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Provincially-Funded Insulin Pump Therapy and Glycaemic Control: Real-World Experience in London, Ontario

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A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in
Epidemiology and Biostatistics

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**PROVINCIALY-FUNDED INSULIN PUMP THERAPY AND GLYCAEMIC CONTROL:
REAL-WORLD EXPERIENCE IN LONDON, ONTARIO**

(Thesis format: Monograph)

by

Selina Laura Liu

Graduate Program in Epidemiology & Biostatistics

A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science

The School of Graduate and Postdoctoral Studies
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London, Ontario, Canada

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Abstract

Background: Limited “real-world” evidence exists supporting insulin pump therapy (IPT) benefits in adults with type 1 diabetes mellitus (T1DM).

Methods: A retrospective matched cohort study compared the change in glycated hemoglobin (A1C) and incidence of adverse events before and after IPT start in adults with T1DM at St. Joseph’s Healthcare in London, Ontario started on IPT between September 2008 – August 2011 to those of a matched control cohort. Paired t-tests, McNemar’s test and negative binomial regression were used.

Results: 174 matched pairs were included. At 1 year, glycaemic control significantly improved in IPT users but not in controls—the mean paired difference in A1C change was -0.3% ($p=0.041$, $n=133$ pairs)—and severe hypoglycaemia was lower in IPT than controls ($p=0.016$).

Conclusions: Provincially-funded IPT in adults with T1DM was associated with clinically significant improvement in glycaemic control and severe hypoglycaemia, providing “real-world” evidence supporting continued IPT funding in adults with T1DM.

Keywords

Type 1 diabetes mellitus, insulin pump therapy, glycaemic control

Dedication

This thesis is dedicated to the loves of my life: my husband Paul, and my daughter Ella.

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List of Abbreviations

A1C	glycated hemoglobin
ACE	angiotensin-converting enzyme
ADP	Assistive Devices Program
ANOVA	analysis of variance
BMI	body mass index
CAD	coronary artery disease
CBG	capillary blood glucose
CDA	Canadian Diabetes Association
CGMS	continuous glucose monitoring system
CVD	cerebrovascular disease
DCCT	Diabetes Control and Complications Trial
DEC	diabetes education centre
DKA	diabetic ketoacidosis
EDIC	Epidemiology of Diabetes Interventions and Complications
ESRD	end-stage renal disease
FSA	forward sortation area
IPT	insulin pump therapy
LADA	latent autoimmune diabetes in adults
LOCF	last observation carried forward
MDI	multiple daily injection
MOHLTC	Ministry of Health and Long-Term Care
NDSS	National Diabetes Surveillance System
PCDSP	Primary Care Diabetes Support Program

PVD	peripheral vascular disease
RCT	randomized controlled trial
RD	registered dietitian
RN	registered nurse
SJHC	St. Joseph's Health Care
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TDD	total daily insulin dose

Chapter 1: Introduction

1.1 Overview and Statement of the Problem

Diabetes mellitus is a common metabolic disorder characterized by chronic hyperglycaemia, and can be broadly classified by etiology into Type 1 and Type 2. Type 1 diabetes mellitus (T1DM) is a result of insulin deficiency due to pancreatic beta-cell destruction. It is most commonly due to an autoimmune process and requires daily insulin treatment. In 2013, it was estimated that ~ 381 million people worldwide, including ~2.6 million people in Canada, have diabetes mellitus, of which 5-15% have T1DM.¹ The prevalence of T1DM, and of diabetes mellitus overall, is increasing.¹

Insulin is the mainstay of treatment in T1DM, and the goal of insulin treatment is to achieve blood glucose levels as close to normal levels as safely as possible. Strict glycaemic control has been shown to decrease microvascular and neuropathic complications, and also potentially reduce macrovascular complications, in patients with T1DM. However, the benefits of strict glycaemic control must be balanced against the risk of hypoglycaemia.

Intensive insulin treatment is the standard of care in T1DM, and it can be delivered through use of insulin pump therapy (IPT) or a multiple daily insulin injection (MDI) regimen.² Insulin pump therapy is the use of a small, portable external pump attached to a subcutaneous catheter to deliver a continuous basal infusion of insulin throughout the day, as well as intermittent bolus insulin doses for meals. An MDI (or “basal-bolus”) regimen is the use of injections of long- or intermediate-acting insulin once or twice daily combined with injections of rapid- or short-acting insulin with each meal.

Meta-analyses of randomized controlled trials comparing IPT to MDI regimens in different patient populations have shown that IPT improves glycaemic control.³⁻¹¹ However, the evidence is less clear regarding the benefit of IPT in improving other clinically relevant outcomes, such as severe hypoglycaemic events and quality of life,

and it is not known whether IPT ultimately reduces the risk of glycaemic-responsive complications. Further, the relevance of these results to the “real-world” is not clear.

A major barrier to IPT is the financial burden associated with its use—the average price of an insulin pump is ~\$7,000.00 CAD, and the average cost of pump-associated supplies is ~\$250.00 CAD per month,¹² which may be prohibitive to those without access to private insurance coverage. In September 2008, the Ontario Ministry of Health and Long Term Care (MOHLTC) began funding of IPT for eligible adults with T1DM through the Assistive Devices Program (ADP), and, until recently, Ontario was the only province in Canada to provide funding for IPT for adults.

As a tertiary care referral centre for Southwestern Ontario, St. Joseph’s Health Care (SJHC), London provides a regional resource for care of T1DM. Patients with T1DM are seen at the Diabetes Clinics at St. Joseph’s Hospital and the Primary Care Diabetes Support Program (PCDSP) at the affiliated St. Joseph’s Family Medical Centre. Out of 71 ADP IPT provider sites for adults in Ontario, SJHC is one of the largest, and is also the main ADP IPT provider site within the South West Local Health Integration Network. Therefore, our patient population may be considered representative of adults with T1DM province-wide, and thus the Diabetes Clinics of SJHC provide a “real-world” setting in which the effectiveness of ADP-funded IPT can be closely examined. Since 2011, the Diabetes Clinics of SJHC have used WebDR, an electronic medical record (EMR) system, for routine clinical care.

To date, the impact of ADP-funded IPT on glycaemic control in adults with T1DM in Ontario has not previously been assessed. This study was the first to evaluate this issue. In addition, this study was the first use of WebDR for research, and demonstrated its utility as a comprehensive researchable database.

1.2 Thesis Objectives

The purpose of this study was to describe the IPT experiences of adult patients with T1DM under routine clinical care in the Diabetes Clinics at SJHC in London, Ontario, and to assess the clinical impact of IPT funded through the Ontario MOHLTC ADP.

The main research question was:

Does ADP-funded IPT improve glycaemic control and reduce adverse outcomes at 1 year in adults with T1DM followed by the Diabetes Clinics at SJHC?

To answer this question, the primary objectives were as follows:

Objective 1: To establish a cohort of adults with T1DM who started on IPT from September 1, 2008 – August 31, 2011, using a regional diabetes-specific EMR database, for future studies in T1DM.

Objective 2: To describe the demographic and clinical characteristics of this cohort.

Objective 3: To compare the glycaemic control of this cohort at 1 year after IPT initiation to that of a matched cohort of adults with T1DM not on IPT.

Objective 4: To compare the frequency of adverse DM-related events in this cohort at 1 year after IPT initiation, to that of the matched non-IPT cohort.

The secondary objective of this study was to test the validity of WebDR, the EMR in use at the Diabetes Clinics of SJHC, as a researchable database.

Chapter 2: Diabetes Mellitus

2.1 Definition and Types of Diabetes Mellitus

Diabetes mellitus is a common metabolic disorder characterized by chronic hyperglycaemia due to inadequate insulin secretion, inadequate insulin action, or both.² Diabetes mellitus can be broadly classified by etiology into Type 1 (T1DM) and Type 2 (T2DM). T1DM is most commonly due to autoimmune destruction of the pancreatic beta-cells, i.e. Type 1A diabetes (which also includes LADA - latent autoimmune diabetes in adults), but occasionally, non-immune-mediated beta-cell destruction can occur, i.e. “idiopathic” or Type 1B diabetes.^{2,13} Both the 1A and 1B subtypes result in insulin deficiency and hyperglycaemia which, if left untreated, causes serious acute and chronic consequences.

2.2 Epidemiology of Type 1 Diabetes Mellitus

In 2013, the worldwide prevalence of all diabetes (both T1DM and T2DM) was estimated to be 8.4% or ~381 million people, while the prevalence of all diabetes in Canada was 10.2% or ~2.6 million people.¹ Since T1DM accounts for 5-15% of all cases of diabetes, it can be estimated that there are approximately 38.1 million people worldwide and 260,000 people in Canada with T1DM.

The worldwide incidence of T1DM has marked geographic variation, with age-adjusted incidence rates ranging from 0.1 per 100,000 per year in China and Venezuela to 40.9 per 100,000 per year in Finland.¹⁴ Moreover, the incidence of T1DM is increasing yearly, with an overall worldwide increase of 3% per year among children under the age of fourteen.¹

It is difficult to estimate the exact prevalence and incidence of T1DM in adults in Ontario, as statistics from the Canadian National Diabetes Surveillance System (NDSS) are based upon population-based administrative data which do not distinguish between T1DM and T2DM. However, given that T1DM accounts for 5-15% of all cases of diabetes, it is assumed that the NDSS statistics reflect this same proportion. Similar to the trend worldwide, the most recent NDSS report also showed increasing prevalence and incidence of diabetes in Canada from 1998/99 – 2008/09, with Ontario having the third highest age-standardized prevalence and second highest age-standardized incidence nationwide.¹⁵

2.3 Pathogenesis of Type 1 Diabetes Mellitus

Type 1 diabetes mellitus is characterized by pancreatic beta-cell destruction by either immune-mediated (type 1A) or idiopathic/non-immune-mediated processes (type 1B). The exact cause of T1DM is not known, though in the case of immune-mediated (type 1A) diabetes, it is believed that one or more environmental factors may trigger development in genetically susceptible people.¹⁶

The major genetic determinant of the risk of T1DM is contained within the HLA genotype, with DR3-DQ2/DR4-DQ8 being the highest risk genotype.¹⁷ Other genes implicated in the susceptibility to T1DM are the insulin gene¹⁸ and the gene for PTPN22, a lymphoid-specific phosphatase involved in T-cell receptor signaling.¹⁹

Proposed environmental triggers for the development of T1DM include viral infections, such as congenital rubella,²⁰ enterovirus,²¹ and rotavirus,²² and dietary factors such as cow's milk²³ and early exposure to cereal in infancy.²⁴

2.4 Management of Type 1 Diabetes Mellitus

The Canadian Diabetes Association (CDA) recommends that management of T1DM be focused around the individual patient, with support from a multi-disciplinary team of diabetes experts.² Important facets of T1DM care include monitoring blood glucose levels, physical activity, appropriate nutrition, and insulin administration. The goal of T1DM management is the prevention of acute and chronic complications in order to reduce morbidity and premature mortality.

