Alleviating the burden of carbohydrate counting with an insulin-and-pramlintide closed-loop system for people living with type 1 diabetes

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April 2022

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master's of Science.

Abstract

Treatment regimens for the management of type 1 diabetes are quite demanding, which can make reaching recommended targets difficult. Closed-loop systems, also called artificial pancreas systems, are known to ameliorate both glycemic and psychosocial outcomes for affected individuals. Existing systems, however, rely on users to announce the carbohydrate content of their meals to calculate appropriate insulin boluses. This is a complex practice which carries the potential for errors, further challenging disease management.

This thesis focuses on investigating the psychosocial impact of a novel fast-acting insulin (Fiasp, NovoNordisk, Bagsværd, Denmark)-and-pramlintide closed-loop system with a simple meal announcement strategy, designed to reduce the burden of carbohydrate counting without degrading glucose control. This system was first evaluated in an inpatient feasibility study (4 adults, 35.0 ± 16.3 years (range: 20.5 to 56.0 years), HbA1c 8.5 ± 0.4% (7.9 to 8.9%), and 3 adolescents, 14.4 ± 1.2 years (13.0 to 15.3 years), HbA1c 8.3 ± 1.3% (7.4 to 9.8%)), and then in an outpatient pilot study (4 adults, 50.1 ± 7.3 years (39.2 to 55.0 years), HbA1c 7.7 ± 0.4% (7.2 to 8.2%)). In both cases, time spent in target range (3.9-10.0 mmol/L) on the Fiasp-and-pramlintide arm with simple meal announcement was similar to that on the Fiasp-alone arm with full carbohydrate counting. Pilot analyses suggest participants' eating habits were rendered more flexible, and their mealtime concerns alleviated, while on the system. A larger scale crossover trial assessing the qualitative experience of 15 adults (39.4 ± 13.8 years, HbA1c 7.2 ± 0.9%) and 15 adolescents (15.6 ± 1.3 years, HbA1c 8.4 ± 0.9%) using this system is currently underway.

Résumé

Les traitements conçus pour la gestion du diabète de type 1 sont laborieux, ce qui peut rendre difficile l'atteinte des cibles glycémiques recommandées. Les systèmes à boucle fermée, aussi appelés pancréas artificiels, améliorent, chez les individus concernés, à la fois leurs résultats glycémiques et psychosociaux. Cependant, les systèmes qui existent aujourd'hui demandent des utilisateurs qu'ils indiquent la teneur en glucide de leurs repas afin de calculer des bolus d'insuline appropriés. Cette pratique complexe peut mener à des erreurs, compliquant davantage la gestion de la maladie.

Cette thèse se concentre sur l'étude de l'impact psychosocial d'un nouveau système à boucle fermée avec insuline à action rapide (Fiasp, NovoNordisk, Bagsværd, Denmark) et pramlintide, ainsi qu'une stratégie d'annonce de repas simplifiée, conçue pour réduire le fardeau du calcul de glucides sans dégrader le contrôle de la glycémie. Ce système a d'abord été évalué dans une étude de faisabilité à l'hôpital (4 adultes, 35,0 ± 16,3 ans (plage : 20,5 à 56,0 ans), HbA1c 8,5 ± 0,4 % (7.9 à 8.9 %), et 3 adolescents, 14,4 ± 1.2 ans (13,0 à 15,3 ans), HbA1c 8,3 ± 1,3 % (7.4 à 9.8 %)), puis dans une étude pilote ambulatoire (4 adultes, 50,1 ± 7.3 ans (39,2 à 55,0 ans), HbA1c 7,7 ± 0,4 % (7.2 à 8.2 %)). Dans les deux cas, le temps passé dans la plage cible (3,9-10,0 mmol/L) pendant l'intervention Fiasp et pramlintide avec annonce simplifiée de repas était similaire à celui de l'intervention Fiasp seule avec calcul de glucides. Des analyses pilotes suggèrent que les habitudes alimentaires des participants ont été assouplies et que leurs inquiétudes au sujet des repas ont été réduites avec l'utilisation du système. Un essai croisé randomisé à plus grand échelle étudiant l'expérience qualitative de 15 adultes (39,4 ± 13,8 ans, HbA1c 7,2 ± 0,9 %) et 15 adolescents (15,6 ± 1,3 ans, HbA1c 8,4 ± 0,9 %) utilisant ce système est actuellement en cours.

Acknowledgements

I would like to begin by thanking my supervisor, Dr Ahmad Haidar, for his incredible support, patience, and guidance over these last few years; I am honored to have been able to work alongside you, and have learned and grown beyond my wildest expectations.

To my parents, I would like to express my deepest gratitude for the unconditional support and faith you've given me my entire life; it is only thanks to you that I have the confidence to pursue my dreams, whatever they may be.

To Hedya and Juliette, who are more than family, thank you for being my biggest and loudest cheerleaders; you are the silver lining to two years spent cooped up at home.

I would like to thank our wonderful team of endocrinologists, Dr Michael A. Tsoukas, Dr Laurent Legault, Dr Julia E. Von Oettingen, Dr Jean-Francois Yale, and Dr Natasha Garfield, as well as Dr Michael Vallis and Dr Preetha Krishnamoorthy, for your guidance and support throughout these studies; a special thank you to Emilie Palisaitis and Nikita Gouchie-Provencher for your mentorship and constant encouragement.

I am incredibly grateful to the Research Institute of the McGill University Health Centre, the Canadian Institutes of Health Research, and the Experimental Medicine Division of McGill University for their financial support.

Finally, I would like to extend an immense thank you to the participants of these studies for their curiosity, enthusiasm, and for sharing so much of their time, lives, and experiences with me.

Contributions of Authors

In this thesis, a Fiasp insulin-and-pramlintide closed-loop system designed to reduce the burden of carbohydrate counting was tested in an 8-participant feasibility, a 4-participant pilot study, and a 30-participant outpatient trial.

My contributions to this thesis were the design and conduct of the pilot study and subsequent trial, including participant recruitment, training, and follow-up, as well as amending trial documentation and communicating with the Research Ethics Board and Health Canada; I also wrote the manuscript and carried out a qualitative analysis of the participant interviews.

Dr Michael A. Tsoukas, first co-author and principal investigator, contributed to all three of the studies' design, supervision, and conduct, admitting and following participants for the duration of the studies, as did Dr Laurent Legault, Dr Julia E. Von Oettingen, Dr Jean-Francois Yale, and Dr Natasha Garfield. Dr Michael Vallis contributed to the design of the pilot and larger study, and provided support throughout the qualitative data analysis process, which was conducted in collaboration with Madison Odabassian. Jennifer René and Emilie Palisaitis helped design and conduct the studies; Nikita Gouchie-Provencher also contributed to the studies' conduct. Anas El Fathi, Joanna Rutkowski, Adnan Jafar, and Milad Ghanbari carried out statistical data analysis. Dr Ahmad Haidar developed the novel algorithm investigated, oversaw each study's design and conduct, and co-wrote the manuscript.

Chapter 1. Introduction

1.1. Objective and hypothesis

People living with type 1 diabetes require lifelong, exogenous insulin supplementation, administered through different technologies, to maintain their blood glucose levels within a healthy range. Despite closed-loop insulin systems being the closest devices to approximating normal, physiological hormone delivery, achieving desired glucose levels after meals using insulin alone remains challenging for optimal disease management.

The McGill Artificial Pancreas team has previously had success with improving glucose control using a rapid insulin-and-pramlintide closed-loop system that administers both hormones at a fixed ratio, mimicking normal physiology.[1] The objective of this thesis is to investigate whether the glycemic advantage gained by the co-administration of Fiasp and pramlintide in a novel closed-loop system could be mobilized to alleviate one of the burdens associated with diabetes management, namely, carbohydrate counting. To this end, this system was first tested in a feasibility study, followed by a pilot study, and finally a randomized crossover trial.

I conducted the pilot study and subsequent randomized, blinded, crossover trial which compared the three following interventions:

(i) A Fiasp-and-pramlintide closed-loop system with a simple meal announcement meal strategy

(ii) A Fiasp-and-placebo closed-loop system with a simple meal announcement meal strategy

(iii) A Fiasp-and-placebo closed-loop system with a full carbohydrate counting meal strategy

While these trials assessed both glycemic and qualitative outcomes, this thesis focuses on understanding the psychosocial impacts of the closed-loop system evaluated. This will be evaluated through the change in scores of diabetes-specific quality-of-life surveys, as well as thematic content analysis of structured interviews.

We hypothesize that the co-infusion of pramlintide at a fixed rate with Fiasp insulin, in conjunction with a meal strategy that removes the need for carbohydrate counting and replaces it with a simple meal announcement function, will improve participants' quality of life compared to a system with Fiasp insulin-and-placebo with carbohydrate counting.

1.2. Thesis outline

This thesis first summarizes the physiology behind the development of type 1 diabetes, along with basic disease characteristics such as presentation, epidemiology, and complications. An extensive appraisal of existing treatments and devices available to people living with type 1 diabetes follows, with a focus on the current landscape of closed-loop technologies, in both their commercial and experimental forms. The central role of carbohydrate counting in type 1 diabetes management is examined, as this is the practice targeted by the novel closed-loop system. The published manuscript presented in this thesis describes the results of the feasibility and pilot studies evaluating the experimental system. Finally, the qualitative impact of closed-loop systems, as described in literature, and through thematic analysis of participant interviews, is discussed.

Chapter 2. Background and Literature review

2.1. Type 1 Diabetes

2.1.1. Physiology

As glucose is the brain's main source of energy,[2] several complex mechanisms ensure that a stable, continuous supply of the molecule is maintained in the bloodstream. Clusters of pancreatic cells known as the islets of Langerhans release hormones responsible for maintaining glucose homeostasis in vertebrates:[3]

- Insulin, secreted by β-cells, and glucagon, secreted by α-cells, are the two key players involved in attempting to keep blood sugar within a narrow range of 4.0-6.0 mmol/L through opposing blood glucose lowering and elevating properties, respectively.
- Amylin, also released by β-cells, has glucose-lowering effects; somatostatin is released by δ-cells and exhibits inhibitory control over both insulin and glucagon.

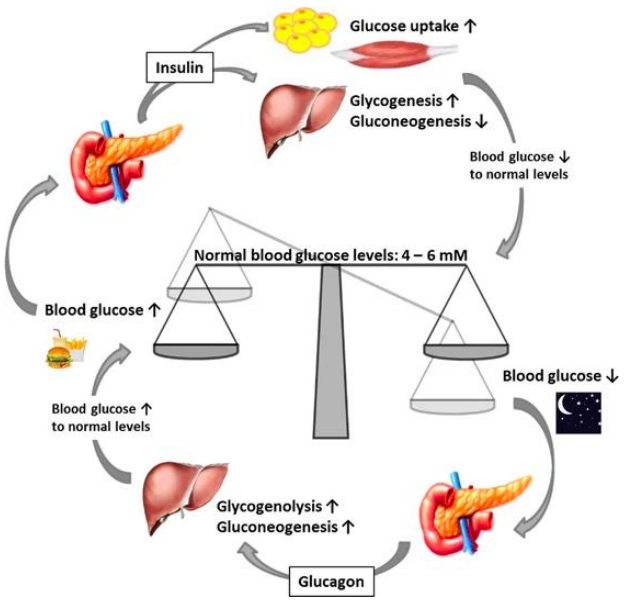

Figure 1: Maintenance of blood glucose levels by glucagon and insulin. When blood glucose levels are low, the pancreas secretes glucagon, which increases endogenous blood glucose levels through glycogenolysis. After a meal,

when exogenous blood glucose levels are high, insulin is released to trigger glucose uptake into insulin-dependent muscle and adipose tissues as well as to promote glycogenesis.[3]

The tight balance between insulin and glucagon secretion is partly dependent on circulating blood glucose levels: when they rise following a meal, pancreatic insulin secretion is triggered, and its plasma concentrations increase up to 4-fold.[2] Once in circulation, insulin stimulates glucose storage as glycogen (glycogenesis) in skeletal muscle cells and as triglycerides in adipocytes.[4] Insulin binds it receptors on these cells' membranes, initiating a signaling cascade that increases the quantity of GLUT-4 transporters on their surface to allow glucose entry through passive transport due to elevated circulatory levels. Insulin also signals the cessation of glucose production through liver gluconeogenesis,[4] and binds to specific alpha cell receptors in the pancreas to inhibit glucagon secretion.[5]

Conversely, when blood glucose levels drop, glucagon is released by pancreatic α-cells as a protective measure against hypoglycemia (low blood glucose levels), to ensure the brain's energy source is preserved.[5] Glucagon stimulates liver glycogenolysis and gluconeogenesis, and suppresses glycogenesis and glycolysis to preserve the glucose remaining in circulation.[5]

In a healthy pancreas, these two hormones work in tandem to achieve blood glucose levels necessary for proper brain function, such that, over the course of the day, circulating blood glucose levels average out to approximately 5.0 mmol/L or 90 mg/dL, varying within the following range:[2]

- A maximum of 9.2 mmol/L or 165 mg/dL following a meal
- A minimum of 3.1 mmol/L or 55 mg/dL between meals (i.e. fasting) or following exercise

Type 1 diabetes is a chronic illness thought to be caused by the autoimmune destruction of insulin-producing pancreatic cells.[6] Initially, the elevated blood glucose levels (hyperglycemia) characteristic of type 1 diabetes were thought to be exclusively a consequence of insulin loss.[7] However, in the absence of insulin, both direct and indirect regulatory effects are lost and glucagon

secretion is unrestrained: the bihormonal hypothesis postulates that it is the combined dysregulation of both these hormones, and the subsequent loss of their counter-regulatory activities, that contributes to disease pathogenesis.[7]

In red blood cells, the A1c component of the hemoglobin A molecule normally reacts with glucose to form a ketonimine, known as glycated hemoglobin A. The rate of glycated hemoglobin formation is proportional to the concentration of glucose in the blood. Given that blood cells have a life cycle of 90-120 days, glycated hemoglobin (HbA1c) is used as a retrospective indicator of a person's average blood glucose levels over that timeframe.[8,9]

2.1.2. Presentation and diagnosis

Type 1 diabetes was historically thought of as a disease of childhood, as 50-60% of cases present in youth below 16-18 years of age,[10] with peaks in disease presentation at 5-9 years old, then again at puberty.[11] Although symptoms may vary, the loss of insulin and its glucoregulatory effects result in chronic hyperglycemia, eliciting a triad of characteristic symptoms upon disease presentation: polydipsia (excessive thirst), polyuria (excessive urination), and polyphagia (excessive hunger).[6,12] Additionally, one third of patients present with life threatening diabetes ketoacidosis (DKA), a condition caused by an acid shift in the blood due to ketone formation from excess gluconeogenesis and lipolysis in the absence of insulin.[13,14]

Diabetes can be diagnosed by any of the following means:[9,12]

- Fasting blood glucose levels above 7 mmol/L (126 mg/dL)
- Blood glucose levels above 11.1 mmol/L (200 mg/dL) at any time of the day, with accompanying symptoms
- A glycated hemoglobin (HbA1c) test result above or equal to 6.5%

- Blood glucose levels above 11.1 mmol/L (200 mg/dL) following an oral glucose tolerance test

