Pilot Outpatient Assessment of a Fully Closed-Loop Dual-Hormone (Insulin and Pramlintide) Artificial Pancreas System

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AMP: Adenosine monophosphate

HbA1c: Hemoglobin A1c or glycated hemoglobin

GADAs: Glutamic acid decarboxylase autoantibodies

ICAs: Islet cell autoantibodies

LADA: Late autoimmune diabetes in adults

HAAF: Hypoglycemia-associated autonomic failure

USA: United States of America

GLP: Glucagon-like peptide

SGLT2i: Sodium-glucose linked transporter 2 inhibitors

IQR: Interquartile range

SD: Standard deviation

Abstract

Type 1 diabetes is an autoimmune disease characterized by the destruction of pancreatic beta cells. The only current treatment is lifelong intensive insulin replacement therapy. Technological advances in the last few decades have allowed for increases in treatment satisfaction and efficacy in the spheres of both multiple daily injection therapy and continuous subcutaneous insulin infusion therapy. However, all current methods require carbohydrate counting, a widespread prandial bolus management technique, that is both tedious and error-prone and contributes to disease burden. Despite the advance, most pediatric and adult populations living with type 1 diabetes fail to reach glycemic targets, particularly of HbA1c < 7.0%. Closed-loop systems, also called artificial pancreas systems, have improved glycemic outcomes. However, they have not permitted optimal glycemic control and present a management burden, still requiring carbohydrate counting.

This thesis aimed to test a fully automated (meaning it requires no carbohydrate counting) dual-hormone artificial pancreas system in an outpatient setting using two different insulin types, insulin aspart and a faster insulin aspart (Fiasp), paired with pramlintide each at two different ratios: 8 µg pramlintide/U insulin and 10 µg pramlintide/U insulin. The outpatient pilot trial consisted of 12 participants (7 females, age 39.5 (15.1) years, HbA1c 7.34% (0.64)) with five, 14-hour interventions (1 control, 2 faster aspart, 2 insulin aspart). The primary outcome investigated was time spent in the target glucose range (3.9-10.0 mmol/L). In the control intervention, median time in range was 78.6 % [65.3-92.9], comparable to the faster aspart and pramlintide with 8 µg/U 76.19% ([64.6-86.9], p=0.31) and 10 µg/U 78.79% ([68.8-86.0], p=0.09) interventions, as well as the aspart and pramlintide intervention with 10 µg/U, 77.4% ([72.09-82.74], p=0.23). The time in range was lowest for the aspart and pramlintide

intervention with 8 g/U, 65.88% ([59.9-83.6], p=0.74). These results are a preliminary demonstration of the feasibility of a fully closed-loop dual-hormone artificial pancreas system. However, larger and longer studies are needed to demonstrate efficacy.

Résumé

Le diabète de type 1 est une maladie auto-immune caractérisée par la destruction des cellules bêta du pancréas. Le seul traitement pour le diabète de type 1 est l'insulinothérapie intensive à vie. Les progrès technologiques réalisés au cours des dernières décennies ont permis d'améliorer la satisfaction et l'efficacité du traitement, tant dans le domaine de la thérapie par injections quotidiennes multiples que dans celui de la thérapie par perfusion sous-cutanée continue d'insuline. En outre, le comptage des glucides, une technique répandue de gestion des bolus prandiaux, est un processus fastidieux et fait sujet aux erreurs, qui contribue au fardeau élevé de la maladie. Cependant, la plupart des enfants et des adultes atteints du diabète de type 1 ne réussissent pas à atteindre les objectifs glycémiques, en particulier une HbA1c < 7.0 %. Les systèmes en boucle fermée, également appelés pancréas artificiels, ont montré une amélioration des résultats glycémiques, mais ils n'ont pas permis un contrôle optimal de la glycémie et représentent un fardeau de gestion, nécessitant un comptage des glucides.

L'objectif de cette thèse était de tester un système de pancréas artificiel à double hormone entièrement automatisé dans un cadre ambulatoire en utilisant deux types d'insuline différents, l'insuline asparte et l'insuline asparte plus rapide, chacun à deux ratios différents: 8 µg/U et 10 µg/U. L'essai pilote ambulatoire comprenait 12 participants (7 femmes, âge 39,5 (15,1) ans, HbA1c 7,34% (0,64) avec 5 interventions de 14 heures (1 contrôle, 2 insuline a action rapide, 2 insuline aspart). Le principal résultat étudié était le temps passé dans l'intervalle glycémique cible (3,9-10,0 mmol/L). Dans l'intervention de contrôle, le temps médian passé dans l'intervalle était de 78,6% [65,3-92,9], comparable à l'aspart et au pramlintide plus rapides avec 8 µg/U 76,19% ([64,6-86,9], p=0,31) et 10 µg/U 78,79% ([68,8-86,0], p=0,31). 31) et 10 µg/U 78,79% ([68,8-86,0], p=0,09), ainsi que l'intervention aspart et pramlintide avec 10 µg/U, 77,4% ([72,09-

82,74], p=0,23). Le temps dans l'intervalle était le plus minime pour l'intervention aspart et pramlintide avec 8 g/U, 65,88% ([59,9-83,6], p=0,74).

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Contributions to the Thesis

My contributions to this thesis were the design and conduct of the trial, the submission to the REB and Health Canada, and the creation of all study documentation, including the protocol and informed consent form. I managed all participant coordination for the first eight participants and had help for the final four. I recruited participants, coordinated daily logistics including managing medication and coordinating staff, analyzed the data, wrote the manuscript, communicated with regulatory bodies, and closed the study.

Dr Michael A. Tsoukas, second author and principal investigator, contributed to the study's design, supervision, and conduct, admitting, and following participants for the duration of the study. Melissa-Rosina Pasqua also contributed to the supervision, and conduct, admitting, and following of participants. Elisa Cohen helped design and conduct the studies. Joanna Rutkowski helped with algorithm design, data generation and analysis, and technical setup. Dr Ahmad Haidar developed the novel algorithm, investigated, and oversaw the study's design and conduct, and helped with the revision of this thesis. The manuscript is to-be-submitted, and we are submitting it to be published in the journal of Diabetes Technology and Therapeutics.

Chapter 1: Introduction

1.1 Diabetes Mellitus

Diabetes Mellitus is a disease of metabolic processes which results in elevated blood glucose levels, termed hyperglycemia. The disease encompasses type 1 and type 2 diabetes as well as maturity-onset diabetes of the young, gestational diabetes, neonatal diabetes and diabetes due to secondary causes such as endocrinopathies and steroid use, among others.[1]

The International Diabetes Federation indicated that diabetes is a leading global health emergency as of 2021.[2] In Canada, diabetes is becoming increasingly prevalent, with an estimated prevalence of 9.4% of the population living with diagnosed diabetes, 22.5% of whom met the diagnostic criteria but were unaware of it, and 6.3% of the population with prediabetes.[3] Globally, diabetes mellitus has a high disease burden, with 1 in 11 adults having diabetes mellitus, 90% of whom have type 2 diabetes.[1] Worldwide, over nine million people are living with type 1 diabetes.[4]

The onset of diabetes varies by type. Type 1 diabetes generally presents earlier in life, with peaks of diagnosis from 4-6 and from 10-14 years old.[1] In contrast, type 2 diabetes presents later in life due to the considerable influence of lifestyle in developing the disease.[1]

1.2 Objective and Hypothesis

1.2.1 Objective

As discussed above, individuals living with type 1 diabetes require intensive insulin therapy. The management of type 1 diabetes requires careful prevention of hypoglycemia, mitigation of hyperglycemia, and burdensome carbohydrate counting for every meal. Innovations in the field, as discussed, have allowed management to be simplified. However, the management burden of the disease remains immense with the continued need for carbohydrate counting.

The McGill Diabetes Technology Lab has conducted numerous trials in attempts to alleviate carbohydrate counting, leveraging various strategies including simple meal announcement, and an inpatient fully closed-loop system.[5,6] The project in this thesis aimed to test the efficacy of a fully-closed loop insulin and pramlintide system in its ability to mitigate carbohydrate counting.

The interventions were as follows:

- Faster aspart alone in a hybrid closed-loop system with carbohydrate counting
- Faster aspart with pramlintide in a fully closed-loop system at an 8µg/U ratio
- Faster aspart with pramlintide in a fully closed-loop system at a 10µg/U ratio
- Insulin aspart with pramlintide in a fully closed-loop system at an 8µg/U ratio
- Insulin aspart with pramlintide in a fully closed-loop system at a 10µg/U ratio

The relevant literature including the current treatment modalities, their strengths and weaknesses, the different types of insulins available, and adjunctive treatments, as well as the design and conduct of the trial and the results of the trial, will be presented in this thesis.

1.2.2 Hypothesis

We hypothesized that the fully closed-loop insulin and pramlintide system will not degrade the time in the target glucose range compared to the insulin-alone hybrid closed-loop system.

1.3 Thesis Outline

The following thesis will contain a description of diabetes management principles including intensive insulin therapy, technological solutions for diabetes management and novel adjunctive therapies. Then, a manuscript outlining the work I have carried out investigating the use of a fully closed-loop insulin and pramlintide system will be detailed. Finally, a discussion of

the research in context, outlook for the field and a conclusion will be included followed by a list of references used to compile this thesis.

Chapter 2: Review

2.1 Physiology of Normal Glucose Control

The pancreatic islets of Langerhans comprise two central endocrine cells involved in glucose homeostasis: the insulin-producing beta cells and the glucagon-producing alpha cells.[1] The beta cells are responsible for insulin production, a peptide hormone with endocrine action that controls glucose re-uptake into the cell.[7] Under healthy conditions, with increased blood glucose, the pancreas senses the change in glucose concentration and, as a result, increases insulin release and decreases glucagon release.[7] Insulin mediates the entry of glucose into the cell via GLUT G-protein coupled receptors and an intracellular calcium signalling cascade into adipose and muscle cells which stimulates glycogen formation, and reduces gluconeogenesis to decrease glucose levels.[7] Glucose deposition as glycogen in the liver, and uptake in peripheral tissues, thus decreases blood glucose levels, which are balanced by glycogen release if they fall too much.[8] Glucagon acts on the liver to increase glycogen breakdown and increase gluconeogenesis.[7,9] Glucagon release is stimulated when a low blood glucose level is sensed by glucagon-producing alpha cells.[1] However, under conditions of prolonged hypoglycemia, growth hormone and cortisol are secreted, increasing fat metabolism and blood glucose levels.[8]

The concerted actions of insulin and glucagon, which can be seen in Figure 1, allow glucose levels to be kept within a tight range (3.9-6.1 mmol/L), which is required for health and for preventing complications.[9] Insulin has many additional actions on target organs which are affected by diabetes and contribute to the pathogenesis of the disease (Figure 2).[9]

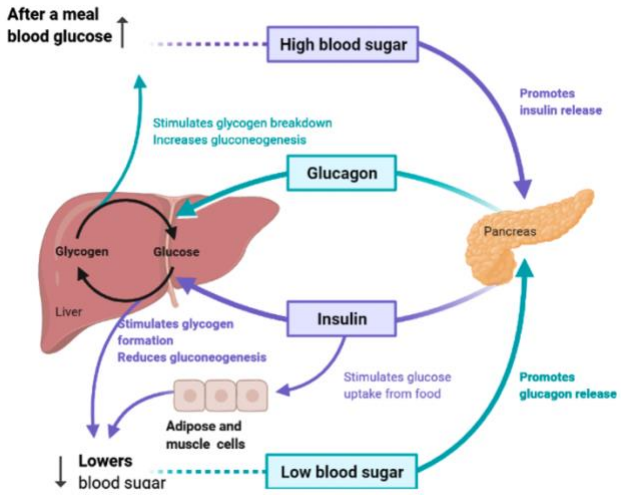

Figure 1: Glucose Regulation Under Healthy Conditions[9]

Target		Glucose Transporter	Hepatic Enzymes	B-Cells Apoptosis	PPAR	AMPK	Tyrosine Kinase Inhibitor	NF-κB
Normal effects		Enhance glucose uptake by tissues	Enhance glucose metabolism	Control program cell death	Control of lipid metabolism	Energy homeostasis	Control growth factor signaling	Control of β-cells survival
Changes by diabetes	↓	GLUT translocation Glucose uptake	Insulin signaling Liver glycogen	Apoptotic regulatory genes Caspases	Lipid metabolism	AMPK activation Glucose homeostasis	Insulin sensitivity Insulin secretion	
	↑	Insulin resistance	Insulin resistance Glucose production	Oxidative stress Insulin resistance Mitochondria dysfunction	Hyperglycemia Hyperlipidemia hyperinsulinemia	Insulin resistance	Islet cell function	Proinflammatory cytokines Oxidative stress NF-κB expression

Figure 2: Effect of Insulin on Selected Organs and Proteins[9]

2.2 Pathophysiology of Diabetes

The cells and processes involved in the two main subclasses of diabetes, type 1 and type 2 diabetes, are similar but not identical.[1] Here, the pathophysiology of the two types of diabetes will be outlined.

