glucagon and attenuate postprandial hyperglycemia better than pramlintide [80]. Thus, it is important to assess whether

an artificial pancreas with a glucagon-like peptide-1 agonist can alleviate the burden of carbohydrate counting and outperform the insulin-plus-pramlintide artificial pancreas system.

5.3 Future Work

The next step is to assess how the novel fully closed loop insulin-plus-pramlintide system outlined in this thesis will perform in an outpatient setting and what the implications on quality of life may be. In real-world settings, people with type 1 diabetes tend omit insulin boluses and underestimate the carbohydrate content of meals. Thus, it is important to perform a longer outpatient study to compare if the fully automated artificial pancreas can improve quality of life without degrading glycemic control compared to an insulin-alone artificial pancreas or sensor-augmented pump therapy with little to no interference from the research team.

In order for the system to be used in a real-world setting, the phone-based McGill Artificial Pancreas (MAP) system that automatically controls both insulin and pramlintide pumps with a smartphone must be used. The hope is that in a few years, an insulin and pramlintide co-formulation [81] or a dual-chambered pump will be developed before the system is commercialized in order to alleviate the burden of administering two hormones with multiple pumps and infusion sets. A long-term study with the fully automated system in an uncontrolled environment will provide insight into the efficacy and feasibility of the system.

Chapter 6: Conclusion.

We developed and tested a novel fully automated multi-hormone artificial pancreas that alleviates the burden of carbohydrate counting without degrading glycemic control. First, an insulin-pramlintide-glucagon artificial pancreas was iteratively enhanced until convergence to an

insulin-plus-pramlintide dual-hormone system on nine participants with type 1 diabetes through pilot experiments.

Second, the final version of the algorithm was tested on twenty-four participants through a randomized crossover non-inferiority trial. The fully automated system did not achieve non-inferiority compared to the Fiasp-alone artificial pancreas with full carbohydrate counting; however, the fully closed-loop system had comparable time in range (74% vs. 78%; non-inferiority p=0.28, superiority p=0.36), time spent below 3.9 mmol/L (0% vs. 1.8%; p=0.058), and time spent above 10.0 mmol/L (24% vs. 20%; p=0.093). The most common adverse event with the Fiasp-plus-pramlintide artificial pancreas was mild nausea. There were no serious adverse events or safety concerns with the fully automated dual-hormone artificial pancreas. The results of the study suggest that the fully automated system is safe and effective in alleviating a major burden for type 1 diabetes without significantly degrading glycemic control compared to first-generation insulin-alone hybrid closed-loop artificial pancreas.

A closed-loop system would be particularly beneficial for individuals with suboptimal control, especially those with elevated HbA1c as a result of frequent omission of mealtime boluses. A study showed that missing 4 meal boluses a week can result in a 1% increase in HbA1c [82]. An additional study showed that 65% of adolescents with type 1 diabetes on pump therapy miss one or more mealtime boluses a week [83]. Consequently, a fully automated system that alleviates the burden of carbohydrate counting and meal input may result in improved glycemic control and fewer long-term diabetes complications compared to conventional pump therapy. Future studies need to be conducted with the fully reactive system in outpatient settings to assess feasibility and impact on quality of life in a real-world setting.

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Appendix

Additional Material for Manuscript #2 (Chapter 4)