The main laboratory parameter used to monitor glycaemic control in diabetes is the glycated hemoglobin (A1C). Hemoglobin is a protein in red blood cells that is essential for oxygen transport. Newly formed red blood cells contain hemoglobin that does not have any glucose attached—however, as red blood cells are permeable to glucose, glucose in the blood irreversibly binds to hemoglobin, forming glycated hemoglobin, at a rate dependent on the blood glucose concentration. Given that the average life span of a red blood cell is ~120 days, the A1C reflects the mean plasma glucose over the past 3-4 months. However, it is a weighted average, with blood glucose levels in the preceding 30 days contributing ~50% of the result, and levels from 90-120 days prior contributing ~10% of the result.²⁵ In Canada, A1C is reported in National Glycohemoglobin Standardization Program units, which use a percent.² Therefore, A1C can be expressed as a decimal or a percent (i.e. an A1C of 0.070 = 7.0%).

The Diabetes Control and Complications Trial (DCCT) was a landmark multicentre randomized controlled trial in 1,441 patients with T1DM which compared the effect of intensive vs. conventional insulin therapy on the development of long-term diabetes-related complications.²⁶ In the DCCT, the intensive insulin therapy group strived for strict glycaemic control, with goal blood glucose levels as close to normal as possible, and a target A1C in the normal range, i.e. <0.0605. However, despite not achieving as tight control as targeted (mean A1C attained was 0.072), the intensive insulin therapy group experienced a significant reduction in the onset and progression of microvascular and neuropathic complications.²⁶ Further epidemiologic analyses of the DCCT results

demonstrated a continuous association between A1C and microvascular and neuropathic complications, with no obvious threshold below which complications would be completely prevented. For example, a 10% reduction in A1C was associated with a 43% lower risk of retinopathy progression.²⁷ Taken together, these results highlight the benefits of tight glycaemic control in patients with T1DM. Based on this evidence, the CDA Clinical Practice Guidelines recommend tight glycaemic control, with a target A1C of ≤ 0.070 , in most people with T1DM.² However, it is also recommended that the target A1C level be individualized for patients based on age, duration of T1DM, risk of severe hypoglycaemia, and co-morbidities.²

2.5 Complications of Diabetes Mellitus and Its Management

Uncontrolled hyperglycaemia from suboptimally treated diabetes can result in acute and chronic complications. However, over-aggressive treatment of hyperglycaemia can also be detrimental as it may cause hypoglycaemia. Thus, the benefits of achieving tight glycaemic control to prevent hyperglycaemic-related complications must always be weighed against the risks of inducing hypoglycaemia.

2.5.1 Acute Complications of Uncontrolled Type 1 Diabetes

In those with T1DM, persistent untreated hyperglycaemia can lead to a hyperglycaemic emergency termed diabetic ketoacidosis (DKA). DKA is characterized by hyperglycaemia, anion gap metabolic acidosis, and ketone acid production due to insulin deficiency (relative or absolute) and excess counter-regulatory hormones. It can be precipitated by stressors including omission of insulin, infection, myocardial infarction, trauma, and medications.

The incidence of DKA varies by age and sex but ranges between 4.6 – 8.0 per 1000 person-years among those with diabetes.²⁸ In Ontario, the rate of hospitalization for acute hyperglycaemia (including both DKA and hyperglycaemic hyperosmolar non-

ketotic state, a related but distinct acute hyperglycaemic condition) in adults ≥ 20 years old in 1999 was 458 per 100,000 people.²⁹ There is a wide variation in the range of in-hospital mortality for patients hospitalized for acute hyperglycaemia—reported mortality in Ontario ranged from $<1\%$ in those age 20-34 up to $\sim 16\%$ in those age ≥ 75 years.²⁹

In the earlier days of IPT use, several studies observed that IPT was associated with higher rates of DKA, most often related to pump infusion system malfunction, interrupting the required basal delivery of insulin.^{30,31} In many cases, rising capillary blood glucose values were noted by the patients, but the actual mechanical pump problems (i.e. infusion set blockage, pump failure) were missed, leading to rapid loss of glycaemic control and the development of DKA.^{30,31} With the advent of more sophisticated technology, it was expected that mechanical pump failures would be less frequent—though this has not been found to be the case.^{32,33} A recent study based on patient responses to a standardized questionnaire showed that, even with current modern insulin pump technology, problems with the infusion set, infusion site and pump itself are still common, with most problems occurring within the first year of IPT.³² The most common infusion set problems were kinking and blockage, the most common infusion site problem was lipohypertrophy (occurring with long duration of IPT use), and the most common pump problems were “no delivery”, keypad and battery problems.³² Guilhem et al.³³ prospectively examined the occurrence of insulin pump failures over 6 years, and found that pump failure still occurs frequently, but with an important difference as compared to the early days of IPT: despite the frequent occurrence of pump failure, the major metabolic consequence of pump failure, DKA, was not seen in the majority of patients.³³ It was speculated that patient education and availability of 24-hour on-call assistance were instrumental in helping to limit the development of DKA after pump failure. These studies highlight the importance of appropriate education and training for patients on IPT to help them recognize technical pump problems, and avoid adverse consequences when they do develop.

2.5.2 Chronic Complications of Uncontrolled Type 1 Diabetes

The chronic complications of T1DM can be classified as microvascular, macrovascular or both. The major microvascular complications are retinopathy and nephropathy, while the major macrovascular complications are coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral vascular disease (PVD). Neuropathy can be caused by both microvascular and macrovascular pathology.

Microvascular Complications

Strict glycaemic control can prevent the development of, or slow the progression of, microvascular complications and neuropathy. In the DCCT,²⁶ intensive therapy targeting normoglycaemia both prevented the development and slowed the progression of microvascular endpoints and neuropathy in people with T1DM.²⁶ Intensive therapy reduced the risks of the development of retinopathy by 76% and the progression of retinopathy by 54%, and also reduced the occurrence of microalbuminuria, albuminuria, and clinical neuropathy by 39%, 54% and 60%, respectively, in patients with T1DM.²⁶

Retinopathy

Diabetic retinopathy is a broad term for damage to the retina caused by changes in the retinal blood vessels in patients with diabetes, clinically characterized by the presence of specific retinal lesions. In 2012, the estimated worldwide age-standardized prevalence of any diabetic retinopathy was 77.3%, while that of vision-threatening retinopathy was 38.5%, in those with T1DM.³⁴ In Canada, diabetic retinopathy is the main cause of blindness in adults aged 30-69 years.³⁵ However, detection and treatment of diabetic retinopathy can decrease the risk of vision loss, and thus routine annual screening is recommended for all people with T1DM starting 5 years after diagnosis.² Treatment options for retinopathy include laser therapy, vitrectomy, or intraocular pharmacological therapy.

Nephropathy

Diabetic nephropathy is defined as damage to the glomeruli of the kidney caused by diabetes, resulting in increasing urinary protein excretion and subsequent impairment of renal function. Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in Ontario and in Canada, with over 25% of the cases of ESRD attributed to diabetes, both provincially and nationally.³⁶ Annual screening for nephropathy is recommended in T1DM starting 5 years after diagnosis.² If nephropathy is present (or if absent but the patient is hypertensive), medications to block the renin-angiotensin-aldosterone system are of benefit. In normotensive patients with³⁷⁻⁴² or without⁴¹ microalbuminuria, as well as in patients with overt nephropathy,⁴³ treatment with angiotensin-converting enzyme (ACE) inhibitors has been shown to slow the progression of nephropathy. This benefit appears to occur independently from the effect of ACE inhibitors in lowering blood pressure.⁴⁴ Similarly, treatment with angiotensin II-receptor blockers has been shown to slow nephropathy progression.⁴⁵

Neuropathy

Diabetic neuropathy is comprised of a range of disorders involving nerve damage due to diabetes. Population-based studies have shown that peripheral and autonomic neuropathy in adults with T1DM is common with prevalences of 66% and 54%, respectively.^{46,47} Similar to the recommendations for retinopathy and nephropathy screening, peripheral neuropathy screening is recommended annually starting 5 years after diagnosis of T1DM. As demonstrated in the DCCT,²⁶ strict glycaemic control is key in preventing and slowing progression of neuropathy, but if neuropathy is painful, symptomatic relief may be attempted using anticonvulsants, antidepressants, opioids, or topical nitrate spray.²

Macrovascular Complications

Strict glycaemic control has also been shown to be important in reducing the risk of cardiovascular disease in T1DM. The DCCT demonstrated a non-significant trend toward

decreased cardiovascular events with intensive therapy targeting normoglycaemia.⁴⁸ The Epidemiology of Diabetes Interventions and Complications (EDIC) study⁴⁹ is a long-term follow-up observational study to the DCCT, and it showed that intensive therapy was associated with a 42% reduction in the risk for any cardiovascular disease event and a 57% reduction in risk for the combined outcome of non-fatal myocardial infarction, stroke, or death.