Type 1 diabetes is characterized by the T-cell mediated, autoimmune destruction of the Islets of Langerhans' pancreatic beta cells.[10] The destruction of the beta cells results in a loss of endogenous insulin production and consequently hyperglycemia.[11] Several immune markers characterize type 1 diabetes, namely autoantibodies.[11] The autoantibodies are linked to the autoimmune mediated beta cell destruction.[11] Of note, glutamic acid decarboxylase autoantibodies (GADAs) such as GADA56, islet cell autoantibodies (ICAs), and autoantibodies

to tyrosine phosphatases such as IA-2α, among others.[11] GADA56 is present in approximately 80% of individuals with type 1 diabetes at diagnosis while ICAs are present in 69-90% of individuals and IA-2 α in 54-75% of individuals at the time of clinical presentation.[11]

These immune markers are not typically clinically relevant in the diagnosis of type 1 diabetes in children and young adults.[11] However, they are diagnostically relevant in some cases for adults in whom the destruction of pancreatic beta cells is slow and the disease can be mistaken for type 2 diabetes. This diabetes type is known as Late Autoimmune Diabetes in Adults (LADA).[11] In LADA measuring the levels of autoantibodies, particularly GADAs, can assist in making an accurate diagnosis and treating the correct disease effectively.[11]

In type 1 diabetes, the absence of insulin leads to dysregulated gluconeogenesis, glycogenolysis, and lipolysis, and glucose remains in the blood.[12] The accumulation of glucose in the blood, termed hyperglycemia, is ultimately responsible for many of the complications and the morbidity associated with type 1 diabetes.[13]

Type 2 diabetes is characterized by different insulin issues rather than cellular destruction, insulin resistance and beta cell dysfunction are the predominant problems. Insulin resistance occurs as a product of the disruption of various cellular pathways which cause a decreased response or sensitivity of peripheral tissue cells to insulin, particularly muscle, hepatic and adipose tissues.[11] Early in the pathogenesis of the disease, this decreased insulin sensitivity is compensated by beta-cell hyperactivity to trigger a compensatory increase in insulin secretion and maintain blood glucose levels, preventing hyperglycemia.[11] Over time, as beta cell function declines, these cells can no longer compensate for the insulin insensitivity and progressive insulin deficiency.[11]

The pathogenesis of type 2 diabetes is complex, involving many factors both genetic

(polygenic) and environmental.[11] Additionally, hyperglycemia impairs pancreatic beta-cell functioning and, therefore, decreases insulin secretion, leading to a cycle of hyperglycemia and an impaired metabolic state.[1] In type 2 diabetes, the metabolic demands of the tissues are unmet, leading to the disease's metabolic imbalance.[14]

2.3 Genetic Basis of Type 1 Diabetes

The recognition of T1D as having a genetic etiology is increasing. Specifically, studies have established a link with polymorphisms in the class II Human Leukocyte Antigen genes that encode DQ and DR isotypes and confer genetic susceptibility to type 1 diabetes.[15] However, environmental triggers are thought to ultimately provoke the autoimmune processes in genetically susceptible individuals.[16] Environmental triggers include infectious agents such as viruses that cause beta cell destruction through several mechanisms, including direct cytolytic effects and triggering auto-immune reactions.[17] Ultimately, it is posited that autoreactive T cells are responsible for the auto-immune destruction of b-cells, with CD4+, CD8+ T cells and Th17 cells being the primary culprits.[16]

2.4 Diagnosis of Type 1 Diabetes

Diabetes is primarily diagnosed using four methods:

1) Fasting (8 hours) plasma glucose ≥ 7.0 mmol/L

2) Glycated hemoglobin (HbA1c) ≥ 6.5% (in adults)

3) Two hours post 75 g oral glucose tolerance test plasma glucose ≥ 11.1 mmol/L

4) Random plasma glucose ≥ 11.1 mmol/L.[18]

The presence of c-reactive protein, a by-product of endogenous insulin production, can be measured in the blood and can serve to differentiate type 1 diabetes from type 2 diabetes in the case of uncertainty.[13] It is important to have tools to differentiate between the two, especially as

there has been an increase in the diagnosis of type 2 diabetes during childhood – an increase which can largely be attributed to the child obesity epidemic.[19] Additionally, type 1 diabetes, which was previously thought to be exclusively diagnosed in childhood, is being diagnosed into late adulthood.[18] These factors, in concert, make diabetes diagnostically challenging. However, accurately diagnosing diabetes is essential to initiate proper treatment as the standard of care treatment for type 1 diabetes varies considerably from that for type 2 diabetes.[18]

2.5 Complications

2.5.1 Complications – Acute

Both acute and chronic complications characterize type 1 diabetes.[13] Acutely, diabetic ketoacidosis and hypoglycemia are the most common complications. Commonly, children present with polyuria, polydipsia, and weight loss at diagnosis, while 30% present with diabetic ketoacidosis.[13,20] Diabetic ketoacidosis is a metabolic acidosis that occurs during periods of absolute or relative insulin deficiency, where there is a perceived lack of glucose by the pancreas in the body due to decreased cellular uptake, causing increased hepatic glucose production and decreased peripheral utilization, resulting in hyperglycemia.[21] Low insulin levels and increased levels of catecholamines, cortisol, and growth hormone activate hormone-sensitive lipase which causes the breakdown of triglycerides and, therefore, the release of free fatty acids, β-hydroxybutyric acid and acetoacetic acid.[21] These free fatty acids are absorbed by the liver, converted to ketone bodies and later released into circulation, a process known as ketogenesis.[21] Together, the ketogenesis and hyperglycemia induce osmotic diuresis, resulting in volume depletion.[21]

Diabetic ketoacidosis is an anion gap metabolic acidosis, which is important to characterize clinically for prompt diagnosis and treatment.[21] Diabetic ketoacidosis leads to acute

metabolic disarray, which is the leading cause of diabetes-related deaths in children.[22] In contrast, adult mortality is typically a bi-product of the chronic complications of diabetes.[22]

Hypoglycemia occurs because of increased serum insulin levels. In type 1 diabetes, this is attributed to insulin over-administration, causing hyperinsulinemia and poor defences against reducing glucose levels, which can result in hypoglycemia-associated autonomic failure (HAAF).[18] HAAF encompasses hypoglycemia unawareness, described as an increased tolerance to hypoglycemia that delays or masks symptoms, impeding individuals' intrinsic ability to recognize their need for additional carbohydrate/glucose intake to increase blood sugar levels into the normal range.[23]

Hypoglycemia symptoms tend to be variable, particularly in children and older adults.[23] Typical symptoms of hypoglycemia include pallor, nausea, sweating, anxiety, warmth, palpitations, tremulousness, paresthesia and neuroglycopenic manifestations such as double vision, seizures, or coma.[23] In most cases, hypoglycemia is treated with oral carbohydrate intake, often in the form of juices or pre-packaged snacks.[23] In severe cases or younger populations, individuals may not have the ability to treat their hypoglycemia autonomously and thus require help from a third party.[24] Third-party treatment may include subcutaneous, intravenous or intranasal glucagon, which releases glycogen stores in the liver to increase blood glucose concentrations.[25] However, glucagon is ineffective in fasting patients and those experiencing prolonged hypoglycemia as their glycogen stores are depleted.[23]

2.5.2 Complications – Chronic

Chronic complications of diabetes fall under four main categories: ophthalmologic (retinopathy), neuropathic (acute sensory neuropathy, gastroparesis), nephropathic (microalbuminuria, macroalbuminuria, chronic kidney disease), and cardiovascular (coronary

artery disease, cerebrovascular and peripheral vascular disease).[26] The complications can also be subdivided into two categories: microvascular and macrovascular complications.[27] Microvascular complications (Figure 3) are associated with high glucose levels and damage to small blood vessels and include diabetic retinopathy (the most common microvascular complication), nephropathy and neuropathy. Conversely, macrovascular complications (Figure 3) are associated with atherosclerosis and damage to large blood vessels and include coronary artery disease, cerebrovascular disease, and peripheral vascular disease.[27]

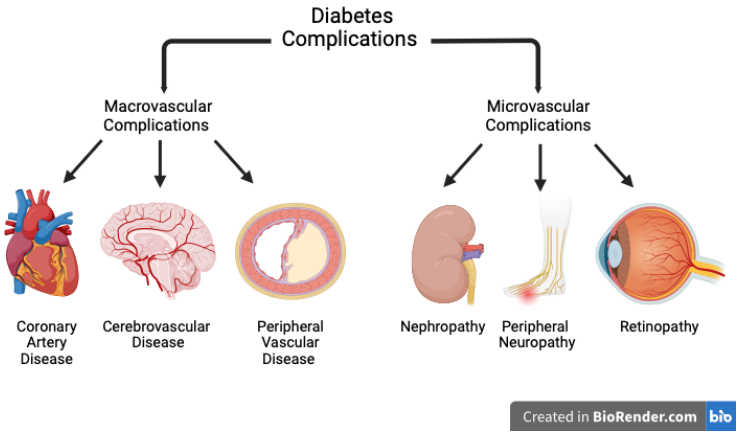

Figure 3: Chronic Complications in Diabetes

The degree and length of exposure to hyperglycemia, measured by HbA1c levels, is posited to be the primary driver of these chronic complications.[26] As such, the standard-of-care treatment aims to reduce and maintain HbA1c at a normal level to minimize the incidence and, ultimately, the progression of these complications.[26] The Diabetes Control and Complications Trial, conducted from 1983-1993, illustrated that initiating early and intensive treatment does indeed reduce long-term complications.[28] In that trial, intensive therapy reduced the adjusted mean risk of retinopathy by 76%, the occurrence of microalbuminuria by 39%, albuminuria by 54% and clinical neuropathy by 60%.[28] The primary adverse event associated with intensive

insulin therapy, as observed in the trial, was a two-to-threefold increase in severe hypoglycemia.[28]

Long-term complications not only decrease life expectancy, but they also increase disease burden, leading to a decrease in quality of life and an increased burden on the health care system to mitigate or decrease disease progression and treat complications.[29]

2.6 Measures of Glycemic Control in Diabetes

HbA1c is the gold standard test to evaluate an individual's glucose control.[30] Hemoglobin is a protein exclusive to red blood cells, which becomes glycated in the bloodstream. [30] The amount of glucose in the bloodstream is reflected by the level of glycation at the surface of the hemoglobin.[30] The Diabetes Control and Complications Trial, published in 1993, was the primary study correlating HbA1c levels with blood glucose levels and establishing target HbA1c goals in diabetes management.[31,30] The HbA1c level is an indicator of the average glucose levels over the last three months, as the lifespan of a red blood cell is 90 days.[30] The treatment recommendation is that HbA1c levels remain <7.0%, irrespective of the method of treatment.[28] This recommendation is based on the findings from the Diabetes Control and Complications Trial, which demonstrated a curvilinear relationship between HbA1c and diabetes microvascular and macrovascular complications, with absolute risk reduction being substantially less at lower HbA1c levels.[28]

However, in recent years, with the advent of continuous glucose monitoring, it has been debated whether the "time in range" metric can be used to assess glucose control, where time in range is mainly denoted by the time spent in the range of 3.9-10.0 mmol/L.[32] An advantage of time in range compared to HbA1c is the information on glycemic variability and the risk of

hypoglycemia.[32] Increasing evidence demonstrates time in range to be strongly correlated with HbA1c and the risk of developing microvascular and macrovascular complications.[32]

An important consideration when deciding what variable to use for measures of glycemic control is that HbA1c encompasses components of both fasting plasma glucose and postprandial glucose, with higher contributions being from fasting plasma glucose at higher HbA1c levels and from post-prandial glucose at lower levels closer to the target (<7.0%).[2] When using time in range, sub-analyses would have to be conducted to discriminate and assess fasting plasma glucose and post-prandial glucose. Currently, suggested time in range targets are a time in range >70 %, time below range (<3.9 mmol/L) <4 % and time below range (<3.0 mmol/L) <1%, while HbA1c recommendations for individuals with type 1 diabetes are an HbA1c of 58 mmol/mol or <7.5%.[32]

Despite these recommendations, only a minority of individuals with type 1 diabetes currently achieve the recommendations pertaining to glycemic targets.[33] The Type 1 Diabetes Exchange, which collected data from 22,697 individuals living with type 1 diabetes from 2016-2018, highlighted that only 17% of youth and 21% of adults achieved their HbA1c targets.[33]

2.7 Insulin

In 1921, the diagnosis of type 1 diabetes was transformed from a fatal condition into a chronic, manageable medical condition with the discovery of insulin by Banting and Best.[34] Since then, insulin analogs have been created by modifying two amino acids of neutral protamine Hagedorn and using recombinant DNA technologies to modify regular human insulin.[35,36] These analogs have been designed with variable properties, including onsets of action and half-lives.