Confirmation of type 1 diabetes is typically done via assessment of islet autoantibodies, followed by C-peptide testing (the by-product of proinsulin cleavage upon insulin secretion, used as a marker for sustained insulin production) and genetic testing if results are inconclusive.[12,15,16]

2.1.3. Epidemiology

Type 1 diabetes makes up only 5-10% of all cases of diabetes across the world,[10,17] while type 2 diabetes comprises the near totality of the rest (80-90%).[9] In type 2 diabetes, peripheral resistance to insulin leads to a period of increased insulin production in an attempt to maintain normoglycemia which ultimately exhausts and/or causes β-cell dysfunction, elevating blood glucose levels.[9,18] Studies suggest that 5-15% of type 2 diabetes diagnoses may actually correspond to cases of type 1 diabetes.[19] The prevalence (existing cases) of type 1 diabetes globally currently stands at 0.095%, and its incidence (new cases) is on the rise.[20] However, incidence varies around the world: Venezuela and China report rates as low as 0.0001% per year, whereas Finland and Sardinia report rates of 0.06% per year and 0.04% per year, respectively.[21] In Canada, the prevalence of diabetes in 2021 was estimated to be 10%, with 5-10% of that population (or 0.5%-1% of the total population) having a diagnosis of type 1 diabetes.[22] Disease prevalence and outcomes are also influenced by socioeconomic factors: cross sectional analyses in Canada have shown that earning a low income and belonging to a visible minority group were significantly associated with a diagnosis of type 2 diabetes,[23] while, for people with type 1 diabetes, low income was significantly associated with elevated HbA1c levels and an increased risk of disease complications.[24]

2.1.4. Pathophysiology and natural history

The Eisenbarth model (the most commonly accepted model for the natural history of type 1 diabetes) proposes that certain individuals have a genetic predisposition to pancreatic β-cell autoimmunity, which is activated after an encounter with an environment trigger.[25] More than 40 putative loci are associated with this dysfunctional immune response. The insulin-dependent diabetes mellitus (IDDM) 1 locus on chromosome 6p21.3 has been identified as providing up to 50% of the genetic susceptibility of type 1 diabetes: it contains the human-leukocyte antigen genes (HLA DR/DQ) responsible for shaping the immune response and developing its tolerance via antigen presentation.[26]

In the appropriate environment, this genetic predisposition may lead to an exaggerated immune response to benign autoantigens like insulin or the islets cells themselves.[10] Possible environmental triggers include viruses (rubella and enteroviruses), toxins, and foods such as wheat, gluten, and cow's milk.[25,27] A higher reported incidence of disease in the winter and fall suggests the existence of weather-specific antigens.[27] The rapid rise in disease incidence has been attributed to environmental rather than genetic (thus evolutionary) factors. The hygiene hypothesis proposes that societal changes such as modernization, smaller families, and removal of children from daycare leads to less exposure to environmental antigens early in life.[10] These immune challengers are crucial to the development of the immune system, and their absence increases susceptibility to atopic disease, possibly extending to type 1 diabetes.[28] A rise in childhood obesity has also been studied as a potential trigger, as metabolic effects increase insulin demands thought to accelerate β-cell damage in genetically predisposed individuals.[27]

Once the immune response is activated, CD8 T cells and macrophages mediate the destruction of pancreatic β-cells, assisted by CD 4 helper T cells and antibody producing B cells.[6]

However, clinical symptoms do not appear until a critical mass of 80-90% of β-cells have been destroyed.[6,27] In the early, asymptomatic or "silent" stage of the disease, type 1 diabetes specific antibodies can be detected, such as islet cell autoantibodies (ICAs), glutamic acid decarboxylase autoantibodies (GADAs), insulin autoantibodies (IAAs), transmembrane tyrosine phosphatase autoantibodies (IA2As), and ZnT8 autoantibodies (ZnT8As).[27] Screening for these markers in relatives of newly diagnosed patients can help with early disease detection and management.[6,12]

2.1.5. Complications

Type 1 diabetes and its treatment are associated with both long- and short-term risks.

Macrovascular disorders relate to cardiovascular diseases (ex: coronary heart disease) that arise as a consequence of chronic hyperglycemia. This is a major cause of morbidity and mortality for men and women with type 1 diabetes, who, respectively, have a four- to seven-fold greater risk of myocardial infarction, stroke, and coronary revascularization.[29]

Microvascular disorders generally refer to a triad of hyperglycemia-related complications frequently observed in patients with long term illness: diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy.[10] Patients must be regularly screened for these conditions following diagnosis.

When insulin levels are low, elevated glucose levels, continued lipolysis, and protein catabolism lead to an accumulation of ketone bodies and a subsequent excess of acid in the blood, a condition known as diabetic ketoacidosis (DKA).[13] Symptoms range from dehydration, vomiting, and abdominal pain, to loss of consciousness and hospitalization in rare cases; more severe complications include cerebral edema, neurological damage due to brain hemorrhages, and death.[13] DKA can arise when insulin needs are elevated following illness or infection, in periods of psychological stress, in the absence of compliance with one's insulin regimen (to avoid

hypoglycemia or manage weight), or even device (pump) malfunction, wherein proper insulin delivery is impeded.[13] DKA rates are elevated in children, ethnic minorities, and those with poor control.[30]

Hypoglycemia may occur in cases of overtreatment, unexpected meal delays, inaccurate carbohydrate counting, and physical activity.[31] Mild symptoms include difficulty concentrating and confusion; cognitive impairment can arise over the long term, and severe cases can lead to seizure, comas, and death.[31] Fear of hypoglycemia is a well-documented psychological phenomenon of importance to clinicians as it can impact treatment behaviour, sleep, and social functioning.[31]

2.2. Treatment and management strategies

2.2.1. Intensive insulin therapy

Intensive insulin therapy attempts to mimic endogenous insulin secretion by delivering *basal* insulin to control fasting blood glucose levels, and intermittent insulin *boluses* to cover prandial requirements as well as to correct glycemic excursions. Several parameters must be taken into consideration when calculating a meal and/or correction bolus: the carbohydrate content of a meal, a person's insulin-to-carbohydrate ratio(s) (ICR), corresponding to the amount of carbohydrates covered by a unit of insulin, their insulin sensitivity factor(s) (ISF), indicating by how much a person's glycemia is reduced for a given unit of insulin, and the glycemic target they aim to reach with their bolus.

The landmark Diabetes Control and Complications Trial (DCCT)[32] and its near 20-year follow up, the Epidemiology and Diabetes Interventions and Complications study,[33] demonstrated that intensive insulin therapy successfully reduces both micro- and macrovascular complications; it has since become the gold standard treatment for type 1 diabetes. The DCCT was also the first

to demonstrate an association between reduced HbA1c levels and preventing the development of long-term complications.[32] As such, the American Diabetes Association recommends that non-pregnant adults and most children with type 1 diabetes aim to achieve HbA1c levels of less than 7%; higher targets (up to 7.5% or 8%) are preferred for special populations, such as those living alone with hypoglycemia unawareness or children who cannot articulate symptoms of hypoglycemia; conversely, pregnant individuals should seek to attain more stringent targets (less than 6% or 6.5%) to avoid congenital anomalies or other complications.[34–36]

2.2.2. Multiple daily injections and Continuous subcutaneous insulin infusion

Multiple daily injection (MDI) therapy is defined as the administration of three or more insulin injections per day.[37] At least one injection of long-acting insulin accounts for the basal component of insulin therapy, while rapid-acting insulin boluses are injected at meals and as correction boluses (Figure 2A). With continuous subcutaneous insulin infusion (CSII), rapid-acting insulin is continuously infused by an insulin pump via a subcutaneous catheter.[37] Meal and correction boluses can be administered via the pump using pre-programmed glycemic targets, ICR, and ISF values, and different basal rate profiles can be selected if requirements vary. Additionally, pumps account for previously administered and active insulin (insulin-on-board or iOB) when calculating future boluses (Figure 2B).

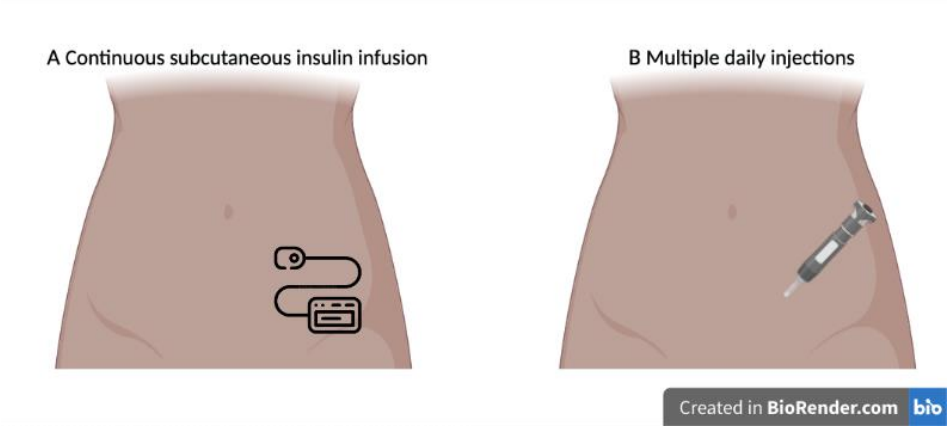

Figure 2: Use of continuous subcutaneous insulin therapy (panel A) and multiple daily injections (panel B) to meet basal/bolus insulin needs (created with BioRender.com).

There is no clear evidence suggesting whether one treatment strategy is superior to the other. While some studies propose a modest improvement in HbA1c and hypoglycemia on CSII therapy versus MDI,[38] the greater cost of CSII therapy[39] as well as its complexity[37] limit its widespread implementation, and MDI therapy remains more common across the world. The National Institute for Health Care and Excellence recommends CSII therapy for children above 12 years old, adults who struggle with disabling hypoglycemia on MDI therapy, those with an HbA1c greater than 8.5%, and children for whom use of MDI therapy is considered unfeasible.[40]

2.2.3. Technologies

2.2.3.1. Continuous Glucose Monitors

Regardless of the treatment strategy employed, a crucial part of proper diabetes management is routine self-monitoring of blood glucose (SMBG) at least 4 times a day, before and after meals, and prior to the administration of treatments for both hypo- and hyperglycemic events.[41] Continuous glucose monitors eliminate the need for the bulky, at times embarrassing lancets and glucose meters used in SMBG.[41] They are composed of a sensor with a subcutaneously inserted electrode which measures interstitial glucose concentrations that are relayed to a receiver or smartphone application via a transmitter.[42] Sensors can be inserted in the abdomen or arm, and either display measurements in real time (Dexcom G6, Dexcom, San Diego, CA, USA; Guardian sensor 3, Medtronic, Northridge, CA, USA) or upon intermittent scanning of the sensor/transmitter (FreeStyle Libre, Abbott Diabetes Care, Alameda, CA, USA).

Guardian 3 sensor

Dexcom G6 sensor and share devices

FreeStyle Libre

Figure 3: Commercial continuous glucose monitors currently available in Canada

Continuous glucose monitoring has been shown to improve glycemic control, reduce the occurrence of hypoglycemia, and provide patients with a better understanding of their diabetes through careful monitoring and the identification of specific patterns of glycemic variation.[41] Use of glucose sensors in combination with both pump[43] and MDI[44] therapy reduces HbA1c levels as well as glycemic variability; however, most improvements are observed when sensors are used at least 70% of the time.[45] Glucose sensors measure glycemic control using the percentage of time glucose levels spend in a defined range, which can then be extrapolated to a corresponding HbA1c level: for instance, 70% of time spent in the target range of 3.9-10.0 mmol/L (70-180 mg/dL) strongly corresponds to an HbA1c level of 7%.[45]

Use of glucose sensors has increased more than two-fold over the past decade, and more than ten-fold in the pediatric population, although uptake remains marked by age and racial disparities, as well as across the globe: sensor use rates vary from 22% in Canada, to 30% in the United States, and 48% of children in Europe.[46–48] Additionally, matters of cost and difficulty of access, issues related to device visibility or frustration at alarms, as well as an emotional and cognitive burden associated with receiving overwhelming amounts of information with device use, have limited more generalized use of glucose sensors.[41]

2.2.3.2. Predictive Low Glucose Suspend

Anxiety and fear due to hypoglycemia can disturb sleep, and repeated hypoglycemic events can lead to cognitive impairments.[31] This has motivated the development of predictive low glucose suspend (PLGS) systems in an attempt to prevent nocturnal hypoglycemia when sensor alerts alone cannot. Rather than simply suspending insulin delivery when sensor readings fall below a certain threshold (low glucose suspend), a predictive algorithm suspends insulin delivery prior to reaching this threshold to avoid it altogether.[49] Several studies evaluating the Medtronic PLGS system demonstrated that it successfully reduced overnight hypoglycemia in children,[50] adults,[50] and at-risk populations with hypoglycemia unawareness,[51] without significantly increasing blood glucose levels thanks to the automatic resumption of insulin delivery after 2 hours. Similar results were seen with the Tandem Basal IQ PLGS (Tandem Diabetes Care, San Diego, CA, USA).[52]

2.2.3.3. Closed-Loop Systems

Closed-loop systems are the most recent advance in diabetes technologies, with the first commercially available system receiving FDA approval in 2016.[53] Closed-loop systems combine CSII and glucose sensor technology with an algorithm to adjust insulin delivery based on continuous blood glucose measurements. Hybrid closed-loop systems refer to those which require users to input the carbohydrate content of their meals to calculate corresponding carbohydrate-matched boluses. In contrast, fully closed-loop systems do not require user inputs in the form of pre-meal boluses, and adjust basal insulin exclusively based on glucose sensor readings. The most commonly used closed-loop algorithms are proportional-integral-derivative controllers which adjust insulin based on past and current changes in blood glucose and their departures from target levels, and model predictive controllers which make adjustments based on mathematical models of predicted changes in glucose values that account for a variety of parameters (insulin absorption

rates, meal intake and boluses…).[54] These systems increase time spent in the target glucose range by ~10% (or 2.5 hours per day) and decrease overall and nocturnal hypoglycemia, while providing a moderate reduction in HbA1c (0.3%).[55] In addition to their clinical advantages, closed-loop systems have been reported to provide psychosocial benefits to both users and their support systems by alleviating certain burdens associated with diabetes management.[56,57]

2.2.4. Insulins

In 1921, Banting and Best were the first to successfully extract insulin from an animal pancreas and test its therapeutic effects.[58] Protamine and zinc were added to formulation of animal insulins in the 1930s to slow down their release through hexamer formation and reduce the number of injections required for effective control.[59] Neutral protamine Hagedorn (NPH) (intermediate-acting) insulin and regular (short-acting) insulin, synthesized through recombinant DNA technology, were used early on in basal/bolus therapy.[59] Today, these insulins have largely been replaced by insulin analogs, synthesized products with one or two amino-acid modifications that enhance their pharmacokinetic and pharmacodynamic profiles to improve stability, affinity to insulin receptors, and/or hexamer breakdown for better absorption:[16]

- Long-acting (glargine, detemir) and ultra-long acting (degludec) analogs are used in MDI therapy to cover basal insulin requirements thanks to their 24-42 h duration of action of without peaks in activity.[60,61]
- Rapid-acting analogs (lispro, aspart, glulisine) are used in CSII therapy and for meal and correction boluses in MDI therapy. Compared with regular insulin, these analogs have an onset of 10-15 minutes (versus 30 minutes to 1 hour), reach higher peak plasma concentrations twice as fast, and have faster clearance rates, all of which reduces the risk of postprandial hypoglycemia due to slow absorption.[62,63]

- Ultra-rapid insulin analogs developed in recent years (faster-acting aspart, ultra-rapid lispro) have earlier onset times (~ 5 min) and greater post-prandial glucose lowering effects.[64,65] These newer insulins are closest to mimicking endogenous insulin activity; their faster onset time offers tighter control and flexibility around mealtimes by responding to glucose level rises earlier.