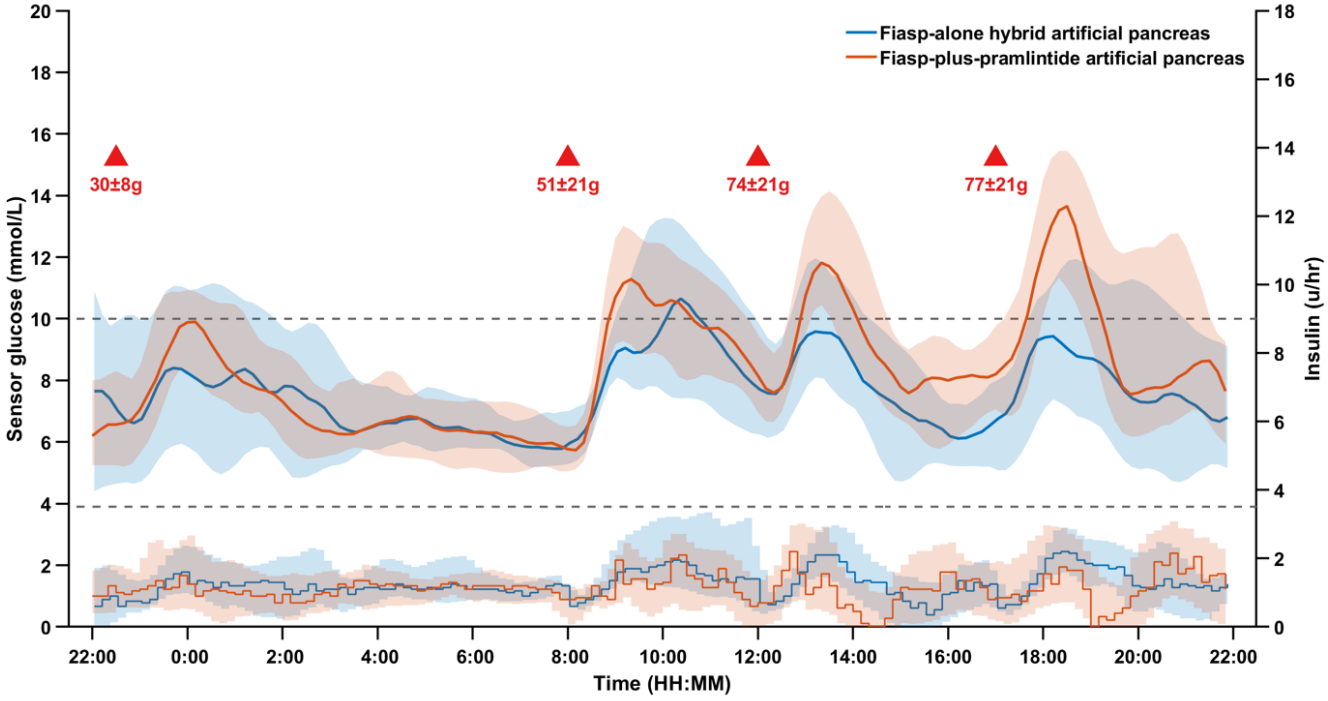
Inclusion Criteria	Exclusion Criteria
1. Males and females ≥ 18 years of age. 2. Clinical diagnosis of type 1 diabetes for at least 12 months. 3. The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not needed. 4. Insulin pump therapy for at least 6 months. 5. HbA1c ≤ 12% in the last 6 months. 6. Women of childbearing age must use a medically acceptable contraception method (condom, pills, intrauterine device, etc) one week prior to using pramlintide until last day of pramlintide.	1. Current or ≤ 1 month use of other antihyperglycemic agents (SGLT2, GLP-1, Metformin, Acarbose, etc.…). 2. Severe hypoglycemic episode within one month of admission. 3. Severe diabetic ketoacidosis episode within one month of admission. 4. Pregnancy. 5. Known or suspected allergy to the study drugs. 6. Gastroparesis. 7. Use of prokinetic drugs that stimulate gastric emptying (domperidone, cisapride, metoclopramide). 8. Clinically significant nephropathy, neuropathy or retinopathy as judged by the investigator. 9. Recent (< 6 months) acute macrovascular event e.g. acute coronary syndrome or cardiac surgery. 10. Current use of glucocorticoid medication. 11. Other serious medical illness likely to interfere with study participation or with the ability to complete the trial by the judgment of the investigator. 12. Failure to comply with team's recommendations (e.g. not willing to eat meals/snacks, not willing to change pump parameters, etc.).

Supplementary Table 1: Inclusion and exclusion criteria assessed at admission visit

	Fiasp-alone closed-loop (n=10)	Fiasp-plus-pramlintide closed-loop (n=10)	Paired comparisons*, P-value
24H OUTCOMES (22:00-22:00)			
Time spent at glucose levels (%):			
3.9–10.0 mmol/L	75 (29)	77 (38)	-3.1 (-29 to 22); 0.79
< 3.3 mmol/L	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 (0.0 to 7.1); 0.50
< 3.9 mmol/L	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 (0.0 to 7.1); 1.0
> 7.8 mmol/L	34 (37)	33 (38)	1.9 (-31 to 35); 0.90
> 10.0 mmol/L	0.0 [0.0–36]	0.0 [0.0–0.0]	0.0 (-71 to 86); 1.0
> 13.9 mmol/L	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 (-21 to 21); 1.0
Mean glucose (mmol/L)	7.4 (2.7)	7.3 (2.7)	0.19 (-2.1 to 2.4); 0.86
SD of glucose (mmol/L)	1.6 (0.96)	1.2 (0.47)	0.41 (-0.20 to 1.0); 0.16
CV of glucose (%)	21 (11)	18 (7.2)	3.4 (-4.5 to 11); 0.36
Total Basal Insulin (U)	0.50 [0.30–0.85]	0.58 [0.39–1.3]	-0.19 (-0.63 to 0.30); 0.47
Total Bolus Insulin (U)	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 (-1.5 to 0.0); 1.0
Total Pramlintide (µg)	-	5.8 [3.9–13]	-

Data are mean (±SD) or median [IQR], unless otherwise specified. P-value of less than 0.05 is regarded as significant. *Median paired difference between the Fiasp-alone and the Fiasp-plus-pramlintide system (95% CI); SD= standard deviation; CV = coefficient of variance.

Supplementary Table 2: Comparison between Fiasp-alone closed-loop system and Fiasp-plus-pramlintide closed-loop system during exercise period (from 15h00 to 16h00).



Supplementary Figure 1: The median [IQR] profiles of glucose levels and basal insulin deliveries during the Fiasp-alone closed-loop system (red) and Fiasp-plus-pramlintide closed-loop system (blue) interventions (n=24). The shaded IQR areas indicate upper and lower 25% of participants.