Typically, rapid and short-acting insulins are used as bolus/correction doses in multiple daily injection therapy, whereas long and intermediate-acting insulins are used as basal insulins.[37] In continuous subcutaneous insulin infusion therapy, short, rapid or ultra-rapid-acting insulin is used for both basal and bolus/correction dosing.[37] Ultra-rapid and rapid-acting insulins permit a more rapid onset of insulin action as well as faster dissipation of post-meal-related insulin action.[38] These are helpful, especially in fully closed-loop systems as rises in glucose can be accounted for more rapidly, helping to increase time in range.[38]

Many factors affect subcutaneous insulin absorption, which can limit its efficacy and degrade glycemic control, as a result of unintentional and unpredictable increases in hyperglycemic and hypoglycemic events.[39] Lipohypertrophy, local fat tissue accumulation at the site of repeated insulin injection, skin temperature, local insulin degradation, injection site choice, obesity, and smoking affect insulin absorption and other pharmacokinetic factors.[39]

In terms of adverse effects, hypoglycemia is the most serious one associated with insulin therapy, as well as being a barrier to achieving optimal glycemic control.[40] To mitigate the risk of hypoglycemia, the American Diabetes Association recommends targeting a higher HbA1c of <8% in vulnerable individuals: older, with a longer duration of disease, increased comorbidities, frequent hypoglycemia episodes and with cardiovascular disease.[40]

Category	Insulin Type (Trade Name)	Onset of Action	Peak Action	Duration of Action
Ultra-rapid Acting	Lispro-aabc (Lyumjev)	1 minute	2-2.9 hours	5 hours [41]
	Faster Aspart (Fiasp)	4 minutes	0.5-1.5 hours	3-5 hours
Rapid Acting	Aspart (Novorapid)	20-30 minutes	1-1.5 hours	3-5 hours
	Lispro (Humalog)	15-30 minutes	1-2 hours	3-4.7 hours

	Glulisine (Apidra)	10-15 minutes	1-1.5 hours	3-5 hours
Short Acting	Regular Insulin (Humulin)	30 minutes	2-3 hours	6.5 hours
Intermediate Acting	Neutral protamine Hagedorn (NPH)	1-3 hours	5-8 hours	Up to 18 hours
Long Acting	Detemir (Levemir)	90 minutes	Not applicable	16-24 hours
	Glargine U-100 (Lantus)			24 hours
	Glargine U-300 (Toujeo)			30 hours
	Glargine biosimilar (Basaglar)			24 hours [42]
	Degludec U-100, U-200 (Tresiba)			42 hours

Table 1: Conventional Injectable Insulin Subtypes and Properties.[36,35,34]

2.7.1 New Insulin Technology

Newer methods for insulin delivery include once-weekly formulation of a degradation-resistant, acetylated insulin icodec.[38] Insulin icodec remains an investigational product and is primarily designed for type 2 diabetes to reduce basal insulin injections and increase treatment acceptance and adherence[43] Using once-weekly insulins in type 1 diabetes will require research on the management of unexpected illness, vigorous exercise, and nocturnal or new-onset hypoglycemia while having substantial long-acting insulin on board.[38]

Oral insulin has been studied for decades but recently has been investigated in type 1 and 2 diabetes.[38] Oral delivery for insulin is appealing as it has the ability to reduce the number of injections and, therefore, injection site reactions, including lipohypertrophy.[38] However, many barriers, primarily in the organization and physiological functioning of the gastrointestinal tract causing inter-individual variability in gastric emptying and low bioavailability, limit their potential for widespread use despite reductions in acute blood glucose levels.[38,44]

Research is underway to explore the creation of smart glucose-sensitive insulins, which can be achieved through three methods: (1) connecting continuous glucose monitors to delivery devices such as the fully closed-loop systems discussed here, (2) encapsulating insulin in glucose-responsive polymers, and (3) glucose-sensitive motif insertion into insulin molecules that confer glucose-responsive changes in bioavailability or hormonal.[45,38] Although approaches (2) and (3) are still in the experimental stage, they hold the potential for reducing the short-term and long-term risks associated with fluctuations in blood sugar levels, by offering hormonal responses aligned with glucose levels without the need for external monitoring.[45,38]

Another new non-injectable insulin is rapid-acting inhaled insulin, which was approved for diabetes. However, the use of inhaled insulins in type 1 diabetes remains to be elicited. Further experimental innovations include subcutaneous patches, ingestible micro applicators that adhere to the gastrointestinal system, and more.[46,45,38] Only injectable insulins are part of the current standard of care practice.

2.8 Carbohydrate Counting

Carbohydrate counting has become the cornerstone of mealtime type 1 diabetes management for multiple daily injection therapy and continuous subcutaneous insulin infusion.[47] The principle relies on the fact that prandial insulin requirements vary with varying amounts of meal carbohydrates.[48]

Despite its efficacy, carbohydrate counting challenges many individuals with type 1 diabetes.[49] Individuals who use carbohydrate counting as part of their treatment plans report mixed feelings toward the practice.[49] While many individuals report being confident in applying carbohydrate counting and in their ability to accurately count carbohydrates with low perceived difficulty, others encounter problems with their practice.[49] While some struggle with the burden

imposed by carbohydrate counting and its effects on their quality of life, others struggle with the perception that their glycemia fluctuates even with appropriate and careful carbohydrate counting.[5,49] Furthermore, research shows that individuals with a lower level of education and a history of or current diagnosis of depression express less confidence in their ability to confidently carbohydrate count.[49]

Various groups of individuals have distinct struggles and perceptions regarding carbohydrate counting. For example, it is estimated that only 23% of adolescents accurately count the carbohydrate content of their meals, while 59% of adults are estimated to assess the carbohydrates they consume accurately.[50] Furthermore, at different ages, different struggles and perceptions by others impact an individual's perception of themselves and their illness in relation to their daily lives.

2.9 Intensive Insulin Therapy for Type 1 Diabetes

The Diabetes Control and Complications Trial[28] and its decades-long follow-up, the Epidemiology and Diabetes Interventions and Complications study,[51] demonstrated that maintaining blood glucose levels as close to physiologically normal as possible using intensive insulin therapy slows the onset and progression of diabetic nephropathy, neuropathy, and retinopathy.[31] Since then, intensive insulin therapy has been the gold standard treatment of type 1 diabetes.[52]

As described in the Diabetes Control and Complications trial, intensive insulin therapy is defined as three or more daily insulin injections or treatment with an external insulin pump.[28] Intensive insulin therapy is based on a basal-bolus model of insulin replacement. The basal insulin is administered to cover physiologic needs; in multiple daily injection therapy, this is done by administering long or intermediate-acting insulin once or twice daily, while in

continuous subcutaneous insulin infusion, a pre-determined amount of rapid-acting insulin is continuously administered.[53]

Bolus insulin is delivered at mealtime, and insulin doses are determined as a function of the number of carbohydrates in a meal and the individual's insulin-to-carbohydrate ratio.[53] Insulin-to-carbohydrate ratios are the number of carbohydrates accounted for by one unit of insulin. These ratios are often initially estimated based on weight or determined by dividing 500 by the total daily insulin dose they require.[54] It is important to note that insulin-to-carbohydrate ratios vary throughout the day as a function of circadian rhythm.[54]

Another critical aspect of bolus dosing is correcting for hyperglycemia or hypoglycemia at the time of the meal to accurately administer a bolus dose without degrading glycemia.[54] This correction is accounted for by using the individual's insulin sensitivity factor, which indicates the amount that blood glucose will be decreased by administering one unit of rapid-acting insulin in the subsequent two to four hours.[54] When administering correction doses, it is essential to be aware of how much insulin has already been administered, known as insulin on board, so as not to underestimate its glucose-lowering effects with its prolonged duration of action.[54]

In recent years, intensive insulin therapy has evolved both in the scope of multiple daily injections and continuous subcutaneous insulin infusion.[35] Intensive insulin therapy can now include continuous glucose monitoring, closed-loop insulin delivery systems, and bolus calculators, to name a few, which will be described in this thesis.[55]

2.10 Multiple Daily Injection Therapy

Multiple daily injection therapy is the primary treatment used by individuals with type 1 diabetes worldwide.[56] The proportion of individuals who use multiple daily injection therapy is different in countries like Canada and the United States of America (USA). In the USA, 40% of

individuals use multiple daily injection therapy, while in Canada, rates of multiple daily injection use vary by province depending on pump funding programs.[57,33] Indeed, in Québec where the study presented in this thesis was conducted, the insulin pump is only covered if therapy is initiated before the age of 18, boasting one of the narrowest coverages in the country.[58]

Multiple daily injection is defined as the administration of three or more insulin injections per day.[56] Typically, one injection is of long-acting insulin, which covers the physiologic basal needs, while the others are rapid-acting injections, which either account for prandial boluses doses or for correcting hyperglycemia.[56] There is also a subset of individuals who use fixed-dose multiple daily injection therapy users who do not count the carbohydrate content of their meals.[56] Despite being able to achieve adequate glycemic control using multiple daily injection therapy, many individuals opt to use insulin pump therapy or add devices such as continuous glucose monitors.[56] However, many barriers, including the cost of insulin pump therapy, the constant need to be attached to a device and issues with cannulas, impede the widespread adoption of insulin pump therapy, as many individuals deem these burdens to be too great.[56] Ultimately, the decision to use insulin pump therapy or multiple daily injection therapy is a personal one that should be made alongside the patient's physician and family.[56]

Multiple daily injection therapy is also making technological strides with the recent advent of smart insulin pens with connectivity and memory (boluses administered, etc..) functions, improving glycemic outcomes and increasing confidence and ease of diabetes management.[59]

2.11 Continuous Subcutaneous Insulin Infusion

Continuous subcutaneous insulin infusion requires individuals to wear a relatively small electromechanical pump that infuses insulin throughout the day at pre-selected basal rates.[60] At

meal times, individuals are expected to administer bolus insulin doses to account for their prandial insulin needs.[60] The pump comprises a motor, a computerized control mechanism, an insulin reservoir and an infusion set consisting of a subcutaneous cannula and tubing.[60] A class of pumps termed "patch pumps" also exists, with an infusion set and reservoir integrated into the pumps, requiring no additional tubing.[60] From the Type 1 Diabetes Exchange, the use of insulin pumps increased from May 2018 to February 2020 by 13%, from 45 to 58% in patients aged 12-26 years old.[61] To summarize, >350,000 individuals in the United States use insulin pumps, representing >60% of individuals with diabetes.[33]

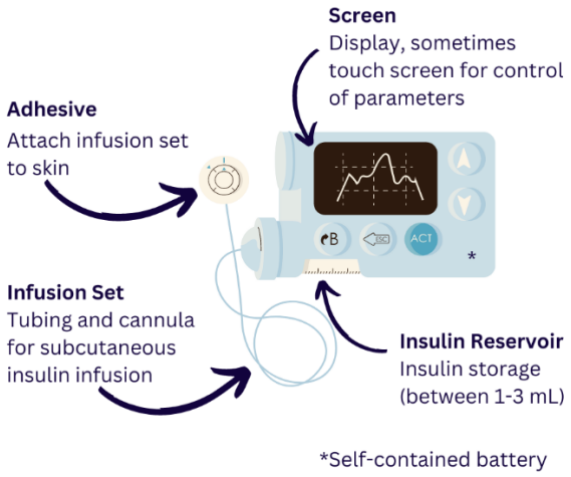

Figure 4: Insulin Pump and Contents

Using insulin pumps (pictured in Figure 4 and 5) combined with continuous glucose monitors is often termed sensor-augmented pump therapy or an open-loop system.[62] Sensor-augmented pump therapy improved HbA1c compared to injection and classic continuous subcutaneous insulin infusion therapy.[63,64] Sensor-augmented pump therapy was considered the gateway to achieving what we now know as hybrid closed-loop and fully closed-loop therapies.[64]

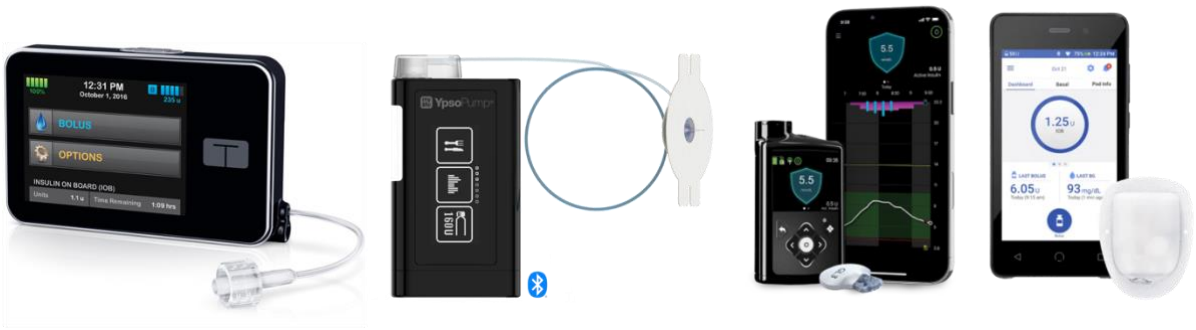

Figure 5: Commonly Used Insulin Pumps Available in Canada[51,52,53,54]

2.12 Continuous Glucose Monitoring

In 1999, the first continuous glucose monitoring system was approved for use by individuals with diabetes.[65] The continuous glucose monitor resulted from the development of technologies that started as Benedict's solution for urine glucose testing and evolved into the Combur-Test before resulting in the continuous glucose monitors we know today.[65] We have come a long way from the first commercially available sensor, the Medtronic Continuous Glucose Monitoring System, which did not provide "real-time" reading but stored glucose data for three days before being downloaded.[62] Continuous glucose monitoring technology has revolutionized multiple daily injection therapy and continuous subcutaneous insulin infusion therapy.[65]

Dexcom G6 and G7 | Freestye Libre 2 and 3 | Medtronic Guardian

Figure 6: Common Continuous Glucose Monitors Used in Canada and Their Newer Versions (To Be Released)[57,58,59]

Continuous glucose monitoring technology relies on inserting a device subcutaneously (as seen in Figure 6) that measures the wearer's glucose levels in their interstitial fluid for the duration of wear. [65] Continuous glucose monitoring is an improvement from self-monitoring blood glucose, which relies on an individual performing finger pricks with a lancet to obtain a drop of blood; the blood is transferred to a reagent strip and the concentration of glucose is determined via insertion into a reflectance photometer for automated reading.[66] With self-monitoring blood glucose, the recommendation was to monitor blood glucose levels at least four times a day: fasting, before meals and before bedtime.[66]

In contrast to self-monitoring blood glucose, continuous glucose monitoring systems can measure interstitial fluid glucose levels every five minutes.[65] This amount of blood glucose readings is beneficial in making insulin parameter adjustments over the long term, unique to every patient.[65] While there is a positive correlation between the frequency of self-monitoring blood glucose and the individual's glycemic control, the breadth of data afforded by continuous glucose monitoring technology permitted a more thorough understanding of an individual's daily glycemic fluctuations.[65] Furthermore, the technology allows wearers to be alerted of hypoglycemia or hyperglycemia in real time, which prevents acute complications, including death, as well as long-term complications.[65]