Insulin type	Onset	Peak	Duration (h)	Molecular structure
Basal				
Long acting				
Detemir U100	1–2 h	None	< 24	Omission of B30 threonine; C14 fatty acid chain added to B29
Gla-100	~ 1 h	None	24	A21 asparagine replaced with glycine; 2 arginines added to C-terminus of B chain
Gla-300	6 h	None	24-36	
Degludec U100 or U200	~ 1 h	None	Up to 42	Omission of B30 threonine; glutamic acid and C16 fatty acid chain added to C-terminus of B chain
Intermediate acting				
NPH insulin U100	1-2 h	4-14 h	4-14 h	
Bolus				
Rapid acting (lispro, aspart, glulisine)	5-15 min	0.5–1.5 h	3 to < 6	Lispro: B28 proline replaced with lysine; B29 lysine replaced with proline Aspart: B28 proline replaced with aspartic acid Glulisine: B3 asparagine replaced with lysine; B29 lysine replaced with glutamic acid
Faster-acting aspart	2.5-4 min	~ 1 h	3-5	Faster-acting aspart: B28 proline replaced with aspartic acid
Short acting (regular human)	30-60 min	2–4 h	6-12	

Table 1: Pharmacokinetic and pharmacodynamic properties of insulins[61]

2.2.5. Adjunct therapies

Intensifying insulin therapy to improve glucose control comes at the risk of aggravated hypoglycemia and weight gain due to its lipogenic properties.[66] Consequently, non-insulin anti-hyperglycemic pharmacological adjuvants may be helpful in the treatment of type 1 diabetes.

Sodium-Glucose Transport Protein 2 inhibitors (SGLT2i) are a group of highly selective drugs (canagliflozin, dapagliflozin, empagliflozin) used off-label for the treatment of type 1 diabetes that specifically block glucose reabsorption by SGLT2 transporters in the proximal tubule of the kidney and increase its urinary excretion.[66] The EASE-1 and -2 trials evaluated the efficacy of 2.5 mg, 10 mg, and 25 mg of empagliflozin in type 1 diabetes and indicated that all 3 doses successfully reduced HbA1c, total insulin dose, weight, and blood pressure, also increasing time spent in target range.[67] However, these studies also revealed a dose-dependent increase in the risk of euglycemic DKA as a result of reduced circulating blood sugar levels and subsequent insulin dose; this risk was highest for females and pump users.[66,67]

Glucagon-like-peptide-1 (GLP1) is a peptide hormone released by L-cells in the small intestine following meals which stimulates insulin secretion while inhibiting glucagon to promote glucose storage, delays gastric emptying, and stimulates satiety; GLP1 receptor agonists (GLP1-RA) are FDA approved for the treatment of obesity and type 2 diabetes.[5,68,69] Given their glucose-lowering effects and current concerns about rising obesity rates in this population, these drugs are also used off-label in type 1 diabetes, and their therapeutic potential is being further investigated.[70]

Pramlintide, an amylin analog, is the first non-insulin therapeutic treatment approved for type 1 diabetes, administered as mealtime injections.[70,71] Amylin is normally secreted by pancreatic β-cells, and, similarly to GLP-1, delays gastric emptying, stimulates satiety, and reduces nutrient-derived glucagon secretion, all of which can reduce glucose levels following meals.[71] Adjustments of up to 50% of insulin doses are recommended when starting pramlintide therapy to account for the risk of hypoglycemia and ensure drug tolerability.[71,72]

2.2.6. Specific management considerations

It is recommended that both adults and children with diabetes engage in at least one hour of moderate-to-vigorous daily activity as a means of reducing cardiovascular disease and other diabetic complications.[73] Pre-exercise intake of carbohydrates and adjustments to insulin doses are necessary to ensure sufficient glucose is available in circulation to fuel energy demands. Additionally, insulin sensitivity is affected by exercise, and the risk of hypoglycemia increases in the 24 hours following exercise.[73] Closed-loop systems offer a potential safeguard against unanticipated changes in insulin sensitivity.

Type 1 diabetes is an illness which largely centres around meals. The macronutrient composition of a meal, and especially its carbohydrate content, has a great impact on post-prandial glycemia.[74] Comprehensive and continued diabetes education is necessary to ensure people with type 1 diabetes are adequately trained to make healthy diet choices, as well as accurately count carbohydrates to correctly match food intake to insulin doses.[75]

As with many chronic illnesses, a great deal of responsibility is placed on the individual to adhere to complex dietary and exercise regimens, as well as adopt extensive self-care and monitoring behaviours to maintain their blood glucose levels within safe ranges. Rates of depression are higher in people with type 1 diabetes than in the general population, a phenomenon which is exacerbated by limited access to healthcare professionals and resources.[76,77] Advances in treatment therapies and technologies that automate some of these responsibilities have the potential to alleviate burdens associated with diabetes management.

2.3. Closed-loop systems

2.3.1. Current state of closed-loop therapy

Two meta-analyses of outpatient clinical trials suggest that a 0.3% reduction in HbA1c can be expected with the use of closed-loop systems.[55,78] In these reviews, closed-loop systems increased time spent in the target glucose range (3.9 mmol/L – 10.0 mmol/L) by 9.6% to 12.6%, which is equivalent to an additional 2.5 to 3 hours in normoglycemia per day. This improvement does not appear to be associated with an increased risk of hypoglycemia, as Bekiari et al. reported a 20 minute reduction in nocturnal hypoglycemia,[55] while Weisman et al. observed a 35 minute reduction in nocturnal hypoglycemia and a corresponding 50% reduction in its relative risk.[78]

The Medtronic MiniMed® 670G system was the first hybrid closed-loop system approved for commercial use by the FDA. A three-month pivotal trial of its at-home use demonstrated a 7% and 5% increase in time in range in adolescents and adults, respectively ($p<0.001$ in both cases), compared to their run-in period, with no episodes of severe hypoglycemia or DKA.[79] The second generation Medtronic Advanced Hybrid Closed-Loop (AHCL) system allows users to choose between the original set point of 6.7 mmol/L and a lower set point of 5.5 mmol/L, and incorporates automatic correction boluses to increase the aggressiveness of insulin adjustments. A 12-week, multi-site, randomized, crossover trial with 14- to 29-year-olds compared time spent with daytime levels above target range and overall time in hypoglycemia with both systems.[80] The AHCL system reduced time in hyperglycemia by 3% during the day compared to the Medtronic 670G, without meaningfully changing time in hypoglycemia ($p<0.0001$ in both cases). Additionally, the AHCL increased time spent in target range by nearly one hour, and HbA1c levels were reduced by 0.5% from baseline for those who used this system first, compared to a 0.3% reduction in HbA1c when starting with the 670G system.

The Tandem Control-IQ hybrid closed-loop system is also approved for commercial use in North America. A six-month, randomized, parallel, controlled trial compared sensor augmented pump therapy (SAP), in which participants use glucose sensors alongside conventional pump therapy, in 56 adults to closed-loop therapy in 112 adults.[81] The closed-loop system increased time spent in target range by 11% compared with SAP ($p<0.001$), or 2.6 hours a day, within just one month of system initiation. HbA1c levels were also improved by 0.33% ($p=0.001$), while hypoglycemic was reduced by 13 minutes per day ($p<0.001$).

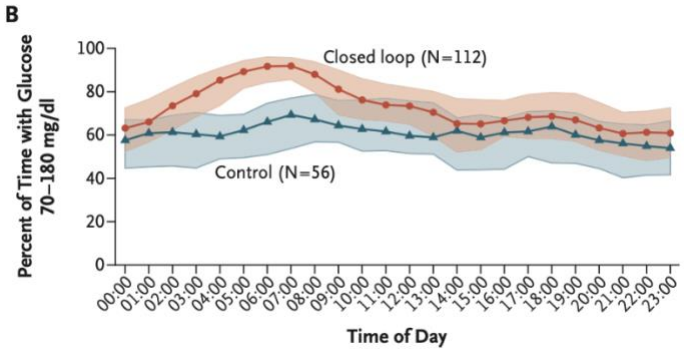

Figure 4: Median and IQR percentage of time sensor glucose levels were within the target range of 70 to 180 mg/dL (or 3.9 to 10.0 mmol/L) with either the closed-loop system or sensor-augmented pump therapy (control).[81]

A similar 16-week study in 6- to 13-year-old children achieved comparable improvements in time in range ($p<0.001$); the authors stated that baseline hypoglycemia rates were unrepresentatively low, and reductions in hypoglycemia were only observed following a 16-week extension trial.[82,83]

2.3.2. Insulin-and-glucagon closed-loop systems

Given the putative role of disrupted glucagon secretion in glycemic dysregulation, it was thought that integrating glucagon into closed-loop systems might overcome some of the limitations of single hormone systems. The rationale behind this is twofold: through its continuous subcutaneous infusion, glucagon can have protective effects against routine occurrences of hypoglycemia (eg: during and after exercise, overnight); glucagon infusion may also permit

systems to administer insulin more aggressively without increasing the risk of hypoglycemia, thus achieving tighter glycemic control.[84]

In 2010, the first study to test a dual-hormone closed-loop configuration in humans evaluated an insulin-and-glucagon fully closed system in 11 participants for 24 hours.[85] The system relied entirely on sensor measurements to adjust hormonal delivery. Two patterns of insulin pharmacokinetics emerged, separating participants into those with fast insulin absorption who achieved average glucose levels of 7.8 mmol/L with less than 1% of time in hypoglycemia, and those with slower insulin absorption. The latter experienced at least one hypoglycemic event requiring rescue carbohydrates due to elevated post-prandial insulin levels, despite receiving higher glucagon delivery than the other group ($p=0.02$). After adjusting the algorithm to account for a slower pharmacokinetic profile, hypoglycemia requiring treatment was successfully avoided in these participants, and average glucose levels of 9.6 mmol/L were achieved. Post-prandial hyperglycemia was observed in both groups, which the authors suggest could be mitigated by the administration of meal-priming boluses, which would also reduce elevated basal insulin delivery and the subsequent risk of hypoglycemia following meals.

A randomized crossover study compared single- and dual-hormone hybrid closed-loop therapy to conventional pump therapy in 20 adults and 10 adolescents over 24 hours.[86] In the control arm, participants were encouraged to adjust their insulin delivery per their standard practice. Time in range increased by 17% and 21% ($p=0.002$ and $p<0.001$), respectively, compared with conventional pump therapy; the dual-hormone system reduced time in hypoglycemia by 1% compared with the insulin-alone closed-loop system ($p=0.018$).[86] Another randomized, crossover trial compared overnight single- and dual-hormone hybrid closed-loop systems with conventional pump therapy in 33 children.[87] Both hybrid systems improved time spent in target range (19%,

p=0.001, and 35%, p<0.0001, respectively), but only the dual-hormone system reduced overnight hypoglycemia when compared with the control arm (-1.7%, p=0.0048).[87] The dual-hormone system also increased time in range by 8% compared with the single-hormone system (p=0.016).

2.3.3. Adjunctive pramlintide therapy

As previously discussed, pramlintide is an attractive pharmacological adjuvant for the treatment of type 1 diabetes due to its insulin-independent glucose-lowering mechanism of action.[71] A meta-analysis reviewing the safety and efficacy of pramlintide injections alongside standard insulin therapy revealed that pramlintide significantly reduces HbA1c levels, body weight, and post-prandial glycemia.[88] These glycemic improvements are accompanied by mostly dose-dependent, tolerable, and transient gastrointestinal side effects like nausea, vomiting, and anorexia, as well as hypoglycemia. A 29-week placebo-controlled, double-blind trial indicated that, in addition to reducing both body weight and mealtime insulin requirements, pramlintide use improved treatment satisfaction for both MDI and pump users.[89]

Few studies have studied the effects of pramlintide alongside closed-loop insulin administration. Weinzimer et al. were the first to do so in a randomized, crossover trial comparing an insulin-alone fully closed-loop system to a fully closed-loop system with 30 µg pramlintide injections at mealtimes, over 24 hours.[90] Time to peak glycemia in the post-prandial period was delayed by approximately one hour (p<0.0001) with pramlintide, and post-prandial glucose excursions were reduced by 1.4 mmol/L (p=0.04). This team later studied fully closed-loop control with a higher pramlintide dose (60 µg) following a three-to-four week dose titration period and observed a one hour delay in peak plasma glucose and a 2.06 mmol/L reduction in post-prandial glucose excursions (p<0.0001 in both cases).[91]

In normal physiology, insulin and pramlintide are secreted in tandem, which has led to investigating the efficacy of the co-infusion of pramlintide and insulin in a basal-bolus manner. In an 11-participant, single arm, pilot study, adults on insulin pump therapy received continuous subcutaneous pramlintide delivery at a basal rate of 9 µg/hour in a secondary pump for 16 weeks, with bolus pramlintide doses titrated to 60 µg.[92] This approach appeared to reduce overall glucose levels throughout the day; however, insulin boluses had to be reduced by 20% to avoid immediate post-meal hypoglycemia.

Haidar et al. were the first to study the closed-loop co-administration of insulin and pramlintide in a 28-participant, inpatient, randomized, crossover trial comparing both a rapid insulin-and-pramlintide and a regular insulin-and-pramlintide hybrid closed-loop system to a rapid insulin-alone system.[1] Pramlintide was delivered at a fixed ratio of 6 µg per unit of insulin, and insulin-to-carb ratios were reduced by 6% following a 10-14-day open-loop optimization period. Mealtime insulin-and-pramlintide boluses were administered in a dual wave pattern, with immediate/extended proportions varying based on premeal glucose levels; this method of bolus delivery was intended to mitigate post-prandial hyper- and hypoglycemia, as well as gastrointestinal symptoms, by distributing pramlintide delivery over a prolonged period and reducing the amount of drug given immediately before a meal.