In addition to glycaemic control, other important measures to reduce cardiovascular risk in T1DM are lifestyle and pharmacologic measures in the management of obesity, hypertension and dyslipidemia, including physical activity and attention to diet, as well as smoking cessation.²

2.5.3 Hypoglycaemia

Hypoglycaemia is a common consequence of insulin treatment. Clinically, it is characterized by Whipple's Triad: 1) the presence of autonomic or neuroglycopenic symptoms, 2) a plasma glucose level <4.0 mmol/L, and 3) resolution of symptoms with administration of carbohydrate. The severity of hypoglycaemia is classified as follows according to the type of symptoms present and whether the patient is able to self-treat: mild – autonomic symptoms and patient can self-treat, moderate – autonomic and neuroglycopenic symptoms and patient can self-treat, severe – patient requires the assistance of another person to treat.² Risk factors for severe hypoglycaemia in patients with T1DM include prior hypoglycaemia, especially tight glycaemic control as reflected by a current A1C <6.0%, hypoglycaemic unawareness, long duration of T1DM, and autonomic neuropathy.² Severe hypoglycaemia in T1DM is common, with prior studies reporting a prevalence between 30-40% per year,⁵⁰⁻⁵² and an incidence between 1.15-3.20 events per person per year.^{53,54} Hypoglycaemia can have a profound negative impact on quality of life, and can discourage patients from striving to achieve tight glycaemic control.

2.6 Insulin in Type 1 Diabetes Mellitus

Insulin is the mainstay of treatment in T1DM. There are a variety of insulin formulations available in Canada with varying onset and peak duration of action (Table 1). The current standard of care for intensive insulin therapy is use of either an MDI regimen or continuous subcutaneous insulin infusion with an insulin pump.²

Insulin injections may be administered using syringes and needles or specially designed insulin pens. In MDI regimens, a basal dose of insulin is given by injection with an intermediate-acting insulin or a long-acting insulin analogue once or twice a day, while bolus doses of insulin are given by injection with a short-acting insulin or a rapid-acting insulin analogue at each meal.² The goal of MDI regimens is to simulate normal pancreatic secretion of insulin.

Table 1 – Insulin Formulations Available in Canada

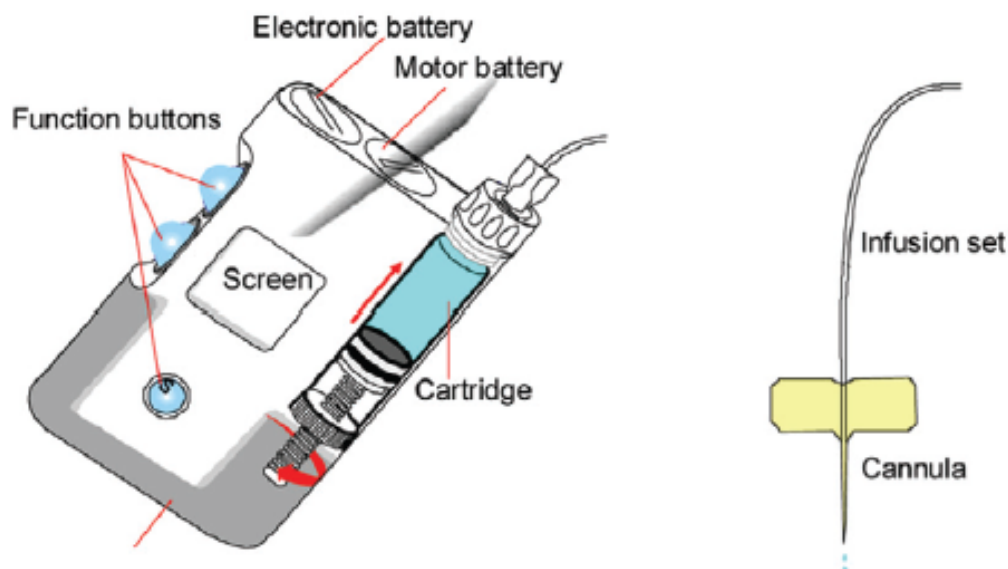
Insulin Type	Generic and Brand Names	Basal or Bolus	Pharmacokinetics
Long-acting basal analogues	Glargine (Lantus) Detemir (Levemir)	Basal	Onset: 90 minutes Peak: Not applicable Duration: up to 24 hours
Intermediate-acting	Humulin-N Novolin ge NPH	Basal	Onset: 1-3 hours Peak: 5-8 hours Duration: up to 18 hours
Short-acting	Humulin-R Novolin ge Toronto	Bolus	Onset: 30 minutes Peak: 2-3 hours Duration: 6.5 hours
Rapid-acting analogues	Aspart (NovoRapid) Lispro (Humalog) Glulisine (Apidra)	Bolus	Onset: 10-15 minutes Peak: 1-2 hours Duration: 3-5 hours
Pre-mixed	Humalog Mix 25 NovoMix 30 Humulin (30/70) Novolin ge (30/70, 40/60, 50/50)		

Adapted from the Canadian Diabetes Association 2009/10 Consumer's guide to diabetes products and medications¹²

Continuous subcutaneous insulin infusion with an insulin pump usually uses rapid-acting analogues. Similar to MDI, IPT strives to mimic physiologic insulin secretion by the pancreas by providing a continuous basal infusion of insulin throughout the day, with boluses given as needed by the patient for meals.

The first subcutaneous insulin pump developed was the “Mill Hill infuser”, described in 1977 by Parsons et al.⁵⁵ The first use of continuous subcutaneous insulin infusion in patients with T1DM was in the United Kingdom⁵⁶ and the United States.⁵⁷

The current subcutaneous insulin pumps consist of a cartridge (reservoir) which may hold up to 300 units of insulin, the pump mechanism (electronic computer components, motor, piston), a battery, display screen and function buttons, and an infusion set containing a small flexible cannula that is inserted under the skin (Figure 1). The original insulin pumps were large, measuring 18.3 x 7.3 x 6.4 cm and weighing up to 400 grams.⁵⁸ However, over the past 35 years the technology has greatly improved such that the current pumps are much smaller and lighter (measuring approximately 8 x 5 x 2 cm and 88-110 grams).¹² Current insulin pumps also have features for easier use, including the ability to program multiple different basal rates of insulin delivery through the day, bolus calculator functions to help calculate the appropriate bolus dose according to the number of grams of carbohydrate consumed, and memory displays of insulin delivery. As the technology develops further, more sophisticated pump features are being offered including insulin pumps combined with continuous glucose monitoring systems (CGMS).



Reproduced with permission from Didangelos T 2011 Diabetes Res Clin Pract⁵⁹

Figure 1 – Schematic of Insulin Pump and Related Supplies

Given the sophisticated features of modern insulin pumps, patients pursuing IPT must undergo specialized training and education to learn not only the basics of using a pump (i.e. infusion set insertion, basal rate programming and bolus dose delivery), but also troubleshooting skills to manage technical pump problems. In addition, the usual components of routine diabetes management are still required (i.e. frequent capillary blood glucose monitoring, accurate carbohydrate counting at meals and snacks, appropriate sick day management etc.).

2.7 Insulin Pump Therapy and Type 1 Diabetes Mellitus

2.7.1 Evidence for the Efficacy of Insulin Pump Therapy in Adults with Type 1 Diabetes Mellitus

Many randomized controlled trials (RCTs) comparing the efficacy of IPT and MDI programs in improving glycaemic control in T1DM have been performed, and several meta-analyses have been done in recent years.³⁻¹¹ All of the meta-analyses have shown a

small but significant improvement in A1C levels with IPT as compared to MDI, though the meta-analyses varied in the studies included, age of subjects (children and/or adults), and types of insulin used in the MDI regimen (i.e. short and intermediate-acting insulins vs. rapid and long-acting insulin analogues).³⁻¹¹

Although it was not designed to compare the efficacy of IPT and MDI in achieving strict glycaemic control, the DCCT provided observational evidence from the intensive therapy group, who self-selected to either IPT or MDI.⁶⁰ When data from participants with at least 4.5 years of follow-up were analyzed according to mode of insulin delivery (IPT n = 124, MDI n=284), the IPT subgroup achieved A1C levels between 0.002-0.004 (i.e. 0.2-0.4%) lower compared to the MDI subgroup with both subgroups being similar in important clinical and demographic characteristics (age, duration of T1DM, baseline A1C).⁶⁰

However, despite the RCT evidence supporting a beneficial effect of IPT use in improving glycaemic control, there is limited observational evidence on the benefits of IPT in routine clinical practice. It is not disputed that results from RCTs provide the strongest level of evidence in answering a question about an intervention's efficacy, but it is often noted that RCT results may be less useful in answering the question of whether the intervention works in routine clinical practice. The subjects of RCTs are usually a highly selected and homogeneous population (as a result of strict inclusion and exclusion criteria), and the intervention studied is given in a standardized manner under ideal settings. These conditions are not the norm in the "real-world". Outside of a RCT, factors other than the intervention can influence the intervention's effectiveness including patient-specific and provider-specific factors.

Despite the meta-analyses of RCTs noted above that have shown a significant benefit of IPT on glycaemic control, worldwide uptake of IPT use is variable. To our knowledge, there have been 19 observational studies⁶¹⁻⁷⁹ (17 prospective or retrospective cohort studies, 2 cross-sectional studies) evaluating the association between IPT and glycaemic control that, because they were observational, may provide a better indication of the

effects of IPT in routine clinical practice (as compared to RCTs). However, even within the observational studies there are differences in design that may not reflect routine care ranging from algorithm-based protocol-driven cohort studies⁶³ to studies of data from regional⁷¹ or national⁷³ IPT registries. Most of these studies have been performed in Europe,^{62,65-68,70,71,73-77,79} with others in the United States,^{61,63,64} New Zealand,⁶⁹ India,⁷² and Australia.⁷⁸ No studies have been performed in Canada, and only 2 studies^{77,78} had a separate control comparison group of non-IPT users. A summary of these observational studies is presented in Table 2.