In multiple daily injection therapy, continuous glucose monitoring has been shown to decrease HbA1c, time spent in hypoglycemia, hypoglycemic fear, and diabetes distress, and increase overall well-being, treatment satisfaction and hypoglycemic confidence.[67] In continuous subcutaneous insulin infusion therapy, the use of continuous glucose monitoring has been shown to decrease HbA1c, time with sensor glucose <3.9 mmol/L, and increase the number of daily insulin boluses, and the frequency of use of the temporary basal rate and manual insulin

suspensions.[68] Continuous glucose monitoring also shows improvements in special populations, including pregnant women[69] and hospitalized patients.[70]

2.13 Closed-Loop Insulin Delivery

Thanks to the advances in insulin pump therapy and continuous glucose monitoring, closed-loop therapy has become possible.[71] Closed-loop systems (Figure 7) consist of an insulin pump and a continuous glucose monitor which communicate, sometimes through an intermediate device wirelessly, to adjust insulin basal and bolus dose adjustments in real time; in other words, they are glucose-responsive insulin delivery systems.[72,71]

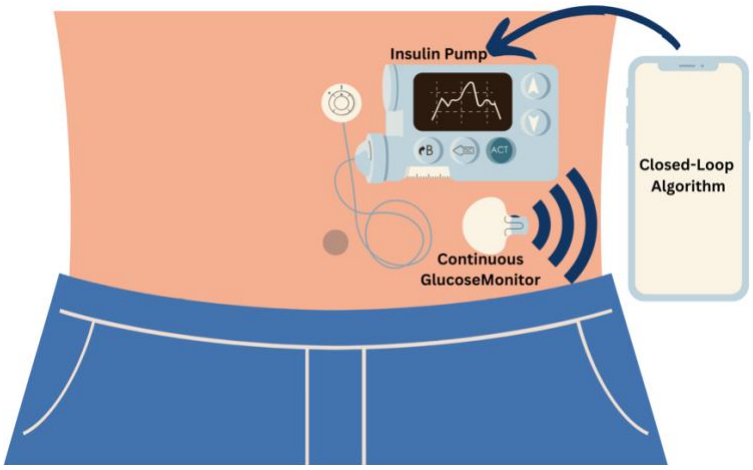

Figure 7: Closed-Loop Insulin Delivery System

While closed-loop technologies have been shown to decrease the risk of diabetic ketoacidosis and severe hypoglycemia, and improve glycemic outcomes, they still do not permit all individuals to meet their glycemic targets.[71]

In general, closed-loop systems decrease the risk of hypoglycemia by integrating glucose sensor data and the amount of insulin on board to reduce or cease insulin delivery.[73] This insulin suspension allows less rapid-acting carbohydrates to be needed for hypoglycemia treatment or prevention (as described above), which also benefits weight management as less calories are consumed.[73] Conversely, for hyperglycemia, the closed-loop systems increase insulin

administration; however, if users are unaware of the increased insulin administration and they deliver manual correction boluses in parallel, they can create a phenomenon known as insulin-stacking which sometimes results in hypoglycemia.[73]

In terms of closed-loop systems, there are many variations which are differentiated based on their method of insulin titration, or dose adjustment. The differentiation is predicated on how each system utilizes the blood glucose level information acquired from the continuous glucose monitoring systems. Some examples include systems with low glucose suspension, predictive low glucose suspension, hybrid closed-loops and fully closed-loop systems.[74]

2.13.1 Low Glucose Suspend and Predictive Low Glucose Suspend

Low glucose suspend devices rely on the basic principle of suspending insulin infusion when sensor glucose levels fall below a pre-specified threshold, indicating hypoglycemia.[74] Insulin infusion resumes after a fixed time interval, when sensor glucose values are concordant with rising glucose levels, or when glucose levels are back in the target range.[74] Low glucose or threshold suspension has been shown to decrease nocturnal hypoglycemia event rate and severity and decrease HbA1c levels compared to sensor-augmented pump therapy.[75]

Conversely, predictive low glucose suspend systems use algorithms that predict future hypoglycemia, often within the next 20 minutes, and pre-emptively suspend insulin delivery before hypoglycemia occurs.[74] Again, insulin administration is resumed when glucose levels are concordant with a rise in glucose or upon breaching a pre-specified threshold.[74] Predictive low glucose suspend systems reduce time spent in hypoglycemia without increasing rebound hyperglycemia and require less carbohydrate supplementation to rescue hypoglycemia, typically 9g carbohydrates compared to the recommended 15-20g carbohydrates required in clinical guidelines.[76,77]

A trial conducted by Gomez et al. supports using sensor-augmented pump therapy with predictive low-glucose instead of sensor-augmented pump therapy with low glucose suspend by individuals who have persistent severe hypoglycemia and hypoglycemia unawareness.[78] The results of their three month trial showed an improvement in HbA1c levels (-0.34%, p=0.004), a decrease in severe hypoglycemia rate from 2.47 to 0.87 events/patient-year, and hypoglycemia unawareness (determined by the Clarke questionnaire) resolved in 23/30 patients (p=0.002).[78] These results support the use of predictive low-glucose management systems in individuals previously treated with sensory-augmented pump therapy with low glucose suspend who have persistent severe hypoglycemia and hypoglycemia unawareness.[78]

2.13.2 Hybrid Closed-Loop System

Hybrid closed-loop systems, the main type of systems currently available on the market, autonomously adjust insulin delivery to help achieve pre-specified targets in response to real-time sensor glucose information.[71] However, these hybrid closed-loop systems still require prandial insulin bolusing.[71] Carbohydrate counting therefore remains a necessary diabetes management skill in hybrid closed-loop technology.[73] Despite corrections, the absorption delays of subcutaneous insulin limit the system's ability to optimally correct post-prandial hyperglycemia.[73]

In hybrid closed-loop therapy, four main parameters can be adjusted to optimize treatment: (1) Insulin-to-carbohydrate ratios: This ratio signifies the number of carbohydrates accounted for by the administration of one unit of rapid-acting or bolus insulin.[79] Accurate insulin-to-carbohydrate ratios are essential for optimal glycemic benefits in closed-loop systems as they are not automated by the systems.[73] (2) Active insulin time or duration of insulin action: the amount of time the insulin has glucose-lowering effects is an important parameter to input

when administering manual insulin correction doses.[73] This is a feature unique to Medtronic™ insulin delivery systems. (3) Algorithm glucose targets: the target values the algorithms use to adjust insulin dosages. These are fixed in many systems; however, they can be temporarily adjusted during exercise or overnight when glycemia is more variable or affected by other physiological factors. (4) Basal insulin infusion rates: these must be set correctly in the insulin pumps for times when the closed-loop system is unavailable. An individual's pre-programmed basal rates influence other systems, such as the Tandem Control-IQ and the Medtronic insulin pumps in closed-loop modes.[73] Currently, all available commercial systems still require carbohydrate counting and therefore insulin-to-carbohydrate ratios.

Hybrid closed-loop therapy also shows positive psychosocial benefits, including but not limited to increased confidence and independence in adolescents and young adults,[80] reassurance and reduced anxiety, improved sleep and confidence and "time off" from the burdens and demands of the disease.[81] As with most patient-reported outcomes, various studies report varying amounts of psychosocial benefit; for example, the DCL Trial Research Group reported an improved Hypoglycemia Fear Survey Behaviour subscale but no improvement in Diabetes Distress Scale, both validated surveys to assess the quality of life in diabetes.[82] Hybrid closed-loop therapy has its challenges, including being cumbersome due to bulky pumps and accessories, contending with technical difficulties and connectivity issues, and integrating the system into everyday life.[81]

For some time, there was debate about whether the extremes of age, seldom studied, could benefit from closed-loop therapy outside the context of glycemic outcomes but within the broader psychosocial and financial perspectives. Trials have investigated the use of closed-loop insulin delivery in pediatric populations, demonstrating that glycemic outcomes are improved

and management burdens are reduced on individuals and their families.[83] Similarly, closed-loop therapy is effective for older adults with long-duration diabetes, improving time in range and decreasing time below the range, particularly overnight.[84] Essentially, the findings in the literature support the widespread adoption of closed-loop therapy across the lifecycle.

2.13.3 Fully Closed-Loop Systems

Fully closed-loop systems are appealing as they would eliminate the burden of carbohydrate counting, which is often challenging and seldom wholly accurate.[85] Fully closed-loop systems automatically deliver insulin via subcutaneous insulin pumps as a function of the data acquired from real-time sensor glucose levels.[86] Fully closed-loop systems, therefore, eliminate the need for carbohydrate counting and any forms of meal announcement, including, meal size categorization or simple meal announcement which have been trialed in select studies[87]. While these strategies may reduce burden or improve quality of life, they have not been shown to be non-inferior to carbohydrate counting in terms of glycemic control.[88,89]

In this thesis, I will present the work on a fully automated, dual hormone (insulin and pramlintide), closed-loop system that is the outpatient assessment of previous work completed by Madjpoor, Tsoukas et al..[6,86,90]

2.14 Current Available Closed Loop Systems (Canada)

Currently, in Canada, available closed-loop technologies include the Tandem Control-IQ™ and the Medtronic MiniMed™ 780G. The Tandem Control IQ algorithm operates on the Tandem t:slim X2 insulin pump. The Control-IQ technology leverages an auto-bolus feature as well as an activity setting for sleep and exercise to accommodate different glycemic range targets.[91,92] The auto-bolus is an automatic correction bolus delivered when glucose levels are predicted to rise above the "treatment range".[92] The auto-bolus delivers 60% of the bolus

calculated to be needed to lower glucose to a target of 6.1mmol/L given the user's profile setting.[92] The auto-bolus is delivered up to once an hour if glucose is predicted to be greater than or equal to 10.0mmol/L in the following 30 minutes.[92] During sleep, the target range of treatment values is set to 6.25-6.7 mmol/L, and to 7.8-8.9 mmol/L during exercise with a suspension of basal insulin delivery at 4.4 mmol/L during exercise.[93,94] The system begins to increase basal insulin at 8.9 mmol/L, while it decreases basal insulin as of 6.25 mmol/L.[91]

A meta-analysis of randomized control trials using the Tandem t:slim X2 with Control-IQ reveals an increased time in range for the experimental group (n=256) with an increase from 57% ± 17% at baseline to 70% ± 11% during follow-up, while for the Control group (*n*=113) the time in range was 56% ± 15% at baseline and 57% ± 14% at the conclusion of the study (adjusted treatment group difference=11.5%, 95% confidence interval +9.7% to +13.2%, $P < 0.001$), an increase of 2.8 h/day in the time in the range on average.[95] The analysis also revealed significant reductions in mean glucose, hyperglycemia metrics, hypoglycemia metrics, and HbA1c.[95] Of note, these benefits in time in the target range were observed across the full age range irrespective of race, ethnicity, household income, pre-study continuous glucose monitor use, and pre-study insulin delivery.[95] While all subgroups benefited from the Control-IQ technology and should be considered for therapy initiation, the largest benefit was obtained by participants with the poorest baseline control who utilized the automatic correction bolus, or auto-bolus feature.[95]

The Medtronic MiniMed™ 780G system has an advanced hybrid closed-loop algorithm that innovates on their previous MiniMed™ 670G system.[96] The algorithm adjusts basal insulin delivery automatically every five minutes to reach adjustable targets of 5.5, 6.1 or 6.7 mmol/L with automatic correction bolus delivery every five minutes.[96] However, user-initiated meal

announcements are required for optimal glycemic control.[96] The autocorrections are designed to improve daytime glycemic outcomes, mitigating carbohydrate estimation inaccuracies and accounting for missed or late prandial boluses.[96] A pivotal study in adolescents and adults showed a mean time in range of 74.5% ± 6.9% with an HbA1c of 7.0% ± 0.5% reduced from 7.5% ±0.8% during the run-in.[96,97] In another study, in children, adolescents, and adults, the proportion of users achieving a time in range >70% rose from 12% at baseline to 51% during advanced hybrid closed loop use.[96,98] In a real-world study, 77.3% of users achieved a time in range >70%, time below range (<3.9 mmol/L) of 2.5% ± 2.1%, and time above the range (>10 mmol/L) of 21.3% ± 9.4%.[96] Both the Tandem Control-IQ and the Medtronic MiniMed 780G are hybrid closed-loop systems and require prandial carbohydrate counting.