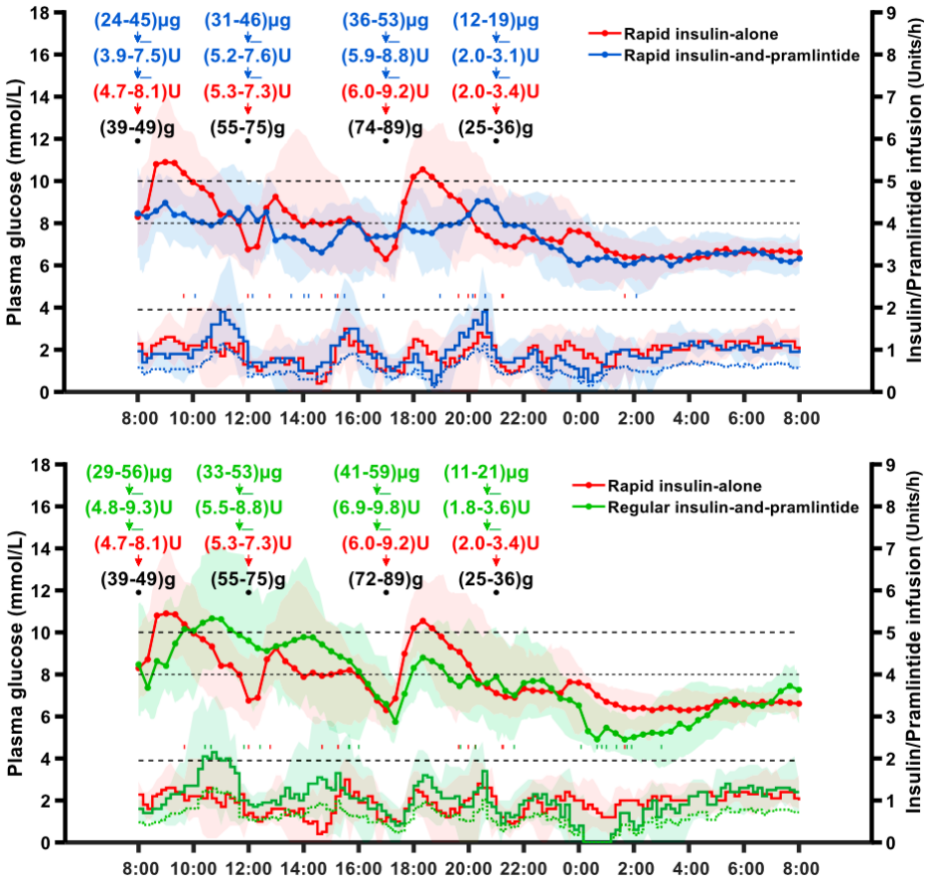

Figure 5. Median and IQR profiles of glucose levels and hormonal deliveries during closed-loop system visits. Meal and hormonal bolus values are indicated as (IQR). Small vertical lines indicate hypoglycemia events. Solid lines indicate glucose levels and basal insulin. Dotted lines indicate basal pramlintide.[1]

In the rapid insulin-and-pramlintide arm, overall time in target range compared with the control arm increased from 74% to 84% (p=0.0014) without an associated increase in hypoglycemia, whereas the regular insulin-and-pramlintide system did not change time in range (69% vs 74%, p=0.22). Despite experiencing transient, mild-to-moderate post-meal gastrointestinal symptoms during the rapid insulin-and-pramlintide interventions (such as nausea, bloating, and heartburn), participants reported the greatest treatment satisfaction during the optimization period for this system, suggesting the side effects due to pramlintide were not so burdensome as to discourage its use.

2.4. Carbohydrate counting

Carbohydrate counting is a well-established practice in the management of type 1 diabetes that attempts to ensure that an appropriate amount of insulin is administered at mealtimes to cover post-prandial needs. To do so, the carbohydrate content of a meal must be accounted for, and a bolus is calculated based on patient-specific insulin-to-carbohydrate ratios. It is recommended that patients attend specific training programs soon after their diagnosis to learn to do so correctly; despite this, patients (especially youths) often require additional support on the part of their caregivers to perform this complex task.[93]

2.4.1. Role in diabetes management

The evidence for the clinical efficacy of carbohydrate counting is conflicting. A seven-participant, prospective, pilot study evaluated glycemic and qualitative outcomes following intensive training by diabetologists and certified diabetes educators in carbohydrate counting-naïve participants.[94] This study found that glycated albumin levels were reduced six and 12 months post-training, and HbA1c levels improved after 12 months. Participants also reported improved treatment satisfaction from baseline as early as three months after receiving training, which persisted after 12 months. However, a systematic review of seven outpatient studies comparing carbohydrate counting interventions to those with usual care or flexible low glycemic diet regimens suggested a more nuanced interpretation.[95] No overall improvements in HbA1c were noted ($p=0.096$), although when considering the six adult-only trials, a 0.4% reduction was observed ($p=0.048$), suggesting that age may play a factor in the efficacy of this practice.[95] In another systematic review of 27 studies, including six randomized, controlled trials and 21 observational, before/after studies, carbohydrate counting was associated with a positive trend in improvement in HbA1c, although it did not reach statistical significance, likely due to

heterogeneity in study design.[96] Its effects on weight change were also unclear, and while most studies revealed significant improvements in psychosocial survey scores with carbohydrate counting, the results were not necessarily clinically relevant.

The efficacy of carbohydrate counting is dependent on users' precision and accuracy. A study assessing 140 adolescents' ability to accurately estimate the carbohydrate content of various meals compared with a dietician's assessment revealed that less than half the participants did so accurately, with 14% making estimation errors of more than 20 g.[97] This study also found that youth with longer-standing diagnoses tended to be less accurate than their newly diagnosed peers, stressing the importance of continuous nutritional education for effective management. A cross-sectional study evaluating the difference between 448 patient- and dietician-estimated meals revealed that patients make an average error of 21±10% (15±8 g) per meal, with 63% of meals being underestimated, possibly out of fear of causing hypoglycemia due to large insulin requirements.[98] Inaccuracy in carbohydrate counting was found to be a predictor of glucose variability in this study ($p<0.05$).

An online survey assessed challenges, barriers, and experiences related to carbohydrate counting.[99] Of 180 respondents, 17% reported finding the practice challenging, while confidence in the practice was significantly associated with higher educational levels and absence of depression. A majority of participants described experiencing persistent fluctuations in glycemia despite performing carbohydrate counting, having difficulty estimating carbohydrates at the start of a meal, and having difficulty estimating how much insulin to administer for meals with complex macronutrient compositions. 77% of pump users expressed interested in future technologies that would minimize the need for carbohydrate counting.

2.4.2. Attempts at eliminating carbohydrate counting

The ultimate goal of research in closed-loop systems is to develop a system which can respond to glucose variations and meet insulin needs entirely independently of user input, accomplishing the task of a truly "artificial pancreas", or a fully closed loop. Current diabetes management regimens, be they traditional intensive insulin therapy or commercial closed-loop systems, require users to administer meal boluses whose doses are mainly determined by carbohydrate counting. Attempts at removing carbohydrate counting in closed-loop systems have been made, historically following one of two strategies: either by completely omitting meal boluses, or by administrating partial (small) pre-meal boluses calculated independently of the carbohydrate content of a meal, while basal insulin adjustments compensate for post-prandial insulin requirements.

Weinzimer et al. compared two such systems in adolescents with type 1 diabetes with two parallel intervention arms: a fully closed-loop arm, and a hybrid closed-loop arm wherein partial boluses representing 25-50% of each meal's normal carbohydrate-matched boluses were administered prior to meals.[100] The administration of partial pre-meal boluses resulted in lower mean glucose levels during the day (8.3 mmol/L vs 8.8 mmol/L, p=0.03) and following meals (10.8 mmol/L vs 12.6 mmol/L, p=0.04) compared with the fully closed-loop system.

As previously seen, early insulin-and-glucagon fully closed-loop systems faced the issue of sustained post-prandial hyperglycemia due to delayed insulin administration.[85] Two five-day, free-living, randomized, crossover trials compared dual-hormone systems with partial weight-based boluses based on qualitative meal estimations to usual pump therapy in adults and adolescents, respectively.[101] In adults, mean sensor glucose throughout the day was reduced with the dual-hormone system (7.4 mmol/L vs 8.8 mmol/L, $p<0.001$), as was time in hypoglycemia (4.1% vs 7.3%, $p = 0.01$). In adolescents, a similar reduction in mean plasma glucose was observed with the

dual-hormone system (7.9 mmol/L vs 8.8 mmol/L, p=0.004); however, is possible that intense monitoring in the camp setting in which the adolescent study was run helped mitigate the risk of hypoglycemia, resulting in similar time below range across both arms (p=0.05). Additionally, in both populations, gastrointestinal side effects like nausea and vomiting were observed up to 5 hours following the last glucagon dose. A later iteration of this system was tested in 39 adults, in an 11-day, free-living, randomized trial comparing the dual-hormone closed-loop system to participants' conventional therapy.[102] The system was designed to function as a fully closed loop, with the possibility of qualitative meals announcements. Participants announced an average of 2.6 meals per day on the system, compared to 5.6 announcements on their control therapy. Mean sensor glucose levels were reduced (7.8 mmol/L vs 9.0 mmol/L, p<0.0001) on the dual-hormone system, as was time spent in hypoglycemia during both day and night (-1.3%, p<0.0001), accompanied by a 16.5% increase in time in the target glycemic range (p<0.0001).

Using a slightly modified strategy which calculates partial boluses based on participant insulin-to-carbohydrate ratios rather than weight, Gingras et al. conducted a 12-participant, randomized, controlled trial comparing the following three interventions: an insulin-and-glucagon system with carbohydrate-matched boluses, an insulin-and-glucagon system with partial boluses based on "regular" or "large" meal estimations, and insulin-alone conventional pump therapy with carbohydrate-matched boluses.[103] Similar post-prandial glucose control was achieved for most meals (p>0.05) across all arms, with the exception of high-carbohydrate meals: the dual-hormone system with carbohydrate-matched boluses improved post-prandial glycemic excursions compared with the simplified meal strategy for such meals (p=0.004). There was no difference in time spent in target range and mean glucose levels between either closed-loop system (p>0.05), but both improved mean plasma glucose levels compared with the control arm (p<0.05). Of note, the

addition of glucagon did not reduce time spent in hypoglycemia, regardless of meal strategy, compared with the control ($p>0.05$).

Blauw et al. recently conducted a 2-week, randomized, controlled trial during which participants' usual pump therapy, with or without sensor use, was compared to an insulin-and-glucagon fully closed-loop system.[104] Participants achieved significantly higher time in target range on the closed-loop system (86.6% vs 53.9%, $p<0.0001$) than on their usual therapy, with further improvements in hypo- and hyperglycemia. Notably, post-prandial glucose levels were reduced after lunch, despite the absence of meal-priming boluses, suggesting the addition of glucagon permitted more aggressive insulin administration while mitigating the risk of hypoglycemia.

Chapter 3. Thesis Manuscript

3.1. Preface

Several experimental closed-loop systems investigating different hormone and meal bolus strategies have been presented above. We propose a novel insulin-and-pramlintide system with a simplified meal announcement strategy which aims to eliminate the need for carbohydrate counting. By delaying gastric emptying, pramlintide should enable postprandial glucose levels to better match insulin pharmacokinetics, reducing the risk of immediate post-prandial hyperglycemia followed by delayed hypoglycemia. This system was tested in both a 24-hour, in-patient feasibility study, and a 12-day, outpatient pilot study, the results of which are presented in the following manuscript, published in *Diabetes, Obesity and Metabolism* in 2021.[105] Structured interviews were conducted throughout the pilot study, as well as its subsequent 30-participant trial, in order to qualitatively assess the impact of reducing the need for carbohydrate counting on users' quality of life. The process of thematic analysis performed for pilot study interviews, including code and theme generation, is presented in the Discussion chapter of this thesis.

3.2. Alleviating Carbohydrate Counting with a FiASP-plus-Pramlintide Closed-Loop Delivery System (Artificial Pancreas): Feasibility and Pilot Studies

Alleviating Carbohydrate Counting with a FiASP-plus-Pramlintide Closed-Loop Delivery System (Artificial Pancreas): Feasibility and Pilot Studies

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Key words: type 1 diabetes, artificial pancreas, pramlintide, simple meal announcement, carbohydrate counting

Word count: 256 (Abstract), 3676 (Main text)
Tables: 3 (Main Text), 2 (Supplementary Appendix)
Figures: 2 (Main Text), 4 (Supplementary Appendix)
References: 28

Abstract

Aims: We report two studies assessing whether a FiASP-and-pramlintide closed-loop system can replace carbohydrate counting with a simple meal announcement strategy (meal priming bolus without carbohydrate counting), without degrading glycemic control compared to a FiASP closed-loop system.

Materials and Methods: We conducted a 24-hour feasibility study comparing (i) a FiASP system with full carbohydrate counting (FCC) to (ii) a FiASP-and-pramlintide system with simple meal announcement (SMA). We conducted a subsequent 12-day outpatient pilot study comparing (i) a FiASP-and-placebo system with FCC, (ii) a FiASP-and-pramlintide system with SMA, and (iii) a FiASP-and-placebo system with SMA. Basal-bolus FiASP-and-pramlintide were delivered at a fixed ratio (1U:10µg). Glycemic outcomes were measured, surveys evaluated gastrointestinal symptoms and diabetes distress, and participant interviews helped establish a preliminary coding framework to assess user experience.

Results: Seven participants were included in the feasibility analysis. Time spent between 3.9-10 mmol/L was similar between both interventions (81%—84%). Four participants were included in the pilot analysis. Time spent between 3.9-10 mmol/L was similar between the FiASP-and-placebo with FCC and FiASP-and-pramlintide with SMA interventions (70%); but lower in the FiASP-and-placebo with SMA intervention (60%). Time <3.9 mmol/L and gastrointestinal symptoms were similar across all interventions. Emotional distress was moderate at baseline, after the FiASP-and-placebo with FCC and SMA interventions, and fell after the FiASP-and-pramlintide with SMA intervention. SMA reportedly afforded participants flexibility and reduced mealtime concerns.

Conclusions: The FiASP-and-pramlintide system has the potential to substitute carbohydrate counting with SMA without degrading glucose control. The feasibility and main outpatient study are registered with ClinicalTrials.gov (NCT03993366 and NCT04163874, respectively).

Introduction

Type 1 diabetes is a chronic disease caused by the autoimmune destruction of insulin-producing pancreatic beta-cells.[1] Automated closed-loop insulin delivery systems have demonstrated improved glycemic control compared to conventional pump therapy.[2]

Meal carbohydrate content is the major nutritional determinant of prandial and post-prandial insulin needs.[3] Current closed-loop systems rely on users to input the carbohydrate content of upcoming meals to deliver matching pre-prandial insulin boluses.[3,4] However, with an estimation error around 20%, accurate carbohydrate counting is a challenging task that adds to the burden of disease management.[5] Emphasis on carbohydrate counting can also negatively influence dietary choices, as the relative ease afforded by nutrition labels leads many to prefer prepackaged, processed foods rather than whole foods, such as whole grains and fruits.[6]

Early closed-loop systems attempted to eliminate carbohydrate counting by omitting mealtime insulin boluses.[7,8] They instead relied on glucose sensor readings to adjust basal insulin delivery and account for meal-related insulin needs. Due to slow insulin absorption,[9] this resulted in prolonged hyperglycemia.[7,8] Other experimental systems delivered partial prandial boluses independent of carbohydrate content, only requiring the announcement of meals,[8,10] which, compared to carbohydrate-matched boluses, also resulted in higher postprandial glucose excursions.[10] A system that replaces carbohydrate counting with simple meal announcement without degrading glucose control has yet to be achieved.

Pramlintide is an analog of amylin, a hormone normally co-secreted with insulin which is deficient in people with type 1 diabetes. Co-injecting pramlintide with insulin at mealtimes delays gastric emptying (enabling insulin's pharmacokinetics to catch up to post-prandial glucose levels), suppresses nutrient-stimulated glucagon secretion, and increases satiety.[11,12] Our team demonstrated that a closed-loop system delivering basal-bolus pramlintide at a fixed ratio with insulin, in addition to carbohydrate-matched boluses, can improve glucose control compared to an insulin-alone system.[13] We aimed to assess the feasibility of a novel insulin-and-pramlintide closed-loop system with smaller, partial prandial boluses, without carbohydrate counting. The algorithm delivered more aggressive post-prandial basal insulin and used a stronger insulin-and-pramlintide ratio. Here, we report results from a 24-hour feasibility study, and a 12-day pilot study assessing glucose and quality-of-life outcomes.