Table 2 – Summary of Observational Studies of the Association Between Insulin Pump Therapy Use and Glycaemic Control

Author (Year)	Type of Study	Separate Control Group?	Country (Data Source)	# of subjects with T1DM on IPT	IPT Duration	Pre-IPT A1C Mean \pm SD	Mean A1C on IPT (or change in A1C)
Mecklenburg ⁶¹ (1985)	Prospective cohort	N	United States (3° care centre)	127	Mean 31.8 \pm 8.37 mo	0.106 \pm 0.002	0.089 \pm 0.001 (at 1 yr) 0.089 \pm 0.001 (at 2 yrs) 0.086 \pm 0.002 (at 3 yrs)
Chanteleau ⁶² (1989)	Prospective cohort	N	Germany (3° care centre)	116	Mean 4.5 yrs	0.077 \pm 0.001	0.067 \pm 0.001
Bode ⁶³ (1996)	Prospective cohort	N	United States (single centre)	55	Mean 3.1 yrs	0.077 \pm 0.015	0.074 \pm 0.012 (at 1 yr, n=55) 0.077 \pm 0.017 (at 2 yrs, n=41) 0.074 \pm 0.017 (at 3 yrs, n=26) 0.074 \pm 0.012 (at 4 yrs, n=20)
Rudolph ⁶⁴ (2002)	Retrospective cohort	N	United States (3° care centre)	107	Mean 36.1 \pm 25.5 mo	0.076	0.071
Linkeschova ⁶⁵ (2002)	Prospective cohort	N	Germany (3° care centre)	103 (60 for optimization, 43 for severe hypo)	Mean 1.7 \pm 1.5 yrs (optimization grp) Mean 1.9 \pm 1.2 yrs (severe hypo grp)	0.078 \pm 0.012 (optimization grp) 0.076 \pm 0.011 (severe hypo grp)	0.072 \pm 0.008 (optimization grp) 0.072 \pm 0.012 (severe hypo grp)
Nørgaard ⁶⁶ (2003)	Cross-sectional	N	Denmark (nationwide audit)	117 (87 with pre-IPT data)	Mean 13.1 \pm 6.3 yrs	0.085 \pm 0.011 (n=87)	0.080 \pm 0.012 (n=87)
Lepore ⁶⁷ (2005)	Retrospective cohort	N	Italy (3° care centre)	82	Mean 31.9 \pm 14.5 mo (range 4-55 mo)	0.094 \pm 0.014	Mean change -0.0115 \pm 0.008
Pickup ⁶⁸ (2006)	Prospective cohort	N	United Kingdom (3° care centre)	30	Median 5 mo (IQR 3-9 mo)	0.085 \pm 0.014	0.073 \pm 0.900

Reda ⁶⁹ (2007)	Retrospective cohort	N	New Zealand (3° care centre)	78	Mean 3.0 ± 2.6 yrs	0.088 ± 0.014	0.079 ± 0.0100 (at 3 mo) 0.079 ± 0.0097 (at 6 mo)
Giménez ⁷⁰ (2007)	Prospective cohort	N	Spain (3° care centre)	153	Mean 2 yrs	0.079 ± 0.013	0.073 ± 0.011 (at 2 yrs)
Riveline ⁷¹ (2008)	Cross-Sectional	N	France (regional IPT registry)	285 T1DM 44 T2DM	Mean 3.5 ± 3.5 yrs (total cohort n=339)	0.091 ± 0.019 (n=339)	0.078 ± 0.014 (n=339)
Sudhakaran ⁷² (2009)	Retrospective cohort	N	India (3° care centre)	17	Mean 2 yrs (range 2-6 yrs)	0.106 ± 0.021	0.080 ± 0.016
Jankovec ⁷³ (2010)	Retrospective cohort	N	Czech (national IPT register)	730	Minimum 3 yrs	0.0965 ± 0.0007	0.0824 ± 0.0007 (at 1 yr) 0.0834 ± 0.0007 (at 2 yrs) 0.0844 ± 0.0007 (at 3 yrs)
Janez ⁷⁴ (2012)	Retrospective cohort	N	Slovenia (3° care centre register)	184	Mean 3.8 ± 0.3 yrs	0.076 ± 0.009	0.069 ± 0.009 (at 1 yr) 0.069 ± 0.006 (at 2 yrs) 0.070 ± 0.006 (at 3 yrs)
Marmolin ⁷⁵ (2012)	Cohort (retrospective & prospective data)	N	Denmark (3° care centre database)	68	2.2 yrs (range 0-25 yrs)	0.080 (range 0.058-0.137)	0.076 (range 0.061-0.095) (median follow-up 3 yrs)
Crenier ⁷⁶ (2013)	Retrospective cohort	N	Belgium (3° care centre)	50	6 mo	0.0804 ± 0.0116	0.0748 ± 0.009 (at 6 mo)
Carlsson ⁷⁷ (2013)	Retrospective cohort	Y	Sweden (EMR from 10 clinics)	272	Minimum 5.5 yrs	0.0839 ± 0.0130	Mean change at 1 yr: -0.0054
Cohen ⁷⁸ (2013)	Retrospective cohort	Y	Australia (3° care centre)	126	6 mo	0.080 ± 0.01	Mean change: -0.0064 (at 6 mo, n=117) -0.0060 (at 1 yr, n=102)
Grant ⁷⁹ (2013)	Cohort (retrospective & prospective data)	N	United Kingdom (3° care centre)	350	Range 6-12 mo	0.078 (total cohort n=350)	Mean change -0.010 (those without mental health problems: n=171)

T1DM, type 1 diabetes mellitus; IPT, insulin pump therapy; A1C, glycated hemoglobin; SD, standard deviation; Y, yes; N, no; 3°, tertiary; mo, months; yr, year; grp, group, hypo, hypoglycaemia; EMR, electronic medical record

2.7.2 “Real-World” Insulin Pump Therapy Use in Type 1 Diabetes Mellitus

The use of IPT in patients with T1DM varies worldwide but remains low in many countries. Recent nationwide audits in the United Kingdom^{80,81} and Australia⁸² have shown the prevalence of IPT use in T1DM to be 2-6% and 10%, respectively.

In Europe, reported IPT use rates in T1DM vary from <5% in Finland, Portugal, Spain, and Russia,^{83,84} 5-10% in Belgium, Czech Republic, Denmark, Greece, Hungary, Ireland, Italy, Poland, and Slovakia,⁸⁴ and >15% in Austria, France, Germany, the Netherlands, Norway, Sweden and Switzerland.⁸³⁻⁸⁵

There are limited data on IPT use rates in T1DM in Asia, which may be related to the small proportion of patients with T1DM in many Asian countries. In India, over 95% of patients with diabetes have T2DM, and so IPT is used primarily in this population, with only ~20% of IPT use in T1DM.⁸⁶ Similarly, in China, only 30% of IPT use is in T1DM.⁸⁷

The highest rate of IPT use in T1DM is in North America. In the United States, it is estimated that ~40% of patients with T1DM use IPT.⁸³ In Canada, the IPT use rate is estimated to be between ~8-15% of eligible people (children and adults).⁸⁸

The large variability in IPT use worldwide may be related to many factors, but worldwide, a large barrier to IPT use remains the costs to patients and the health care system. The major cost of IPT to the patient is the insulin pump and its associated supplies, while the main costs to the health care system arise from delivery of IPT-related services.⁸⁰

2.7.3 Funding for Insulin Pump Therapy in Type 1 Diabetes Mellitus in Canada

In Canada, government funding to patients with T1DM for IPT and its associated supplies is province-specific (Appendix A). Ontario was the first province to implement IPT funding for children beginning January 2007 (retroactive to April 1, 2006). In September 2008, Ontario was also the first province to initiate IPT funding for eligible adults

through the MOHLTC ADP, with eligibility determined based on pre-specified clinical criteria. The ADP collects demographic, glycaemic control and adverse event data (i.e. hypoglycaemia) at program entry and on annual renewal.

Until very recently, Ontario was the only province to provide IPT funding to adults (Alberta began IPT funding for residents of any age in June 2013). Prince Edward Island remains the only province without funding for IPT (child or adult), while the other provinces and territories only have coverage for children and young adults, with differing age limits, eligibility criteria, coverage for pump supplies, and amount of funding.

In Ontario, the ADP provides coverage for the full cost of the insulin pump on initial application paid directly to the insulin pump supplier. The ADP also provides program participants with a grant of \$2,400.00 CAD per year (divided into quarterly payments) for IPT-associated supplies.

2.8 Insulin Pump Therapy for Type 1 Diabetes Mellitus in London, Ontario

Care for adults with T1DM may be managed by Family Physicians, General Internists, or Endocrinologists. As a tertiary care referral centre for Southwestern Ontario, SJHC provides a regional resource for care of T1DM, and is the main IPT provider site for the ADP within the South West Local Health Integration Network (Appendix B).

At SJHC, adults with T1DM who are interested in pursuing IPT through funding by the ADP may be seen by 1 of 12 adult Endocrinologists in the Division of Endocrinology & Metabolism at St. Joseph's Hospital or by 1 of 2 Family Physicians with expertise in diabetes at the PCDS. To initiate the process, interested patients attend a "Pump Information Class" held at the Diabetes Education Centre (DEC). They are then referred by their physician for individual consultations with a registered IPT nurse (RN) and dietitian (RD) at the DEC for a "Pre-ADP Assessment". As part of this assessment,

patients must demonstrate that they meet the ADP eligibility criteria (Appendix C). After meeting the eligibility criteria, patients attend a “Pre-Pump Start Class” and subsequently a “Pump Start Class” at the DEC, at which time they begin a 90 day trial period of IPT. Once the trial has begun, their physician submits an application form on their behalf to the ADP. On this form, clinical data on glycaemic control and adverse events in the year prior are collected (2-3 most recent A1C values, number of episodes of DKA and severe hypoglycaemia) (Appendix D). Other collected information includes demographics, confirmation of eligibility, and the make and model of insulin pump chosen by the patient. If the trial period is completed successfully, patients then schedule follow-up education classes and individual RN and RD appointments as needed.