2.15 Adjunctive Therapies

As established in this literature review, insulin is the primary pharmaceutical treatment for type 1 diabetes.[40] However, insulin therapy alone has not permitted all individuals to reach their glycemic targets, with the type 1 diabetes exchange reporting rates of less than 20% of individuals reaching their glycemic goals.[33] Further, insulin monotherapy does not confer additional protection against diabetes-related macrovascular and microvascular complications.[99]

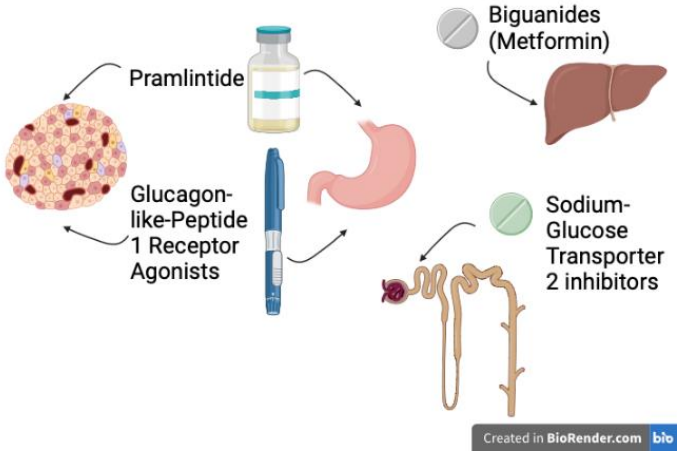

Figure 8: Select Target Organs Involved in Glucose Regulation

2.15.1 Bigaunides (Metformin)

Biguanides, commonly referred to as Metformin, are a class of drugs often used in type 2 diabetes which have been investigated and utilized off-label in type 1 diabetes.[100] Metformin is a complex drug whose mechanism of action on multiple sites remains a topic of debate.[101] To date, it has been established that metformin acts directly or indirectly on the liver to decrease glucose production and on the gut to increase glucose utilization, increase glucagon-like peptide 1 (GLP-1) and alter the microbiome (Figure 8).[101] At the molecular level, metformin enhances insulin sensitivity through 5' adenosine monophosphate (AMP) -activated protein kinase activation and reduces gluconeogenic enzyme expression by decreasing cAMP.[101] All the aforementioned effects contribute to its positive role in glucose regulation. According to the REMOVAL trial, metformin can reduce atherosclerosis progression and weight, mainly mediated by reducing insulin requirements and LDL-cholesterol levels, without increasing the rate of hypoglycemia or diabetic ketoacidosis in individuals with type 1 diabetes.[100,99] However, any improvements in glycemic control seem to be transient.[100] Despite its transient effect and given its affordability, and the fact that it is an oral agent, it remains an attractive option for cardiovascular risk management.[102.100]

2.15.2 Glucagon-like Peptide-1 Receptor Agonists

Another class of adjunctive therapies are the GLP-1 receptor agonists.[99] Physiologically, GLP-1 incretin hormones are secreted by intestinal L cells after glucose consumption to help potentiate insulin secretion from beta cells while suppressing glucagon release from alpha cells through paracrine effects (Figure 8).[103] In addition, GLP-1 incretin hormone slows gastric motility and induces satiety (Figure 8).[103] Pharmacological GLP-1 receptor agonists were designed in two classes: long-acting (exenatide, semaglutide, dulaglutide and albiglutide) and

short-acting (exenatide and lixisenatide).[103] In type 1 diabetes, these GLP-1 receptor agonists have been shown to inhibit gastric emptying, improve post-prandial glycemia, promote weight loss, and potentially improve HbA1c. However, Kobayati et al. suggest that these GLP-1 receptor agonists have the potential to confer cardiovascular, renal, neurological and hepatic protection as well.[103] Preliminary data from Dandona et al. support the initiation of semaglutide soon after type 1 diabetes diagnosis as it is associated with the elimination of prandial and basal insulin.[104] The ADJUNCT ONE trial investigating the use of Liraglutide demonstrated significant placebo-adjusted reductions in HbA1c, body weight, and insulin dose (−0.30%, −5.0 kg, and −12%, respectively, with liraglutide 1.8 mg) at week 26; similar results were observed in the ADJUNCT TWO trial.[105] Ongoing studies will clarify the true potential of GLP-1 receptor agonists as adjunctive therapies in type 1 diabetes.[106,107,108]

2.15.3 Sodium-Glucose Cotransporter 2 Inhibitors

Sodium-glucose linked transporter-2 inhibitors (SGLT2i) are another class of adjunctive agents being investigated in type 1 diabetes.[99]The mechanism of action of SGLT2i's is unique in that their glucose-lowering effects are independent of insulin.[109] Selective inhibition of the sodium-glucose cotransporter 2 on the proximal convoluted tubule of the kidneys reduces the threshold for glucose reabsorption to improve hyperglycemia (Figure 8).[109] Common SGLT2i's used in type 2 diabetes include canagliflozin, dapagliflozin, and empagliflozin.[109] The EASE trials investigated the use of 10 mg, 25 mg and lower 2.5 mg doses of empagliflozin in individuals with type 1 diabetes.[110] The trials demonstrated a decrease in HbA1c and weight at all doses.[110] The efficacy of SGLT2i in closed-loop systems was investigated by Rosina-Pasqua et al., who demonstrated an improvement of 11-13 % in time in range with hybrid closed-loop

therapy and low-dose empagliflozin (2.5mg and 5mg) in individuals previously unable to attain their glycemic targets.[111]

The main side effect of concern with SGLT2i in individuals with type 1 diabetes is diabetic ketoacidosis, including euglycemic diabetic ketoacidosis.[109] However, this class of drugs is attractive as it has been approved for heart failure (with preserved ejection fraction) and chronic kidney disease and has been shown to confer cardiac and renal protective effects.[112,113,114] Other common side effects include genital infections and general volume depletion, which show a dose-dependent incidence.[110]

2.15.4 Pramlintide

In addition to a lack of insulin, individuals with type 1 diabetes also lack endogenous production of amylin.[115] Amylin is a 37-amino-acid peptide hormone which under healthy conditions, is co-secreted with insulin by pancreatic beta cells second to neural and nutrient stimulus. [115] Amylin acts in three primary ways: 1) decreased of gastric emptying, 2) glucagon suppression, and 3) increasing satiety.[115] These functions complement the action of insulin to limit post-prandial hyperglycemia, and prevent excessive caloric consumption.[115] Therefore, in type 1 diabetes, the lack of endogenous amylin and insulin production contributes to increased caloric intake, which is linked to weight gain as well as prolonged post-prandial hyperglycemia, also associated with diabetes complications.[116] As such, a synthetic, soluble analog, Pramlintide (Symlin), has been developed as an adjunct to standard basal-bolus insulin therapy.[117] Pramlintide has been approved as a subcutaneous injection for the treatment of type 1 diabetes since 2005.[118] Pramlintide has a linear pharmacokinetic profile, which implies that the half-life is independent of concentration, and the clearance is independent of both the dose and the schedule, always reaching peak serum levels within 30 minutes of administration.[118,119]

When co-administered with insulin, Pramlintide offers a means of improving glycemic control and achieving glycemic targets (HbA1c <7%), which are seldom met but critical in mitigating long-term complications.[117] A 52-week study by Whitehouse et al. investigating mealtime pramlintide treatment as an adjunct to insulin demonstrated sustained HbA1c improvement, which was associated with a reduction in weight with no increase in the rate of severe hypoglycemia.[120] A study by Ratner et al. demonstrated that pramlintide may be useful in helping individuals who are approaching but not yet reaching their target glycemia with insulin alone without increasing the risk of severe hypoglycemia.[99]

In addition to decreasing HbA1c, pramlintide promotes weight loss and decreases serum fructosamine, a measure of non-enzymatic glycation of circulating proteins, and total cholesterol levels.[118,121] Fructosamine is a marker of glycemic control in instances of unpredictable red blood cell turnover like iron, vitamin B12, or folic acid deficiency, among others.[121]

Pramlintide does have possible gastrointestinal side effects, namely nausea, due to its mechanism of delayed gastric emptying.[122] However, slow titration of the pramlintide dose can reduce the incidence of nausea, and the effects typically dissipate over time.[123,120] Other side effects include anorexia, fatigue, and vomiting, in addition to being associated with insulin-induced severe hypoglycemia.[118]

2.16 Exercise and Diet

Weight control remains challenging for approximately 60% of individuals with type 1 diabetes, despite its ability to decrease cardiovascular disease risk, HbA1c, retinopathy, and microalbuminuria, amongst others[124] Physical activity can help reach weight goals and preserve health; as such, the recommendation for adults with type 1 diabetes is 150 minutes per week,

with no more than 2 consecutive days of cardiovascular training, supplemented by resistance training 2-3 times per week.[125]

However, physical activity is often accompanied by dysglycemia, with aerobic exercise, resulting in hypoglycemia secondary to increased blood flow to subcutaneous tissue, active insulin in the body and increased glucose uptake by peripheral tissues, namely muscle.[124] Conversely, anaerobic exercise results in hyperglycemia second to the increased need to replenish muscle glycogen stores.[124] As such, several barriers to physical activity can exist, such as fear of hypoglycemia, loss of glycemic control, and inadequate knowledge about exercise management.[126] There are many strategies for mitigating the risk of dysglycemia post-exercise, including adjusting the starting range of glucose pre-aerobic exercise (usually 7.0-10.0 mmol/L), adjusting meal macronutrient composition pre-exercise (fat, carbohydrate, and protein content), and accounting for duration of exercise (<30 minutes, 30-60 minutes, 60-150 minutes, and >150 minutes).[124] The SIT-LESS trial published data on frequent short bouts of light-intensity activity punctuating long periods of sitting, demonstrating improvement in acute post-prandial and 48-hour glycemia without increasing hypoglycemia.[127] This strategy is an exciting way for individuals who are fearful of hypoglycemia to incorporate exercise into their routines.

Closed-loop insulin delivery presents an opportunity to optimize exercise with "exercise modes," which could reduce temporary basal rates or suspend basal insulin administration altogether, for example.[124]

There is a wide range of alleged benefits which motivate individuals with type 1 diabetes to follow ketogenic or low-carbohydrate diets.[128] However, more information is needed to substantiate the safety and efficacy of these diets.[128] A systematic review by Turton et al. demonstrates that studies which investigated the ketogenic diet in individuals with type 1

diabetes revealed a plethora of effects ranging from a reduction in HbA1c to non-significant changes in HbA1c.[129] However, despite the split evidence, many individuals follow low carbohydrate diets, which could impact their glycemia as well as their insulin dosing, particularly bolus insulin doses, and may be an area of interest for future closed-loop studies.

Chapter 3: Outpatient Assessment of a Fully Closed-Loop Insulin and Pramlintide Artificial Pancreas System

3.1 Preface to Manuscript

Given the challenges outlined above with glucose control, device complexities, and burden of disease attributable to carbohydrate counting, the Diabetes Technology Lab is developing a fully closed-loop insulin-and-pramlintide system which requires no carbohydrate counting. In the following manuscript, the results of the pilot clinical trial assessing the fully closed-loop system in an outpatient supervised setting. This trial represents the second phase of testing the system and the final one that will precede outpatient, unsupervised use of the system.

As outlined previously, the interventions tested will include the following:

- Faster aspart alone in a hybrid closed-loop system with carbohydrate counting
- Faster aspart with pramlintide in a fully closed-loop system at an 8µg/U ratio
- Faster aspart with pramlintide in a fully closed-loop system at a 10µg/U ratio
- Insulin aspart with pramlintide in a fully closed-loop system at an 8µg/U ratio
- Insulin aspart with pramlintide in a fully closed-loop system at a 10µg/U ratio

The results of this study will be used to optimize the insulin dosing algorithm for the larger, longer outpatient study

3.2 Manuscript

Outpatient Assessment of a Fully Closed-Loop Insulin and Pramlintide Artificial Pancreas System

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Short running title: Fully Closed-Loop Insulin and Pramlintide System

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Keywords: type 1 diabetes, carbohydrate counting, closed-loop delivery systems, artificial pancreas, pramlintide, fully closed-loop

Word count: 4051 (including figures, excluding references)

Type 1 diabetes results from the autoimmune destruction of insulin-producing pancreatic β cells.[130] As a result, exogenous insulin is required for the management of type 1 diabetes.[131] Typically, insulin is administered in a basal-bolus fashion using either multiple daily injections or continuous subcutaneous insulin infusion systems to account for individuals' insulin requirements.[53] Both methods require individuals to count the carbohydrate content of their meals and do not permit all users to achieve their targets for time in the glucose range.[33]

The current gold standard for determining prandial bolus insulin doses is carbohydrate counting.[47] However, carbohydrate counting is an error-prone, labour-intensive task contributing to increased disease burden.[85,5] Given these challenges, efforts are being made to alleviate the burden of carbohydrate counting and increase time in the target range, especially in continuous subcutaneous insulin infusion.

Several commercial and experimental closed-loop systems have been developed, improving time in the target range; however, these hybrid systems still require user input of meal carbohydrate content.[72] Fully closed-loop systems which alleviate carbohydrate counting have been tested using insulin alone[132,87] and insulin plus glucagon.[133] Techniques to simplify mealtime bolus determination have also been leveraged such as simple meal announcement strategies or meal size estimates .[5,89,88] However, mealtime user input remains a requirement.

We developed a novel insulin and pramlintide closed-loop system which eliminates the need for carbohydrate counting or mealtime user input. Pramlintide, a synthetic analog of amylin physiologically co-secreted with insulin from pancreatic β cells, was integrated for its favourable physiological effects—pramlintide delays gastric emptying, increases satiety and suppresses nutrient-derived glucagon secretion, thereby enhancing post-prandial glucose control.[134] Following promising outcomes from our prior open-label, randomised controlled, non-inferiority

trial with a faster aspart plus pramlintide closed-loop system with no meal inputs, which showed participants spending a high time in target range (74.3%) compared to the control (78.1%).[135] We conducted a further evaluation in an outpatient, supervised setting to optimize the algorithm for free-living conditions.

Here, we report the results of this outpatient evaluation in a randomized, crossover pilot trial assessing an insulin-and-pramlintide fully closed-loop system compared to an insulin-alone hybrid closed-loop system in adults with type 1 diabetes. The hybrid closed-loop comparator arm mimics the most advanced commercially available existing therapies.[136] We tested two insulin types, faster aspart and insulin aspart at two ratios of insulin to pramlintide (8 µg/U and 10µg/U) in the fully closed-loop interventions. Although this study had only 12 participants and therefore lacked the statistical power to detect differences in time in range, specifically, superiority between treatments, the outcomes will serve as a basis for refining future iterations of our fully closed-loop system.

Methods

Participants were recruited between April 2022 and February 2023 at the Research Institute of the McGill University Health Centre. Eligibility criteria included adults aged ≥ 18 years, minimum three months of experience with insulin pump therapy, no current or recent (≤ 1 month) use of non-insulin anti-hyperglycemic agents or glucocorticoid medication, no gastroparesis or episode of severe hypoglycemia or severe hyperglycemia/diabetic ketoacidosis in the past three months, no clinically significant nephropathy, neuropathy or retinopathy or recent acute macrovascular event, and use of effective birth control if applicable. This trial was approved by the McGill University Health Centre's Research Ethics Board and by Health

Canada. The study was conducted in accordance with ICH good clinical practices and the Declaration of Helsinki.