Materials and Methods

Study Design

We performed an 8-participant inpatient feasibility study, and a 4-participant outpatient pilot study internal to a larger, main trial.

The feasibility study had a randomized crossover design and evaluated (i) a FiASP-alone closed-loop system with full carbohydrate counting (FCC) and (ii) a FiASP-and-pramlintide closed-loop system with simple meal announcement (SMA) over 24 hours.

The pilot study had a 12-day, three-way, randomized, blinded, crossover design which compared (i) a FiASP-and-placebo closed-loop system with FCC, (ii) a FiASP-and-pramlintide closed-loop system with SMA, and (iii) a FiASP-and-placebo closed-loop system with SMA.

Participants

Participants from previous studies having consented to being contacted about future research were approached about participating in these studies. From March to June 2019, four adults and four adolescents with type 1 diabetes completed the feasibility study; from February to July 2020, four adults completed the pilot study. Participants were recruited to the Montreal Children's Hospital and Royal Victoria Hospital, Montreal, Quebec. Inclusion criteria were ≥12 years old, use of an insulin pump ≥3 months, a diagnosis of type 1 diabetes ≥1 year, and HbA1c ≤12%. Main exclusion criteria were pregnancy or breastfeeding, gastroparesis, use of non-insulin anti-hyperglycemic medication or medication that alters gastrointestinal-motility, and any other serious medical illness likely to interfere with study participation. Participants provided written informed consent. Both studies were approved by the McGill University Health Centre's research ethics board and Health Canada, and were conducted in accordance with the standards of the Declaration of Helsinki.

Feasibility Study Procedures

Each 24-hour closed-loop intervention was preceded by a 3-day, at-home, run-in period during which participants used the study medications on open-loop therapy, with carbohydrate counting. Participants inserted a glucose sensor (Dexcom G5®, Dexcom) on the first day of the run-ins, and switched their usual insulin to FiASP (NovoNordisk) in their personal pumps. Additionally, during the run-ins preceding the FiASP-and-pramlintide interventions, pramlintide (Symlin, AstraZeneca) was delivered in a second pump (MiniMed Paradigm Veo or MiniMed 630G) at a fixed ratio of 5 µg/U of FiASP to reduce the risk of gastrointestinal side-effects[14]. This ratio was increased to 10µg/U of FiASP during the interventions.

Manual closed-loop hormone delivery started at 21h00 and ended at 21h00 the next day. Meal contents and times were self-selected at the first visit and repeated at the second, for each

participant. The closed-loop system's dosing algorithms were based on model predictive control, and were initialized using basal rates, insulin-to-carbohydrate ratios, and total daily insulin dose from admission visits. The algorithms were identical in both arms except that the dosing algorithm in the arm with SMA allowed for slightly more aggressive basal insulin delivery post-prandially to compensate for reduced prandial boluses. During the interventions, every 10 minutes a member of the research staff entered glucose sensor readings into a laptop which ran the dosing algorithms, recommending adjusted basal rates that were manually programed into the pumps. The algorithms also recommended mealtime boluses; glucose targets were set at 6 mmol/L for both basal rate changes and boluses. The algorithms did not recommend automatic boluses outside of mealtimes. Instead, when needed, basal rates were modulated to deliver an amount of insulin equivalent to a corrective bolus over several 10-minute increments, as with our previous closed-loop study.[15]

Pilot Study Procedures

The pilot study used the iPancreas closed-loop system[15] (Oregon Health & Science University, OR, USA) with the same dosing algorithms and glucose targets as the feasibility study. This system consists of a glucose sensor (Dexcom G5®, Dexcom), non-commercial t:slim insulin pumps (Tandem Diabetes Care, CA, USA), and a cellphone (Nexus 5, LG Electronics). The cellphone receives glucose sensor readings and wirelessly adjusts the pumps' basal deliveries every 10 minutes. The system allows for user-initiated meal and correction boluses which participants can administer at any time, and has an exercise feature which elevates glucose targets by 3 mmol/L when activated. The system switches to open-loop mode when communication with either pump or sensor is lost for more than 20 or 30 minutes, respectively.

Participants were admitted to our clinical research facility prior to starting on the system to receive training on the devices. Participants set sensor alarms which they could modify at any

time during the study. They were instructed to treat their hypoglycemia and hyperglycemia as per their standard practice while on the system.

Following this training, participants used the closed-loop system in its single-pump configuration with FiASP-alone for one week to familiarise themselves with it before beginning their interventions. They were contacted for follow-up on days 1, 2, and 7 of each intervention to discuss any concerns or technological issues. The study team was on-call throughout the interventions for clinical and technical support.

For all interventions, participants used a second pump to deliver pramlintide or placebo (saline solution). This was necessary to mask participants and research staff to the study drug in the interventions with SMA, and ensure consistency in quality-of-life evaluations across all interventions. To mitigate potential gastrointestinal symptoms, each intervention began with a 2-day run-in period during which a fixed ratio of 5 µg of pramlintide (or 0.5 units of placebo) to 1 unit of insulin were infused; this period was applied to all three interventions for consistency. During the following 12-day interventions, 10 µg of pramlintide (or 1 unit of placebo) were delivered per 1 unit of FiASP, mimicking a co-formulation. Sensors were changed every 7 days, and reservoirs and infusion sets were changed every 2-3 days. There was a 14-45-day washout period between each intervention to cognitively separate the arms for qualitative assessment.

In our 2018 pramlintide trial with carbohydrate-matched boluses, a smaller pramlintide/insulin ratio of 6 µg/unit was used.[13] Here, we increased this ratio to 10 µg/unit to conserve the prandial pramlintide amount that demonstrated efficacy in our first study, as only partial (therefore smaller) boluses were delivered using the SMA system.

Prandial Boluses

During interventions with FCC, the carbohydrate content of each meal and snack was entered into the algorithm to compute prandial boluses. In the feasibility study, research staff calculated the carbohydrate content of meals and snacks; in the pilot study, this was done by participants. During interventions with SMA, meals were simply announced to the algorithm regardless of carbohydrate content. The bolus calculator assumed a meal with 25g of carbohydrates and delivered prandial boluses based on pre-meal glucose levels, insulin-to-carbohydrate ratios, and the 25g meal. Snacks were not announced during these interventions.

Gastrointestinal Symptoms

In the feasibility study, gastrointestinal symptoms were evaluated two hours after every meal.

In the pilot study, participants completed the Diabetes Bowel Symptom Questionnaire at baseline and after each intervention.[16]

Quality of Life Assessment

In the pilot study, participants completed the following quality-of-life questionnaires at baseline and after each intervention: the Type 1 Diabetes Distress Scale,[17] the Hypoglycemia Fear Survey–II,[18] the INSPIRE questionnaire,[19] and the PRISM-RII Task.[20] They also participated in structured interviews at baseline, after each intervention, and at the end of the study.

Statistical Analysis and Outcomes

These studies aimed to generate pilot data on our closed-loop system with SMA; they were therefore not powered for statistical significance. Time in target (3.9-10 mmol/L), time in hypoglycemia (<3.9 mmol/L), time in hyperglycemia (>10 mmol/L), and mean change in survey scores were assessed. Interviews were transcribed, and E.C. and M.O. developed initial codes on a set of transcripts using a method of thematic analysis with MaxQDA 2020 (VERBI software,

2019). They met to cross-compare, reach agreement on a final coding scheme, and apply the new codes to all transcripts. Recurring themes were identified.

Results

Feasibility Study

Eight participants (4 adults, 4 adolescents) were enrolled in the study from March to June 2019. Seven were included in the analysis (one participant's data were excluded after experiencing an infusion set problem during their intervention with FCC) (Table 1).

Glycemic Outcomes

Mean time in target and time in hyperglycemia was similar between the FiASP-alone intervention with FCC and the FiASP-and-pramlintide intervention with SMA (81±15% and 84±14%, respectively), but median time in hypoglycemia was lower in the latter intervention (4.1%[4.1-6.2] and 2.1%[0.7-2.4], respectively) (Table 2). Glucose profiles are reported in Figure 1a.

Insulin Delivery

Total (45.5±14.4U and 37.1±8.9U, respectively) and bolus (18.1±9.8U and 8.4±6.6U, respectively) insulin delivery was lower on the FiASP-and-pramlintide system with SMA than the FiASP-alone system with FCC (Table 2).

Gastrointestinal Symptoms and Adverse Events

In the FiASP-and-pramlintide arm, 3 participants experienced gastrointestinal symptoms following 4 of the 31 meals. These included mild and mild-to-moderate nausea, mild and moderate bloating, and moderate and moderate-to-severe heartburn. One participant experienced persistent

gastrointestinal symptoms throughout the intervention. No gastrointestinal symptoms were reported in the FiASP-alone arm or during the nights in either intervention (Table 3).

Pilot Study

Four adult participants enrolled and completed the study between February and July 2020 (Table 1).

Glycemic Outcomes

Mean time in target range on the FiASP-and-placebo system with FCC was 70±11%, 70±13% on the FiASP-and-pramlintide system with SMA, and 60±13% on the FiASP-and-placebo system with SMA. Median time in hypoglycemia was 1.0% [0.5-1.7], 1.4% [0.7-2.5], and 0.5% [0.4-0.6] for the three interventions, respectively. Time spent in closed-loop ranged between 88.2-91.2% for all three interventions (Table 2, Figure 1b). Individual glucose profiles are reported in Supplementary Figures 1-4.

Insulin Delivery

Total daily insulin delivery was 49.3±17.6U on the FiASP-and-placebo system with FCC, 46.0±17.3U on the FiASP-and-pramlintide system with SMA, and 52.7±24.2U on the FiASP-and-placebo system with SMA (Table 2).

Gastrointestinal Symptoms and Adverse Events

The Diabetes Bowel Symptom Questionnaire assessed the frequency and severity of several symptoms on a 6-point Likert scale, higher scores indicating a higher frequency and severity. At baseline, participants scored 1.3±0.6 for symptom frequency, and 1.2±0.5 for symptom severity. On the FiASP-and-placebo system with FCC, scores were 1.1±0.4 and 1.0±0.2, respectively, with no non-mild symptoms; on the FiASP-and-pramlintide system with SMA, scores were 1.3±0.7 and 1.3±0.6, respectively, with one participant reporting moderate abdominal

pain; on the FiASP-and-placebo system with SMA, scores were 1.3±0.5 and 1.3±0.6, respectively, with one participant reporting moderate abdominal pain and moderate nausea. No severe symptoms were reported across any intervention (Table 3). In addition, on the FiASP-and-pramlintide system with SMA, two participants reported skin irritations at the site of pramlintide infusion (treated with the application of a topical ointment), and one participant experienced lipodystrophy at both pump infusion sites.

Quality of Life Assessment – Surveys

Diabetes Distress Scale scores indicated that participants reported moderate amounts of overall diabetes related distress at baseline (2.3±1.1), and a high emotional burden of diabetes (3.2±1.7). Overall scores remained moderate with the FiASP-and-placebo systems with FCC and SMA (2.4±1.3 and 2.2±2.0, respectively), and fell with the FiASP-and-pramlintide system with SMA (1.8±0.6). Following a similar trend, emotional burden remained high with the FiASP-and-placebo systems with FCC and SMA (3.4±2.1 and 3.0±1.7, respectively), and fell to moderate with the FiASP-and-pramlintide system with SMA (2.4±1.1) (Table 3).

Participants' hypoglycemia concerns, measured by the Hypoglycemia Fear Survey Worry subscale, fell from a baseline of 2.6±0.9 to 1.5±0.1 after the FiASP-and-placebo intervention with FCC, 1.4±0.3 after the FiASP-and-pramlintide intervention with SMA, and 1.3±0.1 after the FiASP-and-placebo intervention with SMA.

Per the INSPIRE questionnaire, participants viewed closed-loop systems as beneficial at baseline (4.1±1.3) and following each intervention (4.3±0.7 on the FiASP-and-placebo system with FCC, 4.1±0.8 on the FiASP-and-pramlintide system with SMA, and 4.3±0.6 on the FiASP-and-placebo system with SMA) (Table 3).

With the Pictorial Representation of Illness and Self Measure Revised II (PRISM-RII) task, participants visually represented their perceived magnitude of illness using the size of the Illness Perception Measure, and its distance relative to their self per the Self-Illness Separation measure. Overall Illness Perception Measure and Self-Illness Separation scores fell from baseline after all interventions (Table 3).

Quality of Life Assessment – Interviews

Pilot interview analysis generated a preliminary framework and coding scheme with which to later study interview data from the larger trial. The themes brought up during interviews concerned daily food choices made to best manage participants' diabetes, how these choices changed with the use of a closed-loop system, and overall impressions of the system's effectiveness.

In baseline interviews, participants described avoiding certain foods in daily practice, for reasons relating to health or difficulty managing their glycemic impact: "I try to avoid, you know, white bread and pasta and things like that. [...] I just find it's so unpredictable, um and I know I'm going to go sky high" (participant 4).

Participants noted the interventions with SMA permitted them to snack freely, even without administering an insulin bolus: "[…] little snacks are friends now. Wow, that's really neat. Like I can have an apple, I don't have to worry about carbs […] I can eat it and I might go up to 9 (mmol/L), I won't go 16 (mmol/L). So, it's nice, I don't have to worry about that, wow" (participant 3). The intervention with FCC also provided a 'catch-all' for slight errors in carbohydrate counting due to use of a closed-loop system, such that small amounts of carbohydrates did not cause meaningful excursions in glucose levels.

The absence of carbohydrate counting alleviated meal-related worries for all participants: "not having to worry about what I was eating took such a burden off my diabetes, took such a burden off this huge thing in my life. [...] I just felt more relaxed about that part of dealing with the disease" (participant 1). In addition, they described having more flexibility regarding the types of meals they could eat ("Oh, wow, this is cool. I can eat whatever I like", participant 2). However, participant 3 cautioned against having too much freedom with SMA, opposing the risks of "eat[ing] whatever you want" to the health benefits of FCC: "you're in so much better health, and you're more aware of what you're eating [...] when you're carb counting".

Finally, reflecting on all interventions, participant 1 reported that SMA "eliminated [the] error" due to carbohydrate counting, as miscalculations had a "significant effect" on their glucose control. They noted that, with the exception of specific meals best controlled by precise carbohydrate counting, this novel approach was "as good as or better than [their] ability to carb count."

Discussion

Efforts to develop insulin-alone closed-loop systems that eliminate the need for carbohydrate counting, either by omitting boluses entirely, or only announcing meals, have been limited in their ability to achieve in-target, post-prandial glucose control.[21] Our 24-hour, feasibility study, and 12-day, pilot study evaluating the efficacy of a FiASP-and-pramlintide closed-loop system with simple meal announcement, while not powered to achieve statistical significance, have generated valuable preliminary data suggesting that our novel dual-hormone closed-loop system could alleviate the need for carbohydrate counting without degrading glucose control.