If a patient wishes to continue ADP-funded IPT past the first year, they must apply for a renewal. To do so, they must continue to meet specific ongoing eligibility criteria (Appendix C), and their physician is required to submit a renewal form to the ADP, including their last 2 A1C values and number of hypoglycaemic episodes requiring third-party intervention (Appendix E). Application for repeated renewal of IPT funding is required annually thereafter. Continued close contact with the patient’s diabetes management team (physician, RN and RD) is required throughout the duration of their participation in the program.

2.9 Summary

2.9.1 Research Question and Hypothesis

The main research question of this study was: does ADP-funded IPT improve glycaemic control and adverse outcomes in adults with T1DM followed by the Diabetes Clinics at SJHC?

It was hypothesized that ADP-funded IPT would improve glycaemic control and adverse outcomes in adults with T1DM, as compared to adults with T1DM not on IPT, who are followed by the Diabetes Clinics at SJHC.

2.9.2 Significance of the Research

Use of IPT for the management of T1DM is increasing. Clinical trials have shown that IPT significantly improves glycaemic control in adults with T1DM as compared to insulin treatment by MDI, though there is limited observational evidence on the benefits of IPT in routine clinical practice in Canada, and any potential benefits may be highly dependent on appropriate patient selection. Further, a major barrier that precludes widespread use of IPT is the cost.

Ontario has been a leader in Canada in implementing funding for IPT—first for children, and now adults. From the inception of the adult program in September 2008 until December 31, 2012 the ADP has received 7,363 applications from adults in Ontario seeking funding for IPT. However, to date, there has been no evaluation of the clinical impact of ADP-funded IPT.

This study is the first to evaluate the effect of a provincially-funded program for insulin pump therapy on glycaemic control and adverse outcomes in adults served by a tertiary care diabetes referral centre in Canada.

Chapter 3: Methods

3.1 Overview of Study Design

This study used a retrospective single-centre observational matched cohort design using data from WebDR, the EMR system of the Diabetes Clinics at SJHC in London, Ontario, and from physician paper charts. Patients with T1DM were identified, and from these patients, a cohort of subjects on IPT was selected and individually matched to subjects not on IPT, resulting in matched pairs of IPT subjects and control subjects (as described below). Demographic and clinical characteristics were compared between the IPT and control cohorts, while glycaemic control outcomes and adverse events were compared for each pair before and after the IPT start date of each pair's IPT subject.

3.2 Ethics Approval

This study was approved by the Western University Health Sciences Research Ethics Board (Appendices F and G). No patient contact occurred and informed consent was not required as the data used was secondary data collected as part of routine clinical care.

3.3 Data Sources

WebDR is a web-based EMR database system that was developed for clinical and research use at SJHC (Appendix H). WebDR was populated from migration of data from the DAD (a prior EMR used by select Diabetes Clinics in London over the past decade) and by manual data entry from physician paper charts (performed in 2010-2011). Thus, WebDR contains patient data from as early as 2000.

Routine clinical use of WebDR began in September 2011 at the PCDSP and in October 2011 at St. Joseph's Hospital. All patients seen at the Diabetes Clinics are assigned a unique WebDR identification number and demographic, clinical, and laboratory data are entered and/or updated at each visit by physicians, including residents, allied health professionals (nurses and dietitians) or by a dedicated medical data entry clerk. As of March 2013, WebDR contained clinical data from 15,478 patients with diabetes, of whom 12,046 had information on type and duration of diabetes.

The researchable database of WebDR is a repository of de-identified data which is stored on a separate server from the clinical application for security and confidentiality purposes. However, the repository and clinical application are linked to allow for daily data updates. There is one dedicated Database Manager with the unique ability to perform queries of the researchable database.

For this study, data was extracted from WebDR. However, as this was the first use of WebDR for research, for all data extraction the WebDR data was compared to the physician paper chart to ensure accuracy and completeness of the study data. Where WebDR data was missing or different compared to the physician paper chart, data from the physician paper chart was extracted and used in the analyses.

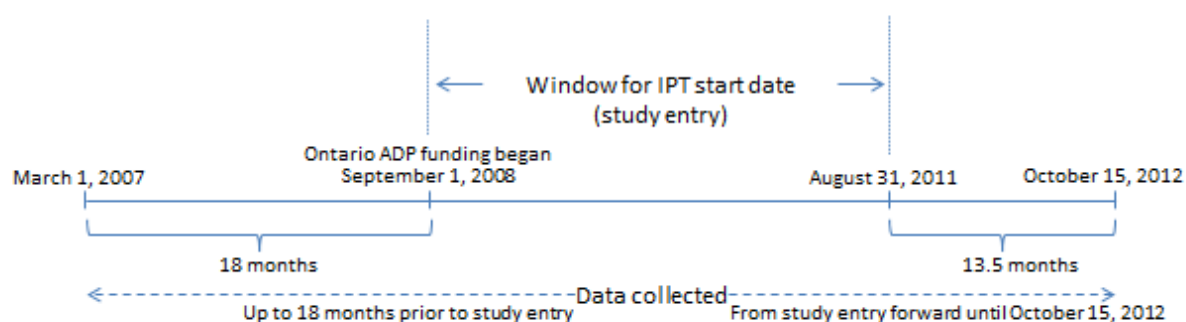
Validation of WebDR data was performed (Appendix I). The gold standard for comparison was the physician paper chart. A random sample of 10% of the study cohort records was selected for validation, with 4 variables selected for validation (baseline A1C value, baseline A1C date, follow-up A1C value, follow-up A1C date). Accuracy was assessed according to 3 levels of agreement (match, no match, not recorded).

The overall level of agreement between WebDR and the reference standard was fair to good, with a range of matches from 69.4% to 80.6%. There were no instances of "no match"; however, the range of "not recorded" values was 19.4% to 30.6%.

For all patient records, after completion of the validation, the data found to be missing in WebDR were extracted from the physician paper chart and subsequently entered into WebDR to improve its accuracy for future research use.

3.4 Study Population and Cohort Selection

The target population consisted of all adults age ≥ 19 years with T1DM followed by the Diabetes Clinics at SJHC and who were entered into WebDR. Subjects on IPT (the insulin pump therapy cohort) were entered into the study at their IPT start date (which could be any time between September 1, 2008 and August 31, 2011) and data from 18 months prior to their IPT start date until October 15, 2012 was collected. The time frame for IPT start date was chosen to (a) coincide with the start of the Ontario MOHLTC ADP funding of IPT for adults, and (b) to allow for data to be collected up until at least 13.5 months after the latest possible IPT start date (i.e. August 2011). This minimum 13.5 month follow-up period was chosen to allow for assessment of the primary outcome (glycated hemoglobin, or A1C) at 1 year, and since A1C is an estimate of glycaemic control over ~ 3 months, a window of 12 ± 1.5 months was selected. Subjects not on IPT (the matched control cohort) were entered into the study according to the IPT start date of the pump cohort subject to whom they were matched, and data from 18 months prior to study entry until October 15, 2012 was collected. Subject follow-up length was variable (Figure 2).



IPT, Insulin Pump Therapy; ADP, Assistive Devices Program

Figure 2 – Timeframes for Insulin Pump Therapy Start and Data Collection

3.4.1 Definition of Type 1 Diabetes Mellitus

The diagnosis of T1DM was determined by an Endocrinologist at St. Joseph’s Hospital or a Family Physician at the PCDSP, and either recorded in the physician’s paper chart and subsequently transferred to WebDR, or directly manually entered into WebDR at the patient’s first visit to clinic. Subjects with T1DM were identified via a WebDR query of diabetes type.

3.4.2 Assembly of the Insulin Pump Therapy Cohort

Subjects on IPT were identified via a WebDR query of medication lists for insulin pump-compatible insulins (i.e. rapid-acting analogues) and insulin doses (i.e. basal insulin rates per hour and bolus insulin doses per gram of carbohydrate). Dates of IPT start (and IPT stop, if applicable) were obtained from WebDR, or, if missing, from the physician’s office paper chart. However, the format of the documented IPT start date varied by subjects. Some subjects had the full IPT start date—i.e. day, month, year—recorded, while others only had month and year. For all IPT subjects, month and year were extracted from WebDR; if this information was missing, it was obtained from the physician paper chart. Within the paper chart, IPT start month and year were extracted from a copy of the initial MOHLTC insulin pump ADP application form if available. However, if a copy of this form was not in the paper chart, IPT start date was extracted from the SJHC DEC pump

start class notification form (preferred) or a clinic progress note which documented the IPT start month and year.

Only those patients who started IPT in September 2008 or later were considered for inclusion, as this was the start month of the Ontario MOHLTC funding of IPT through the ADP. Confirmation of IPT use was performed by cross-reference to the list of patients who started on IPT maintained by the SJHC DEC. It was judged that this was an accurate independent method of verification of IPT use during the time period of interest as it was mandatory for all patients starting on ADP-funded IPT to be seen by an insulin pump nurse and dietitian at the DEC prior to initiation of IPT.

3.4.3 Assembly of the Matched Control Cohort

Subjects not on IPT (and thus potential control subjects) were identified among remaining patients with T1DM in WebDR who were not identified by the WebDR to be using IPT. A WebDR query was performed to generate a list of these subjects, along with their current age, and current duration of T1DM.

This study examined the relationship between IPT use and glycaemic control. As there are many potential confounding factors for this relationship (i.e. factors associated with both IPT use and with glycaemic control), matching was used to limit confounding bias. The primary matching variable was duration of T1DM. The secondary matching variables were current age and year of study entry. Matches were identified manually as described below.

Control subjects were matched to IPT subjects starting with exact duration of T1DM in years, and then matched as closely as possible for current age in years measured as the absolute difference between the age of the IPT subject and the control subject. In situations where there was more than 1 potential control subject with the same *absolute* age difference compared to the IPT subject (e.g., if a potential control subject was 2 years younger and another was 2 years older), the older subject was selected as the matched control. If there was more than 1 potential control subject with the *same*

age difference compared to the IPT subject (e.g. both were 2 years younger), the first subject on the list was selected. The date of study entry of control subjects was the “t=0 date”, which was defined as the corresponding IPT start date of the IPT subject to whom they were matched.