The study's primary outcome was the difference in time in range between the fully closed-loop insulin and pramlintide system and the insulin-alone hybrid closed-loop system. Secondary outcomes included time below and above the target range. Safety endpoints included adverse events, notably gastrointestinal symptoms.

Study Design

We conducted an open-label, randomized, controlled, crossover pilot trial comparing 5 interventions: (1) faster aspart alone in a hybrid closed-loop system with carbohydrate counting with (2) faster aspart with pramlintide in a fully closed-loop system at an 8µg/U ratio (3) faster aspart with pramlintide in a fully closed-loop system at a 10µg/U ratio, and (4) insulin aspart with pramlintide in a fully closed-loop system at an 8µg/U ratio and (5) insulin aspart with pramlintide in a fully closed-loop system at a 10µg/U ratio. The fifth and sixth interventions were optional for participants. Intervention arms were separated by a 2–29-day washout period.

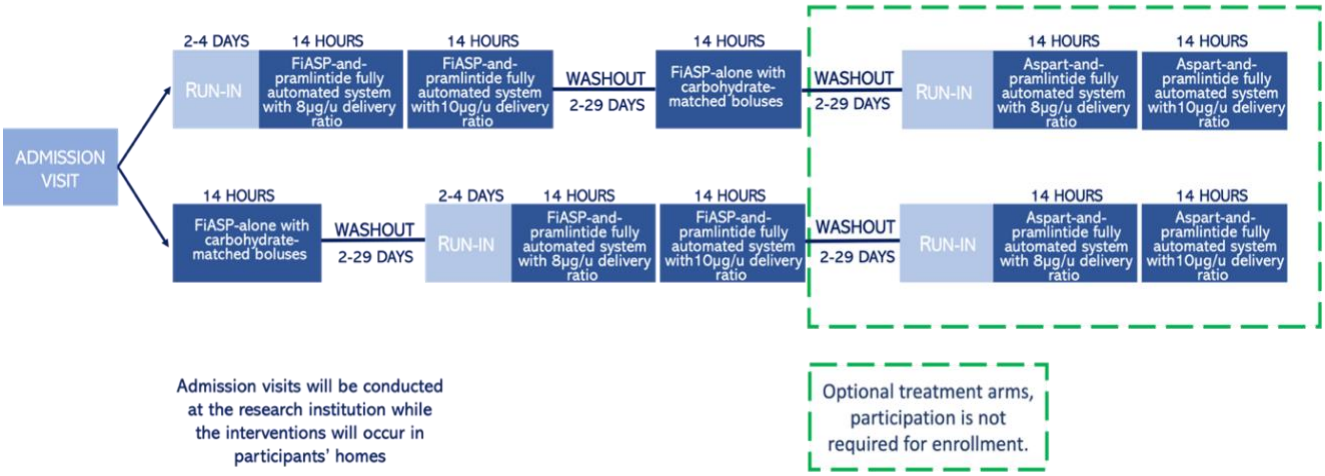

Figure 9: Study Design

Study Procedures

The study was conducted according to the order outlined in Figure 9. During the admission visit, the participants' height, weight, and insulin therapy parameters (total daily insulin dose, basal rates, insulin-to-carbohydrate ratios, etc.) were recorded. Participants underwent admission visit procedures including ascertainment of inclusion and exclusion criteria by the study physician. Participants were given study materials or asked where they would like materials delivered to them prior to the start of the intervention or run-in period.

Pramlintide interventions were preceded by a 2–4-day run-in period to mitigate gastrointestinal side effects. During the first half of the run-in (1-2 days), a ratio of 4 µg of pramlintide per unit of insulin was administered, followed by an increase to 6 µg/U in the second half (1-2 days) of the run-in period.

For the duration of the run-in, participants were asked to use the Medtronic study pumps. The run-in system consisted of a continuous glucose monitor (Dexcom G6®, Dexcom, CA, USA) and two insulin pumps either Medtronic Veo, Medtronic 630G, or Medtronic 670G (Medtronic, MN, USA): one for administering insulin and one for pramlintide. A research team member was on-call throughout the run-in periods to provide technical support. A physician was on-call throughout the run-in periods to ensure safety while at home using the study medications and devices.

During all interventions, participants used a Dexcom G6 continuous glucose monitor (Dexcom G6®, Dexcom, CA, USA), and the same two insulin pumps from the run-in period (if applicable), (Medtronic, MN, USA), one for insulin and one for pramlintide (if applicable). A tablet computer (Microsoft, WA, USA) running the closed-loop algorithm generated basal and

bolus insulin and pramlintide recommendations. Only the research team operated the tablet with the closed-loop algorithm.

During all interventions, a member of the study staff spent the duration of the intervention period with the participant. Participants were instructed to keep their diet and daily routines unchanged for the duration of the interventions.

All intervention periods were from 8:00 to 22:00. Before the start of the interventions, the dosing algorithm was initialized with participants' total daily insulin doses, insulin-to-carbohydrate ratios, and hourly basal rates. The algorithm generated a basal and/or bolus dose recommendation during the interventions every 10 minutes based on participants' sensor glucose levels. The research staff would immediately adjust the basal insulin and/or pramlintide delivery and/or administer the boluses as recommended. Participants were blinded to their sensor glucose values for the duration of the interventions.

During the hybrid closed-loop intervention with carbohydrate counting, participants were instructed to independently determine their meals' carbohydrate content using their usual methods. Study staff entered the carbohydrate content into the algorithm, and boluses were administered according to participants' pre-set insulin-to-carbohydrate ratios and their blood glucose levels at the time of the bolus.

During the experimental interventions, participants were not required to assess the carbohydrate content of their meals. The closed-loop algorithm's meal detection function administered small boluses if meals were detected. Bolus doses were calculated based on participants' glucose levels at the time of meal detection and their pre-set parameters. Small bolus amounts were administered to prevent hypoglycemic excursions and safeguard against erroneous meal detection. The insulin to pramlintide ratios were fixed during the interventions.

The algorithms were modified based on the pharmacokinetic profiles and the ratios of the insulins used for the respective interventions.

Participants were free to exercise as they usually would and perform their regular activities of daily living during all interventions. During exercise, the algorithm's "exercise mode" was activated, using more conservative glycemic targets of 9 mmol/L compared to the usual 6 mmol/L to prevent exercise-induced hypoglycemia.

Participants were alerted when their blood glucose levels fell below 4.2 mmol/L or the participant-specified threshold. Participants treated their hypoglycemia as per their usual practice, and research staff documented the treatment. Participants were alerted when their blood glucose levels rose above 18.0 mmol/L for over 60 minutes and were reminded to check for ketones and correction boluses were administered if needed with help of the study endocrinologist. Study staff documented the treatment.

Participants were asked about gastrointestinal symptoms at the start of the intervention and the end of the interventions (08:00 and 22:00) and were asked to report any gastrointestinal symptoms during the day.

Randomization

We used blocked randomization of size four to generate allocation sequences to the two intervention arms which were later concealed in envelopes, and subsequently opened and disclosed to the study coordinator and the participant upon confirmation of study enrollment. Participants who opted to participate in the aspart and pramlintide intervention arm completed those interventions at the end of the sequence.

Outcomes

Glycemic outcomes were evaluated for the 14-hour closed-loop intervention periods (8:00-22:00), excluding the run-in periods. The pre-defined primary endpoint was the time spent in the target range (3.9 mmol/L-10.0 mmol/L). Secondary endpoints included time spent between 3.9 mmol/L and 7.8 mmol/L, above 10.0 mmol/L and 13.9 mmol/L, below 3.9 mmol/L and 3.0 mmol/L, and glucose variability. Safety endpoints comprised all adverse events, including gastrointestinal symptoms.

Sample Size and Statistical Analysis

As this was a pilot study, the sample was not powered to detect differences in time in range between interventions. We have conducted superiority analysis with non-parametric Wilcoxon-Rank tests for non-uniform data and superiority analysis with a paired two-tailed t test for uniform data. All p-values were calculated at a 5% significance level. The analysis was done on an intention-to-treat basis. Participants who did not complete the aspart and pramlintide interventions were excluded from the analysis of the aspart and pramlintide outcomes. All participants completed the hybrid closed-loop interventions and were therefore included in the analysis of those outcomes. The results are reported as median [IQR] and mean (SD).

Results

Twelve participants (7 females, age 39.5 (15.1) years, $HbA1_c$ 7.34% (0.64), body mass index 30.8 (9.2), duration of diabetes 25.1 (13.6) years) were enrolled in the study from April 6, 2022, to February 22, 2023, following the scheme in Table 2. All participants completed the hybrid closed-loop and faster aspart and pramlintide interventions and were included in the analysis. Ten participants completed the additional, optional aspart and pramlintide interventions and were included in the analysis for those outcomes.

As outlined in table 3, in the hybrid closed-loop intervention, median time in range was 78.6% [65.3-92.9], comparable to the faster aspart and pramlintide with 8 µg/U 76.2% ([64.6-86.9], p=0.33) and 10 µg/U 78.8% ([68.8-86.0], p=0.24) interventions, as well as the aspart and pramlintide intervention with 10 µg/U, 77.4% ([72.09-82.74], p=0.30). The time in range was lowest for the aspart and pramlintide intervention with 8 g/U, 65.9% ([59.9-83.6], p=0.42).

The time below range (<3.9 mmol/L), as can be appreciated in table 3, was lowest in the hybrid closed-loop arm (0% [0-2.69]) compared to the experimental. The time below range for the faster aspart arms at the 8 µg/U and 10 µg/U was 0% ([0-6.25], p=0.12) and 2.46% ([0-5.36], p=0.20), respectively. Time below range was 4.83% ([0.6-14.9], p=0.06) and 2.38% ([0.3-10.12], p=0.07) for the aspart arms at 8 µg/U and 10 µg/U ratios, respectively. Time below the range (<3.0 mmol/L) was comparable in the hybrid closed-loop and fully closed-loop arms. In the hybrid closed-loop arm, there was a 0% [0,0] time below 3.0 mmol/L, and on the faster aspart interventions, it was 0% ([0,0], p=0.58) and 0% ([0,1.2], p=0.42) at the 8 µg/U and 10 µg/U ratios, respectively. During the aspart and pramlintide interventions, the time below the range (<3.0 mmol/L) was the lowest at 1.28% ([0,4.7], p=0.34) and 0.6% ([0,2.4], p=0.35), respectively.

Time above the range (>10.0 mmol/L) as illustrated in table 2, in the hybrid closed-loop arm was 21.4% [3.28-33.9] compared to the faster aspart 8 µg/U and 10 µg/U interventions with 19.0% ([11.03-30.65], p=0.24) and 18.8% ([3.6-24.2], p=0.16), respectively. Similarly, on aspart and pramlintide with the 8 µg/U and 10 µg/U interventions had 23.3% ([8.9-32.6], p=0.35) and 17.9% ([4.8-27.0], p=0.17) above range, respectively.

Total daily insulin and bolus insulin doses were decreased on all insulin and pramlintide interventions compared to the hybrid closed-loop intervention (Table 3), with total daily insulin

of 41.6 U [22.5-50.2] and basal insulin of 16.4 U [12.5-21.2]. On the faster aspart with pramlintide arms with the 8 µg/U and 10 µg/U ratios, total insulin decreased to 25.7 U [20.5-43.2] and 27.1 U [23.6-43.9] units, respectively. On the insulin aspart arm with pramlintide, total insulin was 28.5 U [20.8-36.9] and 23.3 U [21.4-27.6] units at the 8 µg/U and 10 µg/U ratios, respectively.

Basal insulin was decreased on all insulin and pramlintide interventions, excluding the faster aspart with pramlintide intervention at the 8 µg/U ratio (Table 3). The basal insulin on the hybrid closed-loop was 16.4 U units, while on the faster aspart with pramlintide arms, it was 18.3 U and 13.92 U at the 8 µg/U and 10 µg/U ratios, respectively. On the aspart and pramlintide at the 8 µg/U and 10 µg/U ratios, basal insulin was 13.0 U and 15.0 U, respectively.

Bolus insulin (Table 3) in the hybrid closed-loop with faster aspart was 18.5 U units compared to the faster aspart with pramlintide 9.1 U and 11.8 U at the 8 µg/U and 10 µg/U ratios and in the aspart with pramlintide 13.9 U and 11.4 U at the 8 µg/U and 10 µg/U ratios, respectively.

The mean sensor glucose (Table 3) was 8.2 mmol/L [7.1-8.9] on the hybrid closed-loop arm. On the faster aspart and pramlintide at the 8 µg/U and 10 µg/U ratios it was 7.7 mmol/L ([6.9-9.4], p=0.36) and 8.0 mmol/L ([7.2-8.4], p=0.27), respectively. Similarly, on the aspart and pramlintide interventions with 8 µg/U and 10 µg/U ratios, mean sensor glucose was 7.9 mmol/L ([6.9-9.0], p=0.86) and 8.2 mmol/L ([6.9-8.5], p=0.30), respectively.

With respect to the automated insulin delivery system, we present the number of meals detected by the algorithm, the number of boluses delivered, the number of hypoglycemia treatments, and the number of hyperglycemia corrections in Table 4. In the faster aspart and insulin closed-loop interventions, the number of meals detected were on average 1.4 and 2.3 at

the 8 µg/U and 10 µg/U ratios, respectively. For the insulin aspart closed loop interventions, the number of meals detected (Table 4) were on average 2.7 and 2.3 at the 8 µg/U and 10 µg/U ratios, respectively. These are in comparison to the 3.3 meals inputted by the participants during the hybrid closed-loop arm.