In both studies, the FiASP-and-pramlintide closed-loop system with SMA resulted in an overall similar time spent in target glycemic range compared to the FiASP-alone and the FiASP-

and-placebo closed-loop systems with FCC, respectively. The pilot study suggested that emotional distress due to diabetes may be lessened with the FiASP-and-pramlintide closed-loop system with SMA, more so than with the FiASP-and-placebo closed-loop system with FCC. SMA as a meal strategy reduced certain concerns, giving participants more flexibility with eating and bolusing practices, and removing the need to administer boluses for small carbohydrate amounts. Following this pilot analysis, survey and interview questions in the main study were modified to further explore participants' meal-related experiences, with a focus on altered eating habits.

Slow subcutaneous insulin absorption limited the success of early attempts to completely omit meal boluses with closed-loop systems, as they resulted in prolonged postprandial hyperglycemia.[8] Delivering prandial pramlintide to delay gastric emptying and reduce postprandial glucose peaks can lessen the impact of postponed insulin absorption.[22] We have previously demonstrated that a closed-loop system co-delivering rapid insulin and pramlintide at a 1U:6µg ratio improves glucose control compared to an insulin-alone closed-loop system administering carbohydrate-matched boluses.[13] The current studies introduce a closed-loop system with FiASP (slightly faster than rapid insulin),[23] a different pramlintide-to-insulin ratio, and an altered algorithm to alleviate the burden of carbohydrate counting without degrading glucose control. Although interpretations are limited, results from the FiASP-and-placebo closed-loop system with SMA indicate greater time in hyperglycemia than in both other arms, suggesting that pramlintide may be needed to maintain glycemic control with this SMA system.

Several factors contribute to the emotional burden of disease experienced by individuals with type 1 diabetes, such as young age, poor glycemic control, and low diabetes empowerment and self-management.[24] Counting carbohydrates to determine mealtime insulin doses is an established method to improve glycemic control.[5,25] However, this task can be burdensome and

time consuming for many, and mealtime glycemic control remains a challenge even with the use of closed-loop systems.[5,21] Systems which simplify the calculation of prandial boluses and increase flexibility at meal and snack times may play a role in lessening the overall burden of diabetes.[8]

The studies' chosen designs reflect their different primary aims: the feasibility study focused on glycemic control with the dual-hormone system compared to the control arm. The pilot study, however, also assessed qualitative outcomes, requiring an additional arm (FiASP-and-placebo with SMA) to evaluate if potential changes to quality-of-life were related to pramlintide or simply to the alleviation of carbohydrate counting, irrespective of glucose control.

Our feasibility study had several limitations. First, our sample size was small. Second, we delivered insulin and pramlintide using two pumps (although in fixed proportions); several insulin-and-pramlintide co-formulations are currently under development[26–28] that will remove the need for a secondary pump in future dual-hormone studies. Third, we used manual closed-loop control, but this was unlikely to affect clinical outcomes since hormonal delivery would have been the same with an automated system. Our pilot study had similar limitations regarding the burden of devices since placebo pumps were needed to ensure consistency and avoid bias in survey and interview responses. Finally, the sample size was small, posing a risk of selection bias, and qualitative data saturation was not likely reached. The larger, main study aims to recruit a greater number and diversity of participants.

These studies are the first to test a novel FiASP-and-pramlintide closed-loop system with SMA that omits carbohydrate counting. Our data suggest that this FiASP-and-pramlintide closed-loop system with SMA may perform similarly to a FiASP-alone closed-loop systems with FCC. A larger study in a free-living outpatient setting is currently underway, whose primary hypotheses are non-inferiority in glucose control and improvement in quality-of-life with use of the FiASP-

and-pramlintide closed-loop system with SMA compared to the FiASP-and-placebo closed-loop system with FCC.

Acknowledgements

This study was supported by funding from JDRF (2-SRA-2018-654-M-B) and the Canada Research Chairs in artificial pancreas systems held by Ahmad Haidar.

Author Contributions

MAT, LL, JEO, JFY and AH supervised the studies. MAT, LL, JEO, JFY, MV, JR, EP and AH designed the studies. MAT, EC, LL, JEO, JFY, NGP, JR, EP and AH conducted the studies. AEF, JR, AJ and MG carried out the statistical analyses, and EC, MV and MO carried out the qualitative analyses. AH designed the dosing algorithms. AH had full access to the data and takes responsibility for the integrity of the data analysis. All authors read and approved the final version of the manuscript.

Author Disclosure Statement

M.A.T. received research support from AgaMatrix, consulting fees from Sanofi, and speaker honoraria from Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Janssen, and AstraZeneca. L.L. has pending patents in the field of artificial pancreas, received consulting fees from Dexcom and Insulet, and has received support for clinical trials from Merck, AstraZeneca, and Sanofi. J.-F.Y. received research support from Sanofi, Bayer, and Novo Nordisk and consulting fees and speaker honoraria from Sanofi, Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Janssen, Takeda, Abbott, Merck, and AstraZeneca. A.E. has pending patents in the field of the artificial pancreas. E.P. owns intellectual property in the field of the artificial pancreas. A.H. received research

support/consulting fees from Eli Lilly, Medtronic, AgaMatrix, and Dexcom and has pending patents in the artificial pancreas area. No other potential conflicts of interest relevant to this article were reported.

Data availability

The raw data (i.e., insulin delivery, glucose levels) could be shared upon reasonable request for academic purposes, subject to Material Transfer Agreement and approval of McGill University Health Center's research ethics board. All data shared will be de-identified.

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Tables

Table 1 - Baseline participant characteristics

	Feasibility study (*n adults=4, n adolescents=3*)	Pilot study (*n=4*)
Age, years		
Adults	35.0 ± 16.3	50.1 ± 7.3
Adolescents	14.4 ± 1.2	NA
Female participants, n (%)	3 (43)	2 (50)
Duration of diabetes, years		
Adults	27.5 ± 16.3	34.3 ± 17.9
Adolescents	10.7 ± 3.5	NA
Total daily insulin dose, U/day		
Adults	48.7 ± 13.7	44.9 ± 15.9
Adolescents	47.6 ± 2.6	NA
Total daily dose/kg, U/kg/day		
Adults	0.7 ± 0.1	0.6 ± 0.2
Adolescents	0.8 ± 0.1	NA
BMI		
Adults, kg/m^2	24.4 ± 4.6	26.3 ± 6.2
Adolescents, z-score	0.3 ± 0.6	NA
Baseline HbA1c, %		
Adults	8.5 ± 0.4	7.7 ± 0.4
Adolescents	8.3 ± 1.3	NA

Data are presented as mean ± SD

Table 2: Part A - Overall (24 hour) comparisons of glycemic outcomes in the feasibility study; Part B - Overall (24 hour) glycemic outcomes in the pilot study.

Part A – Feasibility Study Glycemic Outcomes

	FiASP-alone with FCC *(n=7)*	FiASP-and-pramlintide with SMA *(n=7)*
Time spent at glucose levels (%) (mmol/L):		
3.9-10.0	81 ± 15	84 ± 14
< 3.9	4.1 [4.1–6.2]	2.1 [0.7–2.4]
> 10.0	13 ± 15	14 ± 15
Mean sensor glucose (mmol/L)	7.3 ± 1.0	7.5 ± 1.3
SD of sensor glucose (mmol/L)	2.2 ± 0.8	2.4 ± 0.9
CV of sensor glucose (%)	29.7 ± 7.1	31.1 ± 5.6
Total Insulin (U)	45.5 ± 14.4	37.1 ± 8.9
Basal Insulin (U)	27.4 ± 7.2	28.7 ± 5.4
Bolus Insulin (U)	18.1 ± 9.8	8.4 ± 6.6

Part B – Pilot Study Glycemic Outcomes

	FiASP-and-placebo with FCC *(n=4)*	FiASP-and-pramlintide with SMA *(n=4)*	FiASP-and-placebo with SMA *(n=4)*
Time spent at glucose levels (%) (mmol/L):			
3.9-10.0	70 ± 11	70 ± 13	60 ± 13
< 3.9	1.0 [0.5-1.7]	1.4 [0.7-2.5]	0.5 [0.4-0.6]
> 10.0	28 ± 10	28 ± 12	39 ± 12
Mean sensor glucose (mmol/L)	8.7 ± 0.6	8.8 ± 0.9	9.8 ± 1.2
SD of sensor glucose (mmol/L)	3.0 ± 0.5	3.2 ± 1.0	3.7 ± 0.8
CV of sensor glucose (%)	33.9 ± 4.2	35.5 ± 7.4	37.4 ± 4.0
Total Insulin (U)	49.3 ± 17.6	46.0 ± 17.3	52.7 ± 24.2
Basal Insulin (U)	30.9 ± 10.7	33.0 ± 11.6	36.1 ± 16.6
Bolus Insulin (U)	18.4 ± 9.6	13.0 ± 5.9	16.6 ± 7.7
Time spent in closed-loop (%)	88.2 ± 7.8	91.2 ± 6.2	89.6 ± 5.7

Data are presented as mean ± SD or median [IQR]
FCC, full carbohydrate counting
SMA, simple meal announcement
SD, standard deviation.
CV, coefficient of variation.

Table 3: Part A - Gastrointestinal side effects during the feasibility study; Part B - Survey scores at baseline and following each intervention in the pilot study.

Part A - Gastrointestinal side effects

	FiASP-alone with Full Carbohydrate Counting				FiASP-and-pramlintide with Simple Meal Announcement			
Number of meals[†] followed by:	Mild	Moderate	Moderate to Severe	Severe	Mild	Moderate	Moderate to Severe	Severe
Any gastrointestinal symptom	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (12.9%)	2 (6.5%)	2 (6.5%)	0 (0%)
Nausea	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (6.5%)	0 (0%)	1 (3.2%)	0 (0%)
Vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Bloating	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (9.7%)	1 (3.2%)	0 (0%)	0 (0%)
Heartburn	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.2%)	1 (3.2%)	0 (0%)

Part B - Survey scores

	Baseline	FiASP-and-placebo with FCC	FiASP-and-pramlintide with SMA	FiASP-and-placebo with SMA
Diabetes Bowel Symptom Questionnaire (overall)[‡]	1.2 ± 0.2	1.1 ± 0.1	1.3 ± 0.4	1.3 ± 0.2
Symptom frequency	1.3 ± 0.6	1.1 ± 0.4	1.3 ± 0.7	1.3 ± 0.5
Symptom severity	1.2 ± 0.5	1.0 ± 0.2	1.3 ± 0.6	1.3 ± 0.6
Diabetes Distress Scale (overall)[§]	2.3 ± 1.1	2.4 ± 1.3	1.8 ± 0.6	2.2 ± 2.0
Emotional Burden subscale[§]	3.2 ± 1.7	3.4 ± 2.1	2.4 ± 1.1	3.0 ± 1.7
Hypoglycemia Fear Survey-II (overall)[‡]	2.5 ± 0.3	1.4 ± 0.0	1.6 ± 0.2	1.4 ± 0.4
Behaviour subscale	2.2 ± 0.4	1.4 ± 0.2	1.7 ± 0.7	1.6 ± 0.7
Worry subscale	2.6 ± 0.9	1.5 ± 0.1	1.4 ± 0.3	1.3 ± 0.1
INSPIRE[‡]	4.1 ± 1.3	4.3 ± 0.7	4.1 ± 0.8	4.3 ± 0.6
PRISM (in viewpoint units)				
Illness Perception Measure	61.8 ± 6.5	54.3 ± 14.2	54.3 ± 14.2	50.0 ± 17.3
Self-Illness Separation	10.9 ± 3.2	3.3 ± 3.5	5.1 ± 2.8	3.8 ± 3.9

Data are presented as number (%) or mean ± SD
FCC, full carbohydrate counting
SMA, simple meal announcement
[†] *There was a total of 32 meals/snacks in the FCC intervention, and 31 meals/snacks in the SMA intervention as one participant was too nauseous to eat their scheduled snack (scored moderate-to-severe)*
[‡] *Scores range from 1-5 on Likert scale*
[§] *Scores range from 1-6 on Likert scale; scores between 2.0-2.9 indicate moderate distress, scores ≥ 3 indicate high distress*

Figures

Figure 1a: Median [IQR] profiles of mean glucose levels and basal hormonal deliveries during closed-loop system visits in the feasibility study. FiASP-alone with full carbohydrate counting intervention (blue), FiASP-and-pramlintide with simple meal announcement intervention (red); sensor glucose levels (top), hormone infusions (bottom).

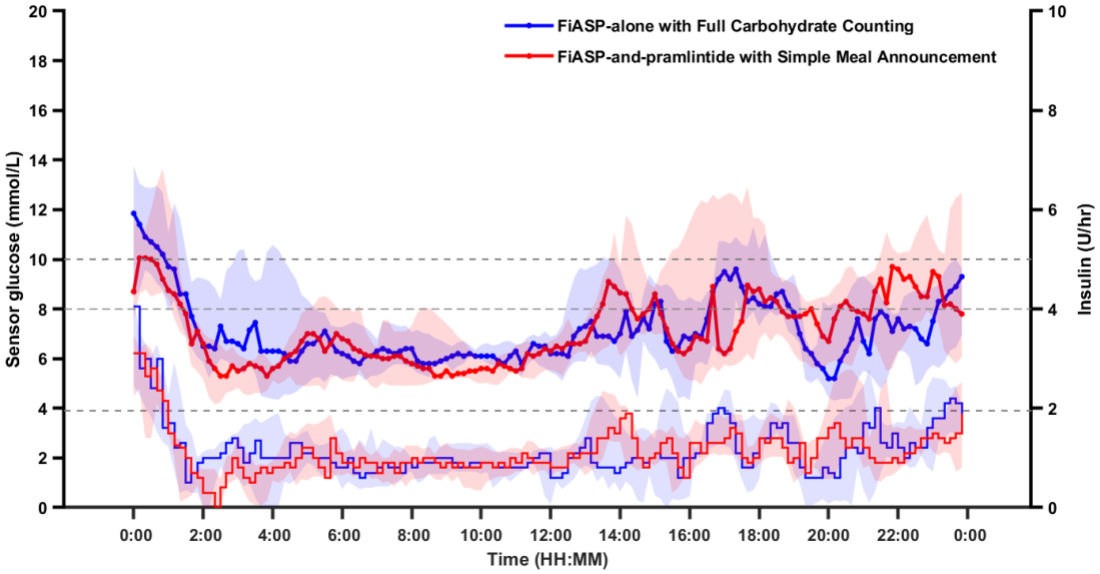
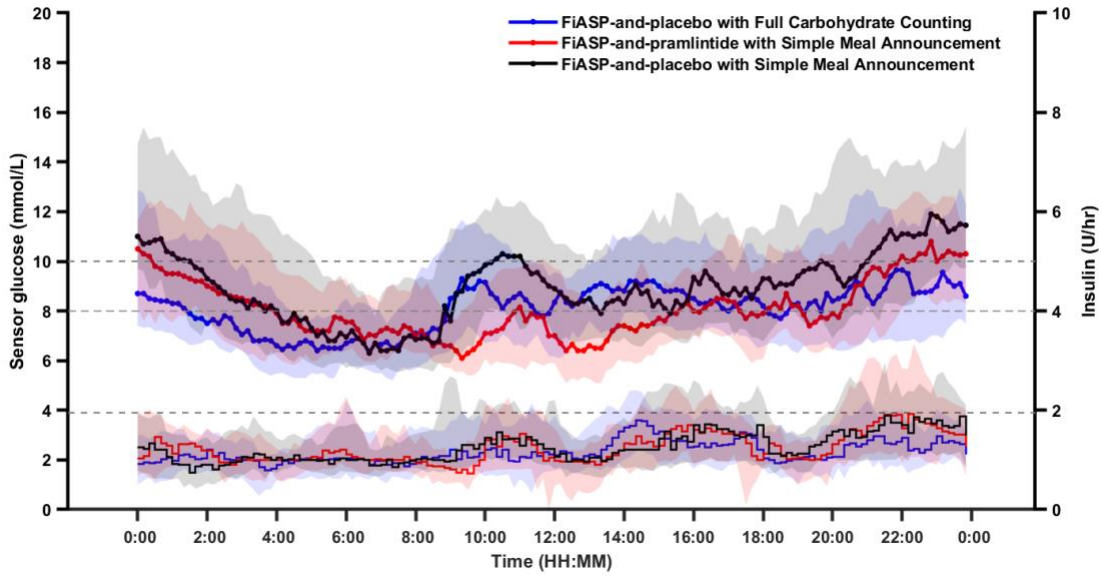


Figure 1b: Median [IQR] profiles of mean glucose levels and basal hormonal deliveries during the 12-day interventions of the pilot study. FiASP-and-placebo with full carbohydrate counting intervention (blue), FiASP-and-pramlintide with simple meal announcement intervention (red), and FiASP-and-placebo with simple meal announcement (black); sensor glucose levels (top), hormone infusions (bottom).