3.4.4 Inclusion Criteria

Patients were included if they were age ≥ 19 years of age at the time of study entry and had a known diagnosis of T1DM for at least 1 year prior to study entry. The rationale for only including those with T1DM for ≥ 1 year was that a) glycaemic control in the first year after diagnosis may not necessarily be representative of long-term glycaemic control, b) data from at least 1 year prior to study entry was required and c) to be eligible to apply for ADP-funded IPT, patients had to demonstrate experience on an MDI regimen for at least 1 year. It was also required that patients had a paper chart available for review, and were actively followed by a SJHC physician during the time period of interest.

Patients on IPT were included in the IPT cohort if they began IPT through the Diabetes clinics at SJHC at age ≥ 19 years at some point between September 1, 2008 and August 31, 2011, and remained on IPT for at least 1 year. The rationale for these requirements were that a) those who started IPT during this time were likely to have done so via ADP funding, and b) data from 1 year after IPT start was required.

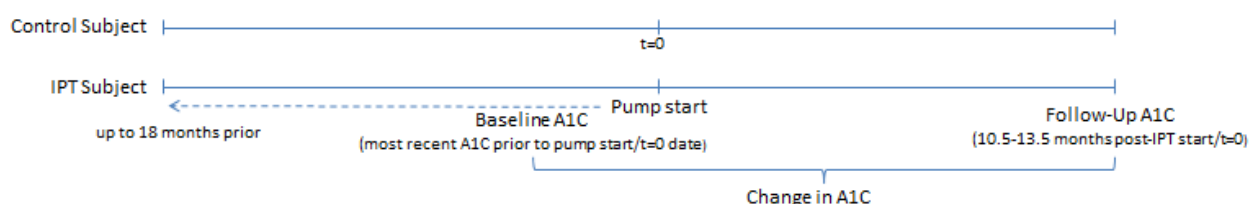
3.4.5 Exclusion Criteria

Patients were excluded if they a) were pregnant within 1 year prior to or within 1 year after study entry, b) did not have a documented baseline A1C level within 18 months before study entry or c) did not have any documented follow-up A1C measurements after study entry. Pregnancy was a reason for exclusion as it is a time during which stricter glycaemic targets are recommended.²

3.5 Outcome Measures

The A1C level was used as the main measure of glycaemic control. The values and dates of A1C measurements were extracted from WebDR (in which values were migrated from the DAD and/or entered manually by trained individuals). If missing from the EMR, values were obtained via review of physician paper charts.

The primary outcome measure was the paired difference in the change in A1C from baseline to follow-up between matched pairs of IPT and control subjects. This was defined as: $[(\text{follow-up A1C}_{\text{IPT}} - \text{baseline A1C}_{\text{IPT}}) - (\text{follow-up A1C}_{\text{control}} - \text{baseline A1C}_{\text{control}})]$. The baseline A1C was defined as the most recent A1C value prior to the IPT start or $t=0$ date, and was required to be within 18 months prior to the IPT start or $t=0$ date. The follow-up A1C was defined as the A1C value closest to 12 months after the IPT start or $t=0$ date; however, since A1C provides an estimate of glycaemia over ~ 3 months, the window for the follow-up A1C was 12 ± 1.5 months (10.5 - 13.5 months) (see Figure 3).



IPT, insulin pump therapy; A1C, glycated hemoglobin

Figure 3 – Definition of Primary Outcome

The secondary outcome measures were a) “the proportion of subjects with optimal glycaemic control at follow-up” defined as the percentage of subjects with an A1C of ≤ 0.070 at 12 ± 1.5 months post IPT start/ $t=0$ date, and b) “the incidence of adverse events at follow-up” defined as the incidence of episodes of diabetic ketoacidosis (DKA) and severe hypoglycaemic events per 100 patient-years at each follow-up year (yearly

follow-up for adverse events was based on the calendar year). Severe hypoglycaemia was defined as hypoglycaemia requiring 3rd-party assistance.² Adverse events were continuous variables obtained via patient self-report, and were reported as incidence rates separately for each type of event at baseline and at each follow-up year.

3.6 Cohort Characteristics – Insulin Pump Therapy and Control Cohorts

The following demographic and clinical characteristics were collected from WebDR and/or physician paper charts at baseline, or at baseline and follow-up, for the IPT and control cohorts: current age, gender, access to private drug plan, city of residence, average yearly household income, physician of record, current duration of T1DM, smoking status, complication status, body mass index (BMI), total daily insulin dose (TDD), number of capillary blood glucose (CBG) monitoring checks per day, number of insulin injections per day, CGMS use, and number of adverse events per year. Baseline characteristics were those documented in the calendar year prior to the IPT start year/t=0 year, while follow-up characteristics were those documented in the calendar year after the IPT start year/t=0 year.

3.6.1 Demographic Characteristics

Current age

Current age was a continuous variable in years derived from the patient self-reported year of birth. Current age was calculated as 2013 – (year of birth). The year 2013 was chosen as the reference year for calculating the current age since data analysis was done in the year 2013.

Gender

Gender was coded as a dichotomous variable with 1 representing males and 0 representing females.

Access to Private Drug Plan

Access to a private drug plan at baseline was defined as access to any non-Ontario Health Insurance Plan drug insurance coverage, and was obtained via patient self-report. It was coded as a dichotomous variable, with 1 for “yes” and 0 for “no”.

City of Residence

City of residence at baseline was obtained via patient self-report. It was coded as a dichotomous variable with 1 for London and 0 for any other city.

Average Yearly Household Income

Average yearly household income at baseline was a continuous variable in dollars derived from linkage of patient self-reported postal code to data from the 2006 Census of Canada. The Census of Canada obtains address information (including postal code) and data on household income for each respondent allowing for calculation of average yearly household income at the Forward Sortation Area (FSA) level, which is the first 3 characters of the postal code (as defined by Canada Post). Data from the 2006 Census of Canada was obtained via Western University’s Equinox data delivery system.

Physician of Record

The physician of record was the physician responsible for the patient’s diabetes care. The variable was categorized into a dichotomous variable as per the physician specialty, with 1 for Endocrinologist and 0 for Family Physician.

3.6.2 Clinical Characteristics

Current duration of T1DM

Current duration of T1DM was a continuous variable in years derived from either the patient self-reported year of T1DM diagnosis or the patient self-reported age at T1DM diagnosis. If the year of T1DM diagnosis was available, current duration of T1DM was calculated as $2013 - (\text{year of T1DM diagnosis})$. As above, 2013 was used as the reference year since data analysis was done in 2013. If the age at T1DM diagnosis was available, the year of T1DM diagnosis was calculated as $(\text{year of birth}) + (\text{age at T1DM diagnosis})$, and then duration of T1DM subsequently calculated.

Smoking status

Smoking status at baseline was obtained via patient self-report, and coded as a dichotomous variable with 1 for “current smoking” and 0 for “no current smoking”.

Complication Status

The complication status at baseline was obtained via patient self-report. The specific complications were cerebrovascular disease, coronary artery disease, peripheral vascular disease, retinopathy, nephropathy and neuropathy, and were each coded as a dichotomous variable with 1 for “presence of complication” and 0 for “absence of complication”. The frequency of each complication was reported separately, and also reported grouped into the dichotomous variables “at least 1 complication” (defined as the presence of any 1 or more complication) and “at least 1 glycaemic-responsive complication” (defined as the presence of at least 1 of retinopathy, nephropathy or neuropathy), with 1 for “presence” and 0 for “absence”.

Body Mass Index

Body Mass Index (BMI) was a continuous variable in kg/m^2 derived from the height and weight of each patient (calculated as weight/height^2). Data on BMI was collected at

baseline and at yearly follow-up. Height was either patient self-reported or measured at the initial clinic visit, and weight was measured by clinic staff at each clinic visit.

Total Daily Insulin Dose

The total daily insulin dose (TDD) at baseline was a continuous variable in units derived from the patient self-reported basal and bolus insulin doses. It was calculated as (total basal insulin doses per day) + (total bolus insulin doses per day).

Capillary Blood Glucose Monitoring Checks

The number of capillary blood glucose monitoring checks (CBG) per day, at baseline and at yearly follow-up, was a continuous variable obtained via patient self-report.

Insulin Injections

The number of insulin injections per day, at baseline (IPT cohort) or at baseline and yearly follow-up (control cohort), was a continuous variable obtained via patient self-report.

CGMS Use

Use of a CGMS was a dichotomous variable, obtained via patient self-report. It was defined as “ever CGMS use”, with 1 for “yes” and 0 for “no”.

3.7 Insulin Pump Therapy-Related Characteristics

For the IPT cohort, the following IPT-related characteristics were collected: age at IPT start, brand of insulin pump, year of ADP application, year of insulin pump trial start and wait time from DEC referral to DEC appointment for the ADP process.

3.7.1 Age at Insulin Pump Therapy Start

Age at insulin pump therapy start, in years, was a continuous variable derived from the documented year of insulin pump therapy start (from WebDR or physician paper chart) and patient self-reported year of birth, calculated as (year of pump start) – (year of birth).

3.7.2 Brand of Insulin Pump

The brand of insulin pump was a categorical variable obtained from a copy of the initial MOHLTC ADP insulin pump application form in the physician paper chart. If this was not available, data on brand of insulin pump was extracted from clinic progress notes. The variable was coded as 1 for Medtronic, 2 for Animas or 0 for other.

3.7.3 Year of ADP Application and Year of Insulin Pump Trial Start

Year of ADP application and year of insulin pump trial start were coded as categorical variables based on the calendar year of the dates of ADP application and insulin pump trial start documented on a copy of the initial MOHLTC insulin pump ADP application form in the physician paper chart. Years were coded as follows: 0 for 2008, 1 for 2009, 2 for 2010, 3 for 2011 and 4 for missing. Of note, the variables 2008 and 2011 were not full 12 month years, given that window for IPT start date was from September 2008 until August 2011, so the variable 2008 represents data from 4 months (September-December 2008) and 2011 represents data from 8 months (January-August 2011), while the variables 2009 and 2010 represent data from the full 12 month calendar years. Further, whether a copy of the initial MOHLTC insulin pump ADP application form was kept in the paper chart varied by physician, and therefore some data on year of ADP application and year of insulin pump trial start was missing.

3.7.4 Wait time from DEC Referral to Appointment

Wait time from DEC referral to appointment in months was a continuous variable based derived from the dates of DEC referral and DEC appointment documented in a copy of the initial MOHLTC insulin pump ADP application form in the physician paper chart.

3.8 Power Calculation

An *a priori* power calculation was performed prior to the start of the study. It was estimated that between 100-250 adults with T1DM from the Diabetes Clinics at SJHC were on ADP-funded IPT. Given this range in sample size, assuming $\alpha=0.05$ and $\beta=0.20$, and estimating the standard deviation of the mean change in A1C over 1 year to be 0.00048, or 0.048% (as per WebDR data from all adult patients with T1DM in 2010), the smallest detectable difference in the mean change in A1C over 1 year between the IPT and control cohorts was between 0.00019, or 0.019% (for $n=100$ per group) and 0.00012, or 0.012% (for $n=250$ per group) (Table 3).

Table 3 – Power Calculation and Smallest Detectable Difference in Change in A1C

SD of change in A1C (σ_{Δ})	Sample Size Per Group					
	50	100	150	200	250	300
0.048%	0.027%	0.019%	0.016%	0.013%	0.012%	0.011%

$$\delta^2 = [(Z_{\alpha} + Z_{\beta})^2 * 2\sigma_{\Delta}^2] / n$$

where:

Δ_c = mean change in A1C in control cohort over 1 year

Δ_p = mean change in A1C in IPT cohort over 1 year

σ_{Δ} = SD of change in A1C over 1 year = 0.048%

δ = smallest detectable difference between Δ_c and Δ_p

n = sample size per group

and assuming $\alpha = 0.05$, $\beta = 0.20$

SD, standard deviation; A1C, glycated hemoglobin; IPT, insulin pump therapy

3.9 Statistical Analysis

Statistical analysis was performed using SAS for Windows (version 9.3). Demographic and clinical characteristics were summarized using means and standard deviations or proportions where applicable. The level of significance for all statistical tests was 0.05, unless otherwise stated.

3.9.1 Comparison of Included and Excluded IPT Subjects

The age, duration of T1DM and gender of the included and excluded IPT subjects were compared using independent samples t-tests (means) or Chi-square test (proportions), as appropriate.

3.9.2 Paired Comparisons

Paired comparisons were performed to compare the current demographic characteristics and baseline clinical characteristics of the IPT and control cohorts, using paired t-tests (means) or McNemar's test (proportions) as appropriate. Paired t-tests were also performed to compare the mean A1C at baseline and follow-up and the mean difference in A1C change scores between the IPT and control cohorts. McNemar's test was used to compare the proportions of subjects with an optimal A1C at baseline and follow-up within each cohort, and to compare the proportions of subjects with an optimal A1C between the IPT and control cohorts. Negative binomial regression was used to compare the incidence of adverse events between cohorts at baseline (i.e. 1 year pre-IPT start/ $t=0$) and at each follow-up year.

3.9.3 Missing Data and Imputation

Two pre-specified analyses were performed. The analyses differed depending on the definition of the timing of the follow-up A1C, and whether imputation for missing data was performed, as follows:

Analysis 1: The follow-up A1C was defined as the A1C value closest to 12 months post-IPT start/post-t=0 within a window of ± 1.5 months (i.e. 10.5-13.5 months) post-IPT start/post-t=0. For subjects without a follow-up A1C between 10.5-13.5 months post-IPT start/post-t=0, the missing data were not imputed and they were excluded from the analysis.

Analysis 2: The follow-up A1C was defined as the A1C value closest to 12 months post-IPT start/post-t=0 within a window of ± 1.5 months (i.e. 10.5-13.5 months) post-IPT start/post-t=0. For subjects without a follow-up A1C in this window but who had an A1C value between 0 -10.5 months post-IPT start/post-t=0, their follow-up A1C level in the analysis was imputed by the “last observation carried forward” (LOCF) method, which effectively widened the window for follow-up A1C in this analysis to 0-13.5 months post-IPT start/post t=0. Those subjects who only had follow-up A1C values >13.5 months post-IPT start/post t=0 were excluded from the analysis.

The proportion of subjects who were missing follow-up A1C values in the IPT vs. control cohorts were compared using McNemar’s test. In addition, the baseline characteristics of the subjects with missing follow-up A1C data were compared to those subjects with non-missing follow-up A1C data within each cohort using two-sample t-tests, Chi-square tests, or Fisher’s Exact test, where appropriate.

3.9.4 Sensitivity Analyses

Effect of Wider Age Differences in Age-Matched Pairs

Since some of the matched IPT-control pairs were not matched within a ± 5 year age difference, a sensitivity analysis was done excluding these pairs to determine if a wider age difference between IPT-control pairs had an effect on the glycaemic outcomes.

Effect of Imputing Follow-Up A1C values from <6 Months Post-IPT Start/t=0

The use of LOCF to impute missing follow-up A1C values assumed that the follow-up, but missing, A1C value did not significantly change from when it was measured to when it was carried forward. However, since A1C is a measure of glycaemia over ~ 3 months, the further from the defined 10.5-13.5 month follow-up window that it was measured (i.e. the closer to IPT start/t=0), the less likely this assumption was to hold true. Therefore, a sensitivity analysis was done using LOCF of only A1C values measured between 6-10 months post-IPT start/t=0 to determine if carrying forward values from earlier than 6 months post-IPT start/t=0 had an effect on the glycaemic outcomes.

3.9.5 Subgroup Analyses

Exploratory analyses were done to examine whether the baseline A1C influenced the change in A1C from baseline to follow-up in each cohort. The analysis was performed separately within each cohort stratified according to baseline A1C into 3 subgroups: ≤ 0.070 , 0.071 to 0.080 , and ≥ 0.081 . For both the IPT and control cohorts, paired t-tests were done to compare the baseline and follow-up A1C in each subgroup. Baseline TDD was also calculated for each subgroup and compared by one-way analysis of variance (ANOVA) to assess for differences in baseline insulin dose that could contribute to differences seen in the change in A1C. If the subgroups were significantly different by ANOVA, post-hoc analysis with the Tukey-Kramer test was performed to determine which groups differed.

Chapter 4: Results

4.1 Study Cohorts

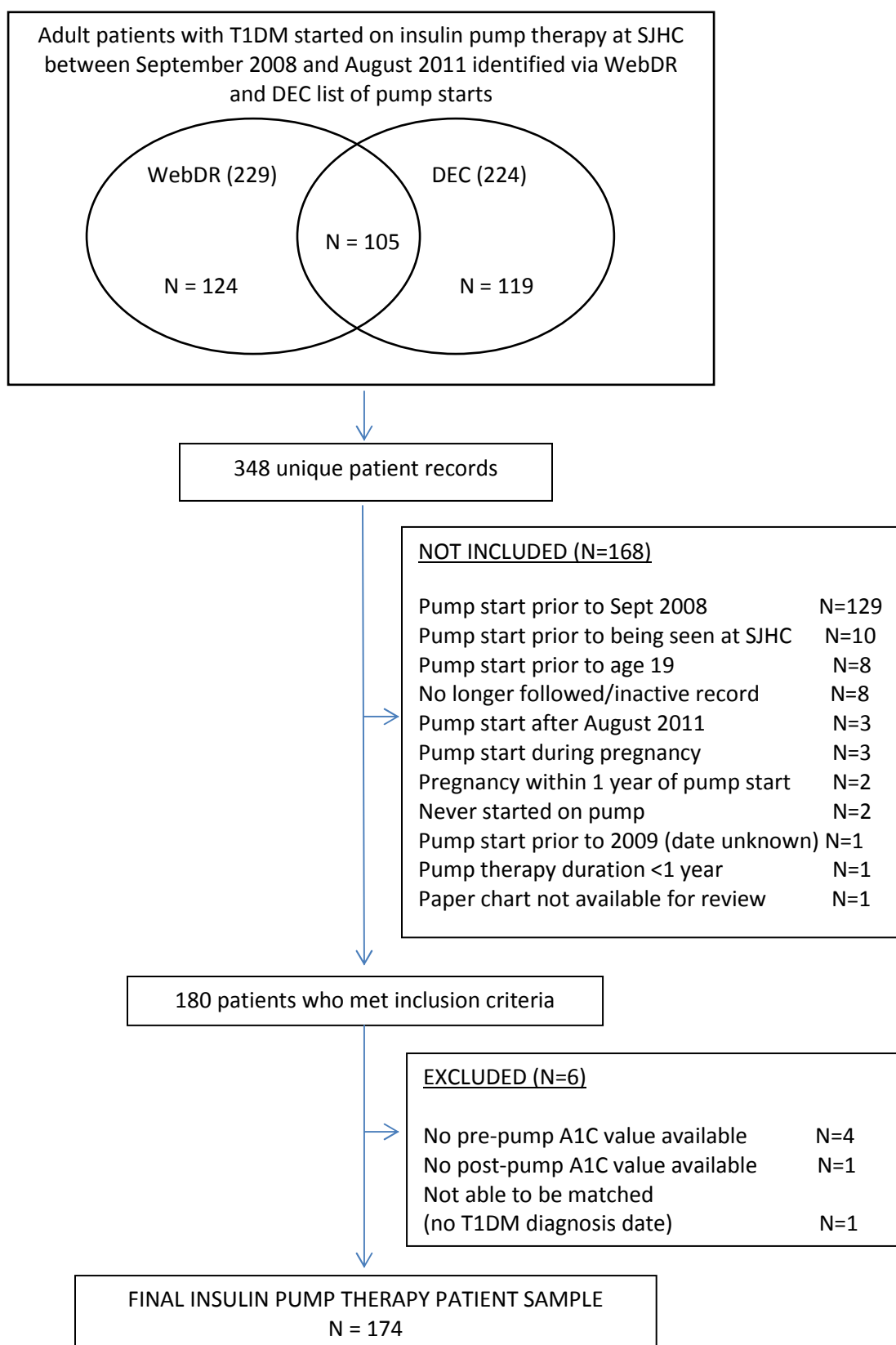
4.1.1 Insulin Pump Therapy Cohort

There were 229 patient records identified by WebDR and 224 patient records identified by the DEC list of adults with T1DM who started IPT between September 1, 2008 and August 31, 2011. Of these, 105 were common to both sources, resulting in 348 unique patient records. Both the WebDR record and physician paper chart record were reviewed for 347 of the patients (1 paper chart was not available for review), and 180 patients were found to meet the inclusion criteria. However, a further 6 patients were excluded, resulting in a final IPT cohort of 174 patients (Figure 4).

Therefore, there were 174 patients on IPT who were not included in the analysis. Comparing the final IPT cohort to those IPT patients who were not included in the study showed that the patients on IPT who were not included were significantly younger ($p<0.001$), and more likely to be female ($p=0.038$), but had a similar duration of T1DM (Table 4).

4.1.2 Matched Control Cohort

Control subjects were first matched to IPT subjects by exact duration of T1DM in years, and then by closest age in years. The age differences of the pairs were normally distributed, and 84.5% ($n=147$) of the 174 IPT-control pairs were matched within ± 5 years (Figure 5).



T1DM, type 1 diabetes mellitus; SJHC, St. Joseph's Health Care; DEC, Diabetes Education Centre; A1C, glycated hemoglobin

Figure 4 – Insulin Pump Therapy Cohort Selection

Table 4 – Comparison of Final Insulin Pump Therapy Cohort vs. Insulin Pump Therapy Patients Not Included/Excluded

Variables	Final IPT Cohort n=174	IPT Patients not included/excluded n=174	p-value
Age (years)	45.0 ± 12.8	39.8 ± 13.2	<0.001[†]
Duration of T1DM (years)	25.2 ± 13.1	23.5 ± 11.8 [*]	0.205 [†]
Sex (Male) – n (%)	80 (46.0)	61 (35.1)	0.038[‡]

IPT, insulin pump therapy; T1DM, type 1 diabetes mellitus

Data are mean values ± SD or number and frequency

^{*} 9 patients of those not included/excluded were missing data on duration of T1DM

Comparison between groups using [†]two sample t-test or [‡]Chi-square test

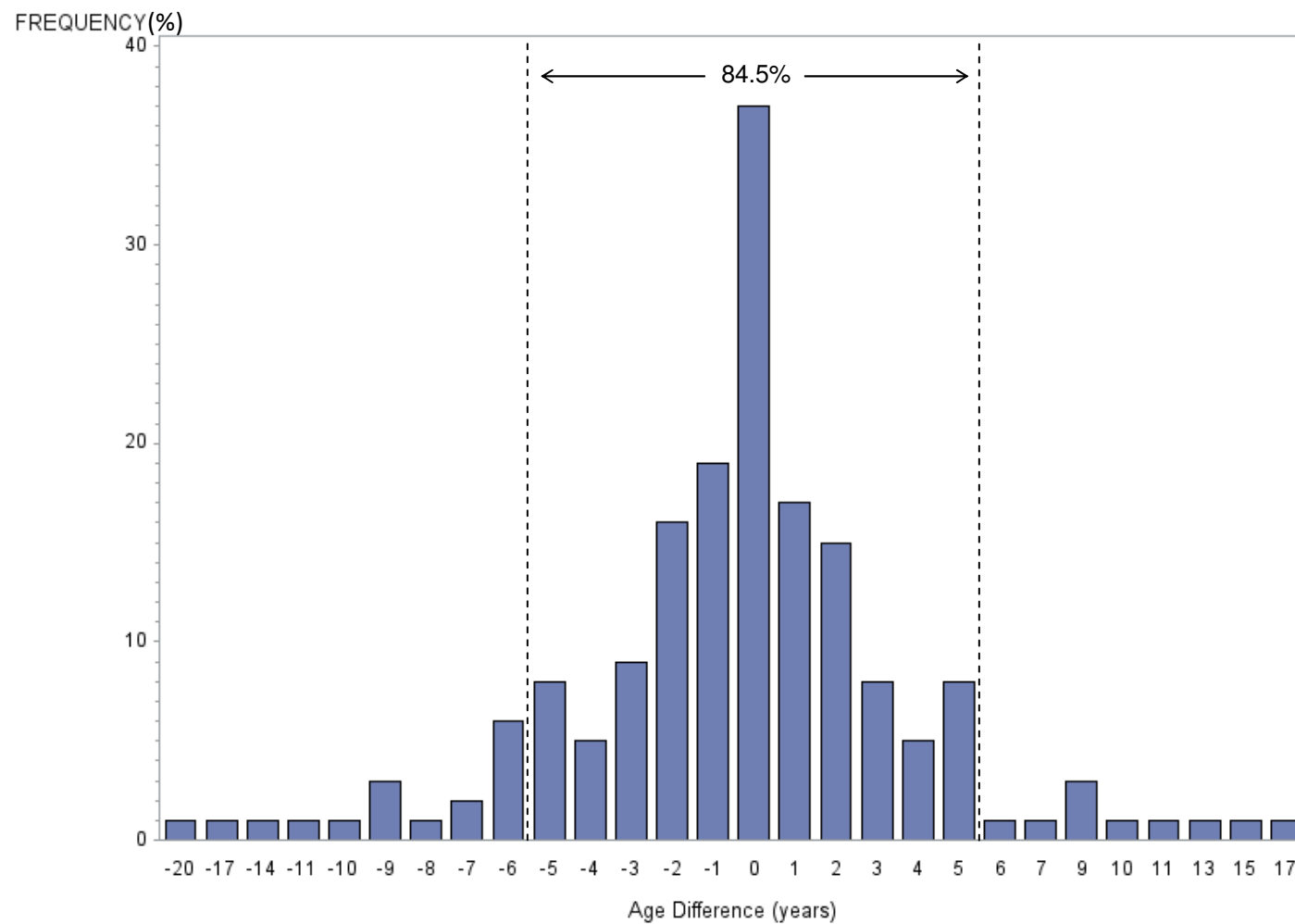


Figure 5 – Distribution of Age Differences Between Matched Pairs of Insulin Pump Therapy and Control Subjects

4.2 Baseline Cohort Characteristics

The baseline demographic characteristics are shown in Table 5. Given that the duration of T1DM and current age were the matching variables, as expected these did not differ significantly between the IPT and control cohorts. The mean duration of T1DM of both cohorts was 25.2 ± 13.1 years. The mean current age was 45.0 ± 12.8 years for the IPT cohort and 45.3 ± 13.2 years for the control cohort ($p=0.350$). There was no significant difference in gender, city of residence, or average yearly household income between the cohorts (all $p>0.05$). However, a significantly higher proportion of control subjects (17.2%, $n=30$) than IPT subjects (6.9%, $n=12$) had a private drug plan ($p=0.006$), and a significantly lower proportion of control subjects (91.4%, $n=159$) than IPT subjects (97.1%, $n=169$) were followed by an Endocrinologist for their T1DM ($p=0.031$).

Table 5 – Baseline Demographic Characteristics of the Insulin Pump Therapy and Control Cohorts

	IPT Cohort n=174	Control Cohort n=174	p-value
Age (years)	45.0 ± 12.8	45.3 ± 13.2	0.350 [†]
Duration of T1DM (years)	25.2 ± 13.1	25.2 ± 13.1	N/A
Gender (Male) – n (%)	80 (46.0)	97 (55.8)	0.100 [‡]
Private Drug Plan - n (%)	12 (6.9)	30 (17.2)	0.006[‡]
City (London) - n (%)	80 (46.0)	90 (51.7)	0.358 [‡]
Physician (Endocrinologist) – n (%)	169 (97.1)	159 (91.4)	0.031[‡]
Average Yearly Household Income (CAD)	$\$70,922 \pm \$12,850$	$\$70,528 \pm \$13,942$	0.799 [†]

IPT, insulin pump therapy; T1DM, type 1 diabetes mellitus; N/A, not applicable

Data are mean values \pm SD or number and frequency

Comparison between cohorts using [†]paired t-test or [‡]McNemar's test

The baseline clinical characteristics of each cohort are shown in Table 6. There was no significant difference in baseline A1C between the IPT and control cohorts (IPT: 0.078 ± 0.011 vs. control: 0.078 ± 0.013 , $p=0.586$), nor any significant difference between the proportions of IPT and control subjects with an optimal (i.e. ≤ 0.070) baseline A1C (IPT: 25.3%, $n=44$ vs. control: 24.7%, $n=43$, $p=1.000$). Similarly, there was no significant differences between the proportions of IPT and control subjects with a baseline A1C ≤ 0.073 (IPT: 35.1%, $n=61$ vs. control: 34.5%, $n=60$) or ≤ 0.075 (IPT: 43.7%, $n=76$ vs. control: 43.7%, $n=76$) (both $p=1.000$). The cohorts also did not differ significantly in their baseline BMI, total daily insulin dose, or number of insulin injections per day.

However, there was a significantly lower proportion of current smokers in the IPT cohort (4.0%, $n=7$) than the control cohort (19.0%, $n=33$) ($p<0.001$). Further, the proportion of subjects with at least one diabetes-related complication was significantly lower in the IPT cohort (34.5%, $n=60$) than the control cohort (44.8%, $n=78$) ($p=0.044$). Similarly, the proportion of subjects with at least one glycaemic-responsive complication was significantly lower in the IPT cohort (33.3%, $n=58$) than the control cohort (43.7%, $n=