The number of prandial boluses (Table 4) delivered was 2.8 and 4.7 on average in the 8 µg/U and 10 µg/U faster aspart and pramlintide closed-loop interventions in comparison to 5.1 and 4.9 for the 8 µg/U and 10 µg/U insulin aspart and pramlintide closed-loop interventions. These are in comparison to the 3.3 prandial boluses delivered on average in the hybrid closed-loop arm. The higher number of boluses delivered during the fully closed-loop interventions can be attributed to the system delivering micro boluses upon meal detection to avoid erroneous meal detection and over administration of insulin leading to hypoglycemia. Despite the increased bolus delivery, total insulin delivered during the intervention period was numerically lower in all fully closed-loop interventions compared to the hybrid closed-loop intervention.

The number of hypoglycemia treatments (Table 4) varied across intervention arms compared to the hybrid closed-loop with an average of 1.2 treatments. During the fully closed-loop faster aspart and pramlintide interventions there were on average 0.58 ($p=0.45$) and 0.92 ($p=0.89$) at the 8 µg/U and 10 µg/U ratios, respectively, compared to on average 1 ($p=1.0$) and 0.3 ($p=0.88$) on the insulin aspart and pramlintide closed loop at the 8 µg/U and 10 µg/U ratios, respectively. Participants were instructed to correct their hypoglycemia according to their usual practice to emulate outpatient conditions.

Two adverse gastrointestinal events were reported during the study. Two participants experienced mild nausea, one of whom experienced a concurrent incident of vomiting. Both instances of nausea occurred during the run-in period preceding their aspart and pramlintide

interventions at the 10 µg/U. The resolution of the mild nausea was within a few hours for the first patient and upon completion of the intervention for the second patient. No additional interventions were needed to achieve resolution.

Discussion

Our study compared a hybrid closed-loop system with insulin alone that required carbohydrate counting to four fully closed-loop systems with faster insulin aspart and insulin aspart with pramlintide, which did not require carbohydrate counting. We observed a comparable time in range between the hybrid closed-loop intervention and the insulin and pramlintide interventions, with no considerable increase in time below the range for the insulin and pramlintide interventions. Therefore, we have concluded that these results support our plan to conduct larger, outpatient studies.

From our results, faster insulin aspart seemed to result in less hypoglycemia (<3.9 mmol/L) compared to insulin aspart, which is consistent with findings from previous trials.[137] Conversely, the faster insulin aspart and the insulin aspart resulted in similar time in hyperglycemia (>10 mmol/L) across trial arms, with a potential benefit compared to the hybrid closed-loop intervention.

Currently, co-formulations of insulin and pramlintide are in development, which will support future research efforts investigating the use of insulin and pramlintide in closed-loop systems by allowing the use of a single pump system rather than multiple pumps, one for each of the hormones.[123] These co-formulations would present a major advantage as dual-pump systems present an increased disease burden and incidence of connectivity errors, namely, insulin pumps unpairing from Bluetooth connections with continuous glucose monitors.[5] While our findings support developing insulin and pramlintide co-formulations with faster aspart and pramlintide, to

our knowledge, current co-formulations are being developed using insulin aspart. However, it is possible that further algorithmic modifications may help bridge the gap between the performance of these two insulins in fully closed-loop systems.[123]

All four insulin and pramlintide interventions decreased total insulin and bolus insulin, while three out of four interventions reduced basal insulin compared to the hybrid closed-loop intervention. The decrease in bolus insulin doses was expected as our dosing algorithm was designed to administer smaller boluses than participants' typical mealtime bolus doses, primarily to safeguard against erroneous meal detection. This fact, in conjunction with pramlintide reducing prandial insulin needs, likely attributable to its suppression of glucagon action, explains the decrease in insulin bolus doses.[138] Of note, the insulin doses measured in this study were only measured during the intervention period, from 8:00 to 22:00. If fully closed-loop nighttime insulin data were to be included in the analysis, we would expect nighttime insulin doses to remain relatively unchanged compared to hybrid closed-loop therapy, as observed in other fully closed-loop studies. Given this, we would still expect a relative decrease in insulin doses during the fully closed-loop interventions compared to the hybrid closed-loop interventions, which are not attributable to nocturnal changes.[139,6]

However, there are other advantages to decreasing insulin doses, as insulin usage is linked to weight gain and electrolyte imbalances.[140] Furthermore, subcutaneous insulin infusion is associated with pain at the injection site and lipodystrophy, which is associated with impaired insulin absorption and increased glucose variability.[141,142] These complications may be reduced with decreased insulin administration.[142]

A considerable concern with closed-loop systems is the increased risk of hypoglycemia with tight glucose control.[143] During the faster aspart and pramlintide intervention at the 10 µg/U

ratio and both the aspart and pramlintide interventions, 8 µg/U and 10 µg/U, rates of hypoglycemia were slightly increased below <3.9 mmol/L compared to the hybrid closed-loop arm. Similar results were obtained for the time <3.0 mmol/L. These reassuring hypoglycemia results do not raise any concern for future iterations of our outpatient system. However, larger, longer studies are needed to confirm this trend.

The study's strengths included its crossover, outpatient design, and the investigation of two insulins with different pharmacodynamic profiles at two different ratios. Testing the different insulin subtypes allows us to generate data about safety and efficacy of each insulin in a fully closed-loop system and for potential future co-formulations. Testing the two different insulins at two different ratios each allowed us to investigate which ratios could be both safe and effective. Ideally, lower ratios would be used to avoid the number of pharmacological agents individuals must use, therefore minimizing side effects.

Limitations of the study include its small size, short duration and supervised setting. The short duration of the study does not represent long-term glycemic outcomes. As this was a pilot study, the population was not powered to assess the differences in glycemic outcomes between interventions statistically, therefore, no firm conclusions can be established from the data. Additionally, the short time frame does not reliably depict long-term trends. Furthermore, the supervised outpatient setting is not fully representative of real-world situations. Participants may have felt restricted in performing daily living activities that could have impacted their glycemic outcomes and the presence of study staff may have impacted their eating behaviours or the treatment of their diabetes. For example, they may have felt comfortable eating larger carbohydrate meals, missing boluses, or treating hypoglycemia when they typically would not.

This fully closed-loop insulin and pramlintide system has the potential to be successful in alleviating carbohydrate counting in the outpatient, free-living setting while maintaining glycemic control. Longer and larger studies with a powered design to detect statistically significant changes are required to confirm these results.

Tables and Figures

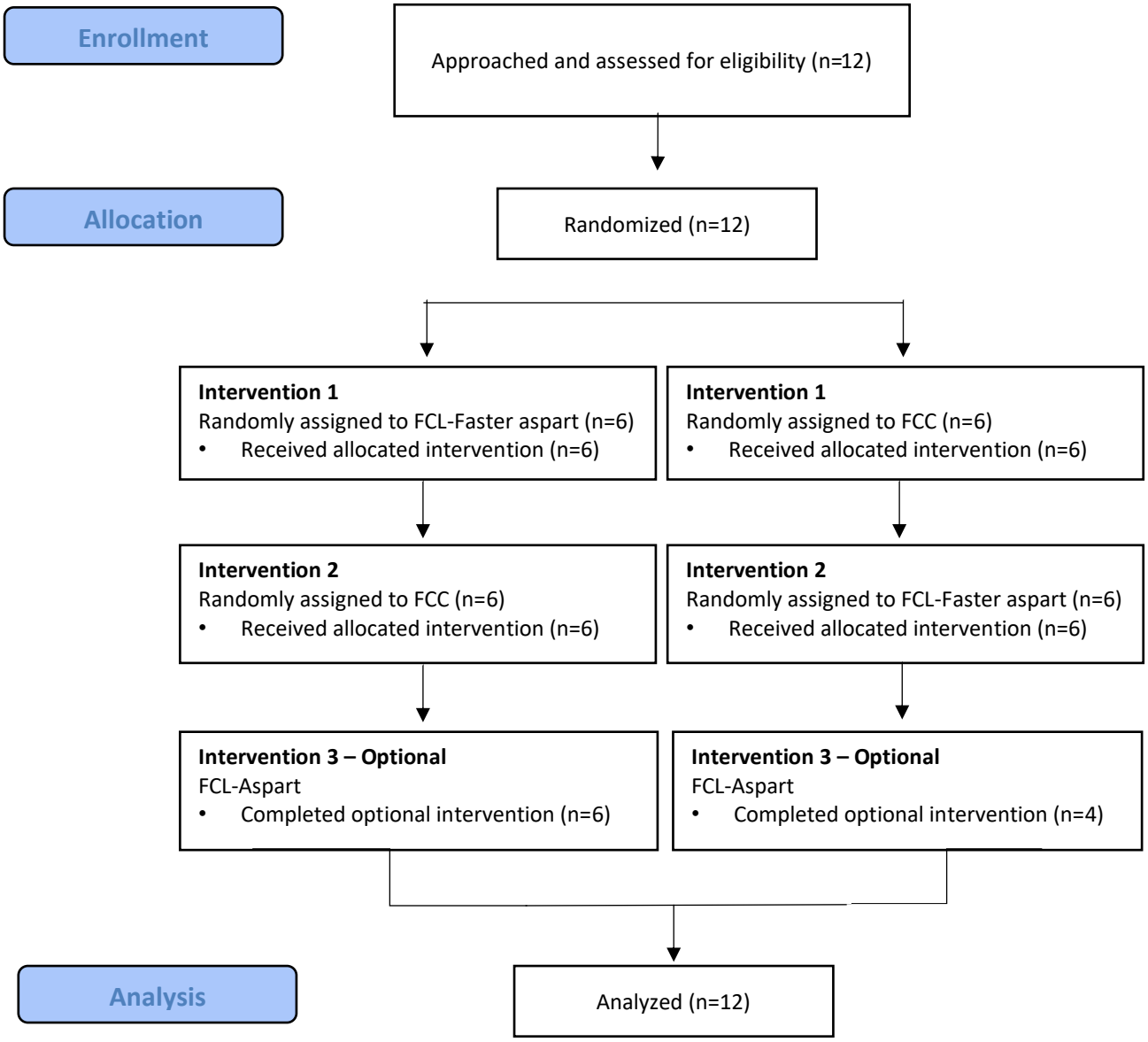

Table 2: Participant Recruitment Scheme

Table 3: Overall Glycemic Outcomes

	Insulin-alone hybrid closed-loop	Faster insulin aspart and pramlintide closed-loop 8 µg/U, IQR, p-value	Faster insulin aspart and pramlintide closed-loop 10 µg/U, IQR, p-value	Insulin aspart and pramlintide closed-loop 8 µg/U, IQR, p-value	Insulin aspart and pramlintide closed-loop 10 µg/U, IQR, p-value
Overall outcomes (n=12)					
Time spent at glucose levels (%):					
3·9–10·0 mmol/L†	78.6 [65.3-92.9]	76.2 [64.6-86.9], 0.33	78.8 [68.8-86.0], 0.24	65.9 [59.9-83.6], 0.42	77.4 [72.1-82.7], 0.30
3·9–7·8 mmol/L	51.2 [40.8-61.5]	52.4 [44.26-73.27], 0.33	54.8 [42.9-65.4], 0.41	44.6 [36.4-54.5], 0.62	44.7 [37.2-58.0], 0.36
< 3·9 mmol/L	0 [0-2.7]	0 [0-6.3], 0.12	2.46 [0-5.4], 0.20	4.8 [0.6-14.9], 0.09	2.4 [0.3-10.1], 0.09
< 3·0 mmol/L	0 [0-0]	0 [0-0] 0.58	0 [0-1.2] 0.42	1.28 [0-4.7], 0.34	0.6 [0-2.4], 0.35
> 7·8 mmol/L	50.6 [39.4-60.1]	45.8 [26.9-56.4], 0.56	46.4 [30.3-53.9], 0.29	51.8 [42.0-53.4], 0.79	51.4 [39.3-60.7], 0.90
> 10·0 mmol/L	21.4 [3.28-33.9]	19.0 [11.0-30.7], 0.24	18.8 [3.6-24.2], 0.16	23.3 [8.9-32.6], 0.35	17.9 [4.8-27.0], 0.17
> 13·9 mmol/L	0 [0-1.2]	0 [0-16.8], 0.31	0 [0-11.0], 0.70	0 [0-17.6], 0.65	0 [0,0], 0.96
> 16.7 mmol/	0 [0-0]	0 [0-6.0], 0.39	0 [0-1.9], 0.60	0 [0-8.0], 0.42	0 [0-0], 0.23
Mean glucose (mmol/L)	8.2 [7.1-8.9]	7.7 [6.9-9.4]	8.0 [7.2-8.4]	7/9 [6.9-9.0]	8.2 [6.9-8.5]
SD of glucose (mmol/L)	2.1 [1.7-2.7]	2.5 [2.1-3.4]	2.5 [2.1-3.4]	2.8 [2.4-4.3]	2.2 [1.9-2.5]
CV of glucose (%)	27.6 [22.6-31.3]	32.6 [30.1-40.5]	33.7 [27.1-40.6]	41.6 [32.7-45.9]	28.5 [24.0-32.3]
Basal Insulin (U/day)	16.4 [12.5-21.1]	18.3 [11.9-23.1]	13.9 [11.4-21.1]	13.0 [11.7-16.7]	15.0 [9.3-21.2]
Bolus Insulin (U/day)	18.5 [7.8-28.1]	9.1 [1.6-14.0]	11.8 [7.3-18.9]	13.9 [6.9-24.2]	11.4 [7.3-15.4]
Total Insulin (U/day)¶	41.6 [22.5-50.2]	25.6 [20.5-43.2]	27.1 [23.6-43.9]	28.5 [20.8-36.9]	23.3 [21.4-27.6]

*P-values are calculated by comparing each intervention to the hybrid closed-loop (control) intervention
¶For the purpose of this study, the values collected for the day are from 8:00-22:00

** Results are reported as Median [IQR]

Table 4: Insulin Dosing Algorithm Outcomes

	Insulin-alone hybrid closed-loop	Faster insulin aspart and pramlintide closed-loop 8 µg/U	Faster insulin aspart and pramlintide closed-loop 10 µg/U	Insulin aspart and pramlintide closed-loop 8 µg/U	Insulin aspart and pramlintide closed-loop 10 µg/U
Insulin Dosing Algorithm Outcomes					
Number of meals detected	3.3[§]	1.4	2.3	2.7	2.3
Number of boluses delivered	3.3	2.8	4.7	5.1	4.9
Number of hypoglycemia treatments	1.2	0.58	0.92	1.0	0.3
Number of hyperglycemia corrections	0.08	0.83	0	0	0

[¶]For the purpose of this study, the values collected for the day are from 8:00-22:00
[§] These are not detected. They are announced by the user.