Chapter 4. Discussion

4.1. Psychosocial burden of type 1 diabetes

While it has been established that abiding by a highly demanding treatment regimen is necessary to manage short- and long-term disease complications, psychosocial burdens associated with living with type 1 diabetes must still be addressed. For both adults and adolescents, rates of depression are twice as high as in the general population, which can interfere with already complex disease care.[106,107] Diabetes distress, specifically, is a documented phenomenon which encompasses the feelings of powerlessness, difficulty with disease management, concerns relating to social and physician support, and negative social perceptions that accompany this chronic illness.[108] Not only do these factors correlate with lower glycemic control, but, along with low levels of social support and diabetes empowerment, they can contribute to worsening the emotional burden of disease.[109]

Certain aspects of management can be especially difficult for younger populations, such as the complex mathematics involved in carbohydrate counting and calculating bolus doses, injecting themselves in hard-to-reach areas, and participation in social and academic activities.[110] Adolescents are a particularly vulnerable population to pay attention to owing to the additional challenges they face at a critical time in their lives. They must balance taking on more autonomy and independence in their treatment decisions with their caregivers' desire to remain involved in their care, and adjust to receiving less support without degrading their glycemic control.[111–113] They also face social pressures relating to wanting to fit in with peers which can negatively affect meal-related behaviors.[114]

2.4.3. Alleviating burden with closed-loop therapy

In past studies examining the qualitative impact of hybrid closed-loop systems, users reported an improvement in quality of life and increased "peace of mind" thanks to the systems' effective glycemic management.[56,115] Users and caregivers felt they could rely on systems to maintain blood glucose levels in safe ranges without requiring additional involvement on their part. Some of the benefits included reduced extreme glycemic variations and stabilized overnight glucose levels, which also led to fewer concerns regarding nocturnal hypoglycemia and improved sleep quality.[56,115,116] At mealtimes, systems were able to control complex foods and foods that were uncommonly eaten, provided users with flexibility and spontaneity by managing errors in carbohydrate calculations, unbolused snacks, and the ability to eat out.[114,117] These factors play an important role in strengthening users' and caregivers' trust in closed-loop systems, alleviating the burden of management, or giving a "break" to all those involved in diabetes care.[57,115,118,119]

2.4.4. Barriers to implementation of closed-loop technology

Trust in experimental closed-loop systems is essential for users to fully benefit from the quality-of-life improvements they provide. This is contingent not only on the systems' proper function, but also on users' comfort with giving up "control" of their management to such devices.[120] Trust can be compromised, however, if devices are faulty or demand too much attention (for example, in the form of alerts and calibrations); when considering the new and/or supplementary devices systems may require, additional frustrations risk increasing disease burden rather lessening it.[57,117,118] Additionally, users may be less inclined to rely on systems if certain situations are poorly managed (such as meals or exercise), or if they must work around systems by overriding or "tricking" them, adding to their burden of management.[117]

The aforementioned technological limitations appear to be the main determinants in whether or not users discontinue closed-loop therapy, suggesting that future iterations of commercial systems must address said issues to ensure the success and effectiveness these novel technologies.[121] Other modifications to consider include remote monitoring and access (permitting caregivers and physicians to easily assist pediatric or otherwise dependent populations), and a simple interface that does not require extensive information on carbohydrate amount and/or exercise duration, replacing such functions by announcements with the press of a button.[120,122]

4.2. Quality of life analysis

4.2.1. Survey outcomes

One of the co-primary endpoints of the 30-participant, randomized, crossover trial that followed the pilot study was improvement in quality of life as measured by the difference in Emotional Burden scores of the Diabetes Distress Scale between the Fiasp-and-pramlintide with SMA arm and the Fiasp-and-placebo with FCC arm. Results (Table 2) indicate that adult participants experienced high levels of emotional burden at baseline, while adolescents scored moderate levels of emotional burden at baseline; in both cohorts, scores did not vary with use of any of the three experimental systems investigated.

Table 2. Primary survey outcomes comparing the Fiasp-and-pramlintide system with simple meal announcement (SMA) and the Fiasp-and-placebo system with SMA with the Fiasp-and-placebo system with full carbohydrate counting (FCC).

	Baseline scores	Fiasp-and-placebo with FCC	Fiasp-and-pramlintide with SMA	Fiasp-and-placebo with SMA	Fiasp-and-placebo with FCC minus Fiasp-and-pramlintide with SMA, p value*	Fiasp-and-placebo with FCC minus Fiasp-and-placebo with SMA, p value*
Full cohort (n=30)						
Diabetes Distress Scale	2.0 (0.7)	2.1 (0.8)	2.1 (0.8)	2.0 (0.8)	0.0 (0.5), 0.74	0.1 (0.5), 0.39
Emotional Burden Subscale	2.7 (1.2)	2.7 (1.2)	2.7 (1.3)	2.6 (1.2)	0.0 (0.8), 0.93	0.1 (0.7), 0.30
Adults (n=15)						

Diabetes Distress Scale	2.2 (0.7)	2.3 (0.7)	2.2 (0.8)	2.1 (0.8)	0.1 (0.7), 0.63	0.2 (0.7), 0.34
Emotional Burden Subscale	3.1 (1.4)	3.1 (1.3)	2.9 (1.4)	2.7 (1.3)	0.2 (1.0), 0.55	0.3 (0.8), 0.16
Adolescents (n=15)						
Diabetes Distress Scale	1.9 (0.7)	2.0 (0.8)	2.0 (0.8)	2.0 (0.8)	0.0 (0.3), 0.75	0.0 (0.4), 1
Emotional Burden Subscale	2.3 (1.0)	2.4 (1.0)	2.6 (1.2)	2.5 (1.1)	-0.1 (0.6), 0.37	0.0 (0.6), 0.80

Scores range from 1-5 on Likert scale. Data are presented as mean (SD).
** A P value <0.05 is regarded as significant. P values are calculated for superiority comparisons.*

4.2.2. Thematic interview analysis

Thematic content analysis of participant interviews from the randomized, crossover trial is currently underway as a means to further explore the impact of these experimental closed-loop systems and offer additional insight into the lived experiences of specific demographic groups.

I conducted structured interviews at admission, after each intervention, and upon study completion for each participant. The interview guide was developed by the study sub-investigator; a psychologist specialized in diabetes and in research in behaviour change, motivation, and adaption to chronic disease. Questions were designed to capture known concerns associated with living with diabetes while giving participants space to freely explore the topics they chose to discuss.

Interviews were analyzed via a method of thematic content analysis, using a grounded theory approach to induce meaning directly from participant responses rather than basing interpretations on existing knowledge or theories.[123] This entailed an iterative, collaborative process between myself and a second researcher to ensure the dataset was robustly built and interpretated.[124] To begin, we were trained on thematic analysis techniques by the study psychologist. We thoroughly familiarized ourselves with pilot interview transcripts by reading them several times before independently breaking down a single transcript into thought (or meaning) units – words, phrases, or even paragraphs referring to a related topic.[125,126] A meeting was then held to discuss and define rules for recognizing thought units. Three additional transcripts (from three different participants)

were then broken down following said rules, and we each began the process of open-coding the transcripts: we applied concise, topical labels, or codes, to each thought unit.[125,127] In a second meeting, early codes were compared, modified, or merged until inter-coder agreement could be reached.[124] At this stage, we made a first attempt at abstracting codes into conceptually relevant categories and sub-categories to create a tentative coding frame.[128] This process blended both inductive and deductive approaches as some categories were informed by interview topics while others arose by meaningfully grouping codes together and identifying new concepts.[127,129] We then returned to the four original transcripts to separately re-code them, testing our coding frame and adjusting it where needed to capture notable missing concepts. In a final meeting with the study psychologist, any discrepancies were discussed, category organization was refined, and final code definitions were agreed upon, consolidating a final scheme. The 14 remaining pilot interviews were then coded by both researchers, adding novel codes if they were found to be relevant. In the last stage of pilot-study interview analysis, categories were further examined to detect patterns and over-arching themes aimed at answering the research question. We both met to compare individual interpretations before writing up the final analysis.

In the pilot study, the main themes pertained to how the closed-loop system with simple meal announcement introduced flexibility into participants' eating habits, permitting them to snack without undue concern, as well as how the novel system performed effectively when compared to the usual standard of carbohydrate counting.

This framework, which was developed using pilot study interviews, will be applied to the interviews from the larger study, although it must remain flexible and open to capturing perspectives that may have eluded early analyses due to the pilot study's small sample size; particular attention will be paid to adolescent-specific experiences.

4.3. Future directions for closed-loop systems

The McGill Artificial Pancreas team is interested in exploring the potential uses and benefits of several different adjunctive agents and closed-loop system configurations.

4.3.1. Insulin and pramlintide

A 24-participant, inpatient, randomized, controlled trial comparing non-inferiority of a Fiasp insulin-and-pramlintide fully closed-loop system to a Fiasp insulin-alone hybrid closed-loop over a 24-hour period was recently completed by Tsoukas et al.[130] Fiasp and pramlintide were administered at a 1u:10µg ratio. The fully closed-loop system achieved 74.3% time in target range, whereas the control arm reached 78.1% in range. Non-inferiority in time in range with a 6% margin was not met overall (p=0.28), due mainly to increased time above 10.0 mmol/L (p=0.0093) during the day, especially in the postprandial period; time above 13.0 mmol/L, however, was not significantly increased. In this fully closed-loop system, post-meal boluses were automatically triggered in response to rising on glucose sensor values. The meal detection algorithm was conservative when administering boluses as it had to balance sensor lag (and consequent delay in rising glucose levels after a meal) and the risk of false positive meal detection, which may explain the elevated post-prandial glycemic excursions observed.

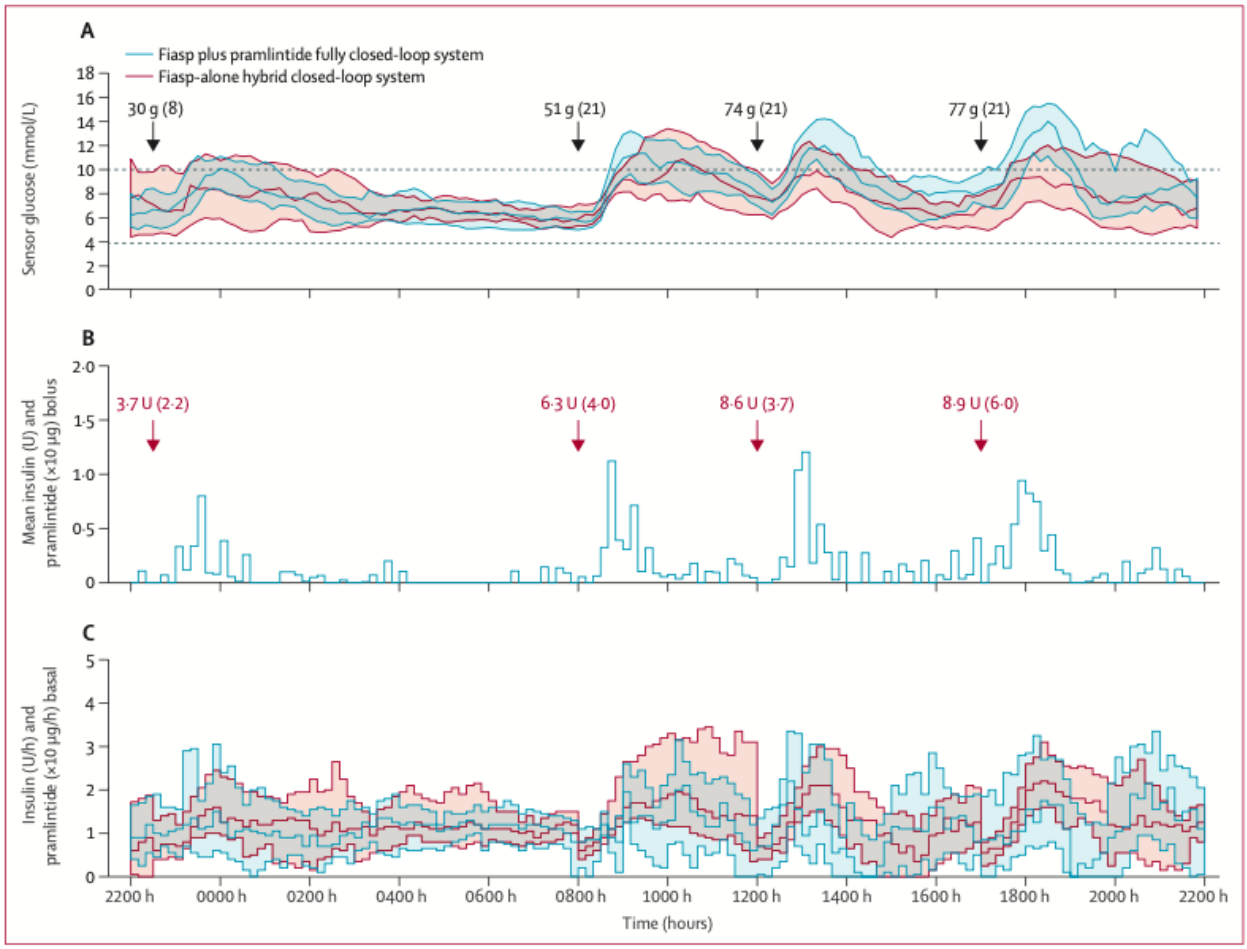


Figure 6*:* Glucose levels and bolus and basal delivery with the Fiasp-alone hybrid closed-loop system and Fiasp plus pramlintide fully closed-loop system (n=24)**.** (A) Median (IQR) glucose values of the fully closed-loop (blue) and hybrid closed-loop (red) interventions. The arrows indicate the time of delivery and average carbohydrate content of each meal. (B) Mean insulin and co-delivered pramlintide boluses (1U insulin:10 µg pramlintide) during the fully closed-loop intervention. The red arrows indicate mean (SD) insulin boluses during the hybrid closed-loop intervention. (C) Median (IQR) insulin basal delivery during the interventions.[130]

Although the primary outcome of non-inferiority was not met, glycemic outcomes in this trial were encouraging, reinforcing the role that pramlintide may have in achieving a fully closed-loop system. This algorithm will soon be tested in an outpatient study to confirm its efficacy in a less controlled setting.

4.3.2. Insulin and SGLT2i

In a 30-participant, open-label, non-inferiority, crossover trial, Haidar et al. evaluated three different meal strategies in combination with 25 mg of empagliflozin (SGLT2i) therapy.[131] In the empagliflozin treatment arm, participants underwent 5-14 days of open-loop optimization before

completing three separate days of closed-loop therapy, each with a different meal strategy, in randomized order: no meal announcement (or fully closed-loop therapy), simple meal announcement prior to mealtimes, and full carbohydrate counting. The placebo-controlled arm included only two randomized meal strategies: simple meal announcement and full carbohydrate counting.

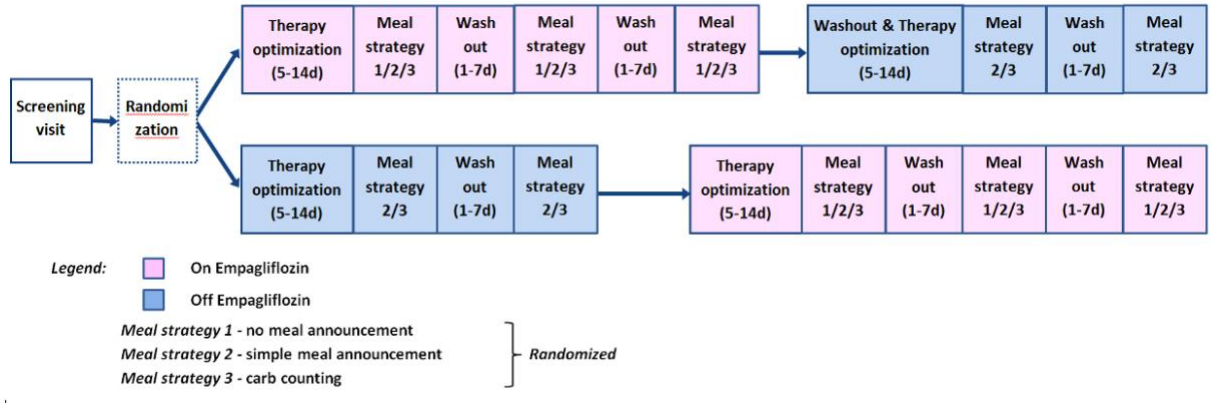


Figure 7: Trial design.[131]

In the absence of meal announcements, the system with empagliflozin did not reach non-inferiority compared with the placebo-controlled arm with carbohydrate counting (p=0.94). However, background use of empagliflozin with the simple meal announcement strategy successfully achieved non-inferiority compared with carbohydrate counting alone (mean glucose: 8.5 mmol/L vs 8.5 mmol/L, p=0.007), and the addition of empagliflozin to full carbohydrate counting reduced mean glucose (7.4 mmol/L vs 8.5 mmol/L, p=0.005), improved time in range (84% vs 70%, p=0.004), and reduced time in hyperglycemia (12% vs 28%, p=0.002) compared with the placebo control.

A separate team recently investigated the addition of another type of SGLT2 inhibitors, dapagliflozin, in the DAPADream study.[132] This double-blind, randomized trial compared a fully

closed-loop arm with twice-daily dapagliflozin to a placebo-controlled arm, in 15 young adults and 15 adolescents. In the dapagliflozin treatment arm, overall time in range ($p<0.0001$) and mean glucose during the night ($p=0.003$) were reduced without an increase in time below 3.9 mmol/L; time in range and mean glucose were also improved in the post-prandial period, following meal challenges. While ketone levels increased with dapagliflozin use, they did not reach a clinically concerning range.

Both of these studies suggest that SGLT2i are a promising class of therapeutic adjuvants when combined with closed-loop therapy. When initiating SGLT2i therapy, however, careful consideration must be placed on which population it is prescribed to: those with a pre-existing history of DKA, low BMI, or low total daily insulin doses may be at higher risk of ketosis with this class of drugs.[133]

4.3.3. Insulin and GLP1-RA

The major remaining limitations of closed-loop therapy concern managing postprandial glycemic excursions. GLP1-RA are an especially attractive group of therapeutic agents to investigate, as their mechanism of action is similar to that of pramlintide, namely delayed gastric emptying and suppression of glucagon release, with the added advantage of a less invasive route of administration (i.e.: weekly injections).[5]

The McGill Artificial Pancreas laboratory will soon begin a double-blind, randomized, controlled trial comparing hybrid closed-loop therapy with weekly subcutaneous semaglutide injections (a GLP1-RA) to a placebo-controlled arm. We aim to recruit 28 participants who will undergo a 9-week titration period prior to each intervention until they reach their maximum tolerated dose, after which 4 weeks of closed-loop assessment will begin. Participants will complete basic laboratory investigations, qualitative surveys (the Type 1 Diabetes Distress

Scale,[134] the Hypoglycemic Fear Survey – II,[135] the INSPIRE questionnaire for adults,[136] the Diabetes Bowel Symptoms Questionnaire,[137] and the Diabetes Treatment Satisfaction Questionnaire[138]) at baseline and following each intervention, and a structured interview at the end of the study. A mixed meal test will also be performed at the end of each intervention for the first seven participants. Use of semaglutide is hypothesized to improve time in target range (3.9-10.0 mmol/L) compared with the placebo control arm. The results of this study may guide future efforts in the development of simplified and less burdensome meal strategies.

Chapter 5. Conclusion

A novel Fiasp-and-pramlintide closed-loop system was developed that aims to reduce the burden of carbohydrate counting by using a simplified meal announcement strategy. This experimental system was first tested in a feasibility study during which 4 adults and 3 adolescents underwent two 24-hour interventions comparing Fiasp-and-pramlintide closed-loop control with a simple meal announcement strategy and Fiasp-alone closed-loop control with full carbohydrate counting. These systems achieved 84 ± 14 % and 81 ± 15 % time in target range, respectively, while median time in hypoglycemia was lower in the Fiasp-and-pramlintide arm (2.1 % [0.7-2.4] vs 4.1 % [4.1-6.2], respectively).

Subsequently, a 4-participant, outpatient, pilot, randomized, crossover study was conducted in adults which compared use of (i) a Fiasp-and-placebo closed-loop system with full carbohydrate counting, (ii) a Fiasp-and-pramlintide closed-loop system with simple meal announcement, and (iii) a Fiasp-and-placebo closed-loop system with simple meal announcement for 12 days. Time in target range was 70 ± 11 %, 70 ± 13 %, and 60 ± 13 %, and median time in hypoglycemia was 1.0 % [0.5-1.7], 1.4 % [0.7-2.5], and 0.5 % [0.4-0.6] on each system, respectively. Pilot participants completed qualitative surveys at baseline and after each intervention; both overall diabetes distress and emotional burden scores fell on the Fiasp-and-pramlintide with simple meal announcement intervention. Thematic content analysis of pilot study interviews indicated that the simplified meal strategy offered participants' greater flexibility and reduced worries related to their eating practices.

15 adults and 15 adolescents recently participated in an outpatient, randomized, crossover trial with an identical design to the pilot study. The coding framework constructed in the pilot study

will be applied to their interviews for qualitative analysis; however, it will likely require modifications to remain sensitive to the different age cohorts' experiences.

Treatment of type 1 diabetes relies extensively on medical devices such as glucose sensors, insulin pumps, and, more recently, closed-loop systems. Despite the latter's documented effectiveness, including their ability to alleviate psychosocial burdens associated with diabetes,[55,57,80–83,117] technology uptake remains low across the world, for reasons relating to both access and user preference.[139] Qualitative data offer rich and important insights into the human elements that inform decisions to initiate and maintain device usage. Future systems should seek to address users' technical and practical concerns to ensure the technologies developed achieve the greatest amount burden relief possible by being both effective and appealing.

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Appendix

Sample interview questions and coding framework

Post-intervention interview: Below are the interview questions participants responded to after each of the three study interventions.

General question	What did you think of using the system over the past 14 days?
Specific follow up questions	Can I ask you more specific questions about the system you used over the past 14 days? - What did you like about this system? - What did you dislike about this system? - What were the advantages of this system? - What were the disadvantages of this system? Can you tell me about your experience with food/meals on this system? - What did you like about this meal strategy? - What did you dislike about this meal strategy? - What were the advantages of this meal strategy? - What were the disadvantages of this meal strategy? - Did this system impact your eating habits? How so? o Types of food? o Frequency? o Timing? - How effective did you find the meal strategy you used over the past 2 weeks at controlling your blood sugar? What were your experiences of hypo- and hyperglycemia on this system? - Can you tell me about hypoglycemia concerns or fears with this system? - Can you tell me about what your management of hyperglycemia was like on this system?
Final question	Is there anything else you'd like to add about your experience with the system you used over the past 14 days?

Sample coding framework: The following table presents a sample of the coding framework established through pilot-study interview analysis, with the codes, categories, and themes relevant to participants' experience with the novel meal strategy compared to their standard practice.

Thought Unit	Code	Category	Theme
"This (FCC) is like, you eat what you want, you do what you want, you have liberty, and if you don't wanna eat, you don't give insulin and if you wanna eat, you do, so for me it's like, just absolute freedom." *(P003, Admission)*	Flexibility/freedom with meals with FCC	Influence of FCC on usual food choices	**Adapting eating behaviours to available meal strategies**
"And you're in so much better health, and you're more aware of what you're eating. Like you eat better when you're carb counting." *(P003, Admission)*	Health benefits of FCC		
"It does make you have a bizarre relationship with food… Sometimes you eat and then you're frustrated because [you're] hungry because then you have the calculate." *(P003, Post Fiasp-plus-placebo with FCC)*	Complicated relationship with food due to FCC		
"When I get frustrat[ed] is when somebody gives me a meal and I don't know how many carbs and I have to guess, that's frustrating." *(P003, Admission)* "I try to avoid, you know, white bread and pasta and things like that. I don't avoid it altogether but it, I just find it's so unpredictable, um and I know I'm going to go sky high… It's often hit and miss, and especially with you know fast carbs like white bread, pasta and all that, so I try to avoid." *(P004, Admission)*	Difficulties managing complex foods with FCC		
"I find the simple meal announcement scary, because we're so used to being on top of things." *(P003, Post Fiasp-plus-pramlintide with SMA)*	Fear/Loss of control over regimen with SMA	Disrupting standard practice with SMA	
"I mean I fe[lt] a little bit out of control at first, I had to get used to that, not having to do a self-calculated extended bolus, I kept the worry about it." *(P001, Post Fiasp-plus-pramlintide with SMA)* "I guess overall the idea of it I love it, the trust in it is a little scary for me." *(P003, Post Fiasp-plus-pramlintide with SMA)*	Distrust in novel SMA strategy		
"It's, that's gonna be the hard thing to go back to, … carb counting." *(P001, Post Fiasp-plus-pramlintide with SMA)*	Dishabituation with carb counting		
"Yeah, I mean I hate to admit I snacked a little more than I otherwise might with the closed loop system." *(P001, End of Study)* "So, yeah I, the fear would be that you just eat whatever you want." *(P003, Post Fiasp-plus-pramlintide with SMA)* "I think on the other 2 I was … more reluctant you know to have snacks, or if I did, again, 'there's quite a few carbs in that snack, maybe I better avoid that', because I wasn't announcing those." *(P004, End of Study)*	Altered eating habits with closed-loop system		
"Because, counting, it gets to a point where, well, we get used to it but… sometimes I tell myself 'Oh, I'd like to be like everyone else, [and] not count anything.'" *(P002, End of Study)* "It just reminds you that, um, this is for life." *(P003, Post Fiasp-plus-placebo with FCC)*	Burden of FCC	Addressing mealtime concerns with SMA	**Effectiveness of a simple meal announcement strategy**
"I guess carb counting I'm always more anxious about lows because I'm worried about, 'Ok I have the blood sugar right, then if I've over calculated what I'm having…', it's like that, that whole thing." *(P001, End of Study)*	Miscalculations with FCC		

"I also found too, I think, I don't remember exactly, but I think that perhaps the, because I was having to guess, for [the FCC intervention] how many carbs I was eating, I may have had some lows because I overestimated." *(P004, End of Study)*			
"I, it was so nice to be able to snack again, just to not have to worry about it. I'm not a huge snack person but it's a snacky time and knowing that that wouldn't be a disaster, or having an extra drink now and again wouldn't be disaster, was really great." *(P001, Post Fiasp-plus-placebo with SMA)* "I could eat what I wanted." *(P002, Post Fiasp-plus-pramlintide with SMA)* "I love the idea of not having to always announce when I'm snacking, because I snack a lot." *(P003, Post Fiasp-plus-pramlintide with SMA)*	Flexibility/freedom with meals with SMA		
"I mean the advantage of simple meal announcement is, like I said, I just have so much to worry about, and having one less thing to worry about is… I mean it's not really one less thing, it's a huge part of our lives as diabetics, it's trying to figure out if we're doing the right thing. Yeah, and I guess that is the biggest advantage there." *(P001, End of Study)* "If it could be like that all the time, it'd be fun. Because it would be like, it's more like everyone's normal, everyday life. You know, not calculating." *(P002, End of Study)* "I liked the fact that I didn't have to add numbers when I had a meal, or that I didn't even have to announce a snack. So that was, which is the ultimate goal of this pump, of this artificial pancreas, is to have this happen. So that was good." *(P004, End of Study)*	Easier/alleviated burden with SMA		
"I guess I found the simple meal announcement did just as good a job as carb counting, and it eliminated my error." *(P001, End of Study)* "It wasn't stressful, you know, I told myself 'Oh, it'll adjust on its own.' You just have to tell it you're eating." *(P002, End of Study)*	Effective SMA strategy	Meal strategies and managing glycemic control	
"Whereas this closed loop system seems to figure that out, and the simple meal announcement was very cautious which, in most of my cases is the right answer to be a little bit more cautious." *(P001, End of Study)*	Trust in the SMA system		
"The only time it really let me down were the meals I already have trouble calculating. If I was eating a really heavy meal, it would occasionally have prob- or not heavy, but like something less healthy, that would usually result in me spiking later." *(P001, End of Study)* "Although it's autocorrecting, it clearly doesn't know what I'm starting with… So, as I said, there were a few times when it was kind of way off base." *(P004, Post Fiasp-plus-placebo with SMA)*	Issues with glycemic control with SMA		
"But it's when I ran into things that I wasn't quite sure on the carbs and I didn't want to run low, I didn't want to run high, but I found it hard for me to use." *(P003, Post Fiasp-plus-pramlintide with SMA)*	Limitations with SMA		
"I think when I was doing carb counting, I maybe was better with, with some situations, … I have strategies that just work better for me." *(P001, End of Study)* "Well as I said, it was better, I thought, that I could type in a precise number of carbs. And also I thought it was more accurate in that respect." *(P004, Post Fiasp-plus-placebo with FCC)*	More control/accuracy in insulin doses with FCC		