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Chapter 4: Discussion

Current commercial closed-loop systems represent significant advances in diabetes management, including improving glycemic control and reducing management burden.[130] However, active participation in the form of carbohydrate counting remains a requirement to achieve optimal glycemic control.[130]

We aimed to develop a fully closed-loop insulin and pramlintide system which requires no user mealtime input, for individuals with type 1 diabetes. The dual hormone system attempts to alleviate prandial carbohydrate counting by using insulin to decrease blood glucose levels and pramlintide to delay gastric emptying and the appearance of glucose in the blood, allowing time for the insulin boluses to decrease blood glucose levels and ultimately minimize post-prandial hyperglycemia.[131]

4.1 Research in Context

Our lab has previously used pramlintide in hybrid closed-loop, simple meal announcement and fully closed-loop systems.[6,5,132,133] Our earlier studies compared insulin-alone closed-loop systems to insulin and pramlintide closed-loop systems. Both systems used full carbohydrate counting and demonstrated an improvement in time in range, largely due to improved daytime glucose control.[132] Later studies investigated pramlintide in systems which used "simple meal announcement," where users only had to input when they were eating.[5,134] The results of our pilot study investigating the simple meal announcement system compared to a hybrid closed-loop system showed the potential to alleviate the need for carbohydrate counting without degrading glucose control.[5] Results of the study comparing the simple meal announcement system with insulin-and-pramlintide demonstrated non-inferior glycemic control measured via time in the target range as compared to the insulin-and-placebo with simple meal

announcement system.[134] These previous studies were the rationale for the clinical trial presented in this thesis.

The final study which prompted the clinical trial presented in this thesis conducted in our lab assessed an open-label, randomized controlled, crossover, non-inferiority trial comparing[6]:

- A Fiasp plus pramlintide fully closed-loop system with no meal input
- A Fiasp-alone hybrid closed-loop system with precise carbohydrate counting

The study comprised two 24-hour interventions (22:00h to 22:00h) completed in random order by 24 adults with the two systems.[6] The percentage of time spent in the target range was 74.3% (IQR 61.5–82.8) with the fully closed-loop system versus 78.1% (66.3–87.5) with the hybrid Fiasp-alone closed-loop system (paired difference 2.6%, 95% confidence interval −2.4 to 12.2; non-inferiority p=0.28).[6] Delivery Overall, the Fiasp and pramlintide fully closed-loop system was not non-inferior to the hybrid closed-loop system.[6] 14 participants experienced a hypoglycemic event with the hybrid closed-loop (58% of participants) compared to eight (33% of participants) with the fully closed-loop system, thereby observing a decreased incidence of hypoglycemic events when using the fully closed-loop system.[6]

In this trial, it was posited that the lack of non-inferiority of the fully closed-loop system relative to the Fiasp-alone hybrid closed-loop system was driven by a high cohort baseline HbA1c which is associated with imprecise carbohydrate counting and compensatory high insulin-to-carbohydrate ratios.[6] In the study presented in this thesis, our cohort was relatively well-controlled, HbA1c 7.3 (6.3-8.4) compared to the previous study with HbA1c 8.1 (6.3-11.8).[6] Given our well but not optimally controlled population, we observed minimal degradations in time in range with the fully closed-loop systems, both with faster aspart and aspart with pramlintide.

This glycemic data, in addition to the fact that participants' dietary patterns were unrestricted, supports the findings in the previous study.[6] Participants were free to eat whenever they desired, however often, and whatever they desired. We noted many nutritional patterns in the study; one participant consumed a primarily lower-carb diet, while others made fresh, balanced meals multiple times daily, and some indulged in high-fat, high-sugar and/or pre-prepared foods. There were also notable differences in the times the meals and snacks were consumed, and the quantity of food consumed per day between participants. The variety in the diet composition and frequency/timing of food ingestion and greater diversity in the macronutrient composition of the meals increase our confidence in the ability of the fully closed-loop system to work in an outpatient, free-living setting.

4.2 Barriers to Fully Closed-Loop Adoption

Commercial fully closed-loop systems for individuals with type 1 diabetes are still not available to this day. There are many barriers to adopting and implementing fully closed-loop systems and many of these vary with age and socioeconomic status, amongst other factors. [83,135]

Adoption of a fully closed-loop system entails, for the most part, agreeing to wear an insulin pump and a continuous glucose monitor, relinquishing control to the system and trusting it will make accurate choices, adhering to self-care tasks relevant to the given technology, and, likely in the future, taking adjunctive medications.[136] Additionally, individuals, and when appropriate, their caregivers, need to be cognitively and emotionally ready to manage the devices in the fully closed-loop systems and solve some of the many technical or technological malfunctions which can arise and be very burdensome. [5] The willingness and motivation to adhere to the treatment, learn the intricacies and attend follow-ups should be considered when initiating new treatment.[136]

Additionally, for users to succeed at using new technologies, they must be well supported. In the Closed-Loop from Onset in Type 1 Diabetes trial also termed the CLOuD trial, participants reported that the teaching and support for individuals is initially more time-consuming with a closed-loop system compared to other insulin regimens.[137] However, they also remarked that after the initial adjustment, they expressed less of a need to contact their healthcare team compared to those on insulin pumps or injection therapy.[137] Yet, this decreased contact could also manifest in fewer opportunities to affirm their diabetes knowledge and detect psychosocial problems.[137] The participants of the Closed-Loop from Onset in Type 1 Diabetes trial essentially highlighted the importance of their local diabetes teams in having comprehensive knowledge and a deep understanding of the closed-loop systems to support them in their routine care and provide clinical guidance.[137]

Lastly, an essential element to consider in adopting new technologies and medications is the cost, as high costs often dampen the widespread adoption of new technologies.[138] In fact, a study by Gillard et al. demonstrated that nationwide reimbursement of intermittently scanned continuous glucose monitor in people with type 1 diabetes results in higher treatment satisfaction, less severe hypoglycemia and less work absenteeism while maintaining quality of life and HbA1c.[138]

The system that we used indeed presents a large cost barrier. Between the two continuous infusion pumps, their infusion sets, the continuous glucose monitor, and the dual hormones, insulin and pramlintide, the system is costly. However, in Quebec, where the study was conducted, insulin pumps are covered for individuals initiating continuous subcutaneous insulin infusion therapy in childhood, thereby reducing the cost for the patients.[58] Further, continuous glucose monitors are covered for the entire population and drug costs are much lower than in

other countries, especially the USA.[139] Lastly, insulin and pramlintide co-formulations and dual chamber infusion pumps are being investigated, which would decrease both the number of devices as well as the costs associated with the therapy, increasing the feasibility of implementation and adoption of our system.[140,141]

4.3 Current Strategies to Increase Safety and Efficacy of Closed-Loop Systems

As outlined in the introduction of this thesis, autoimmune destruction of the pancreatic beta cells in type 1 diabetes decreases not only insulin production but amylin as well, in addition to having multiple systemic effects on whole body metabolism, namely in the hypothalamic-pituitary axis and glucagon secretion.[142] This dysfunction serves as the rationale for the addition of glucagon and pramlintide to our closed-loop systems.

Insulin and glucagon dual-hormone systems have demonstrated a reduction in both hyperglycemia and hypoglycemia compared to usual care insulin pump therapy, both with and without meal announcement.[143,144,145] However, apprehensions remain about using glucagon as it is a hyperglycemic agent. The trouble is that an episode of hypoglycemia can become severe and require extra carbohydrates and/or glucagon to raise blood sugar levels to prevent death and other complications.[146] Also, repeated incidences of hypoglycemia lead to a reduced capacity for response to hypoglycemia, known as hypoglycemia-associated autonomic failure.[146] Hypoglycemia-associated autonomic failure lowers the glucose threshold prior to the epinephrine surge and blunts autonomic symptom responses to subsequent hypoglycemia. This threshold change causes defective glucose counter-regulation and a lack of hypoglycemia symptoms, leading to hypoglycemia unawareness.[146,147] This dysregulation leads to a cycle of recurrent hypoglycemia with a reduced capacity to respond to future hypoglycemia.[146] The aforementioned information continues to increase hesitancy surrounding glucagon use in closed-loop systems.

Another class of drugs being investigated in closed-loop systems is SGLT2i.[148] Pasqua et al. posit that SGLT2i can improve glycemic outcomes, optimize insulin doses, alleviate carbohydrate counting and improve metabolic outcomes while reducing complications.[148] Indeed, improvements in time in range have been observed when using two doses of empagliflozin, 2.5mg and 5mg.[111] The time in range was 59.0 ± 9.0% for placebo, 71.6 ± 9.7% for 2.5 mg empagliflozin, and 70.2 ± 8.0% for 5 mg empagliflozin ($P < 0.0001$ between 2.5 mg empagliflozin and placebo and between 5 mg empagliflozin and placebo) on hybrid closed-loop therapy.[111] However, the risk of diabetic ketoacidosis remains the largest barrier for the implementation of SGLT2i use both in type 1 diabetes and in closed-loop therapy.[148] Pramlintide does not suffer from the same risk of increased diabetic ketoacidosis or infections as SGLT2is.[148,149]

Our lab is currently investigating the use of GLP-1 receptor agonists in a double-blinded, randomized, two-way crossover, outpatient trial. Each intervention consists of 12 weeks of dose titration of the study drug (semaglutide or placebo) and insulin. This is followed by three weeks of closed-loop therapy on the maximum tolerated dose of the study drug. The first 11 weeks will be on the participant's routine insulin pump therapy, and the last four weeks will be on the closed-loop insulin system. The primary outcome of the study investigates time in range. GLP-1 receptor agonists remain an attractive option for closed-loop therapy as they have the potential to increase time in range safely while having additional weight loss benefits, among others.[103] Their widespread use in type 1 diabetes remains to be investigated.

Recently, a new molecule has made its way into the literature; Tirzepatide.[153] Tirzepatide combines dual glucose-dependent insulinotropic polypeptide and GLP-1 receptor agonism to exert its effects. Its safety and efficacy have been extensively studied for type 2 diabetes and

weight loss in the SURPASS and SURMOUNT trials, respectively.[150] Given these positive effects, future studies are warranted to investigate the safety and efficacy of this molecule in type 1 diabetes, particularly with the growing co-morbid obesity epidemic.

Chapter 5: Conclusion

In this thesis, we tested the efficacy of a fully closed-loop insulin and pramlintide system at controlling blood glucose levels in an outpatient supervised setting in a pilot-sized trial. We compared faster-acting insulin aspart at two ratios in a hybrid closed-loop system and a full carbohydrate counting with faster-acting insulin aspart in a fully closed-loop system requiring no carbohydrate counting. An additional interventional arm was added using insulin aspart in a fully closed-loop system requiring no carbohydrate counting. Participation in the additional interventional arm was optional.

The faster aspart alone hybrid closed loop system achieved a mean time in range (3.9-10.0 mmol/L) of 72.4% with a standard deviation of (25.2%). The faster aspart and pramlintide fully closed-loop system achieved a mean time in range of 71.9% (24.2%) at a 1U/8g ratio and 78.7% (13.8%) at a 1U/10g ratio. The aspart and pramlintide fully closed-loop system achieved a mean time in range of 70.4% (14.73%) at a 1U/8g ratio and 77.4% (11.3%) at a 1U/10g ratio. While the faster aspart and pramlintide system outperformed the aspart and pramlintide system at both ratios, the time in range for the latter was still above the recommended 70%. These results demonstrate that both insulin formulations can be viable options in fully closed-loop systems with pramlintide. These findings may therefore, help support the development of novel insulin and pramlintide co-formulations and provide justification for their use in fully closed-loop systems.

However, these data represent the collection from only 12 participants, in an outpatient supervised trial, and therefore size and circumstance limitations are present. Future longer, free-living, larger studies will need to be conducted to confirm the findings presented in this thesis and strength the evidence for the use of a dual-hormone system.

Fully closed-loop systems would eliminate carbohydrate counting and the errors associated with carbohydrate estimation and prandial bolus omissions, hopefully resulting in improved glycemic control and long-term reductions in diabetes-related complications. In addition, elimination of carbohydrate counting would eliminate the disease management burden associated with the practice, allowing the burden of diabetes to be reduced. However, many considerations must be made, and guidelines will need to be formulated before widespread implementation of fully closed-loop systems. Elements to be considered in these decisions include age of initiation, instruction on traditional techniques in case of technological failure, user/patient suitability, and cost among others. Finally, we must always remain cognisant of the limited adoption of technological solutions to treat type 1 diabetes worldwide.-Worldwide, type 1 diabetes remains largely managed by multiple daily injections for reasons, including cost and preference. When creating technological solutions, we must prioritize patient-informed approaches to have the most meaningful impact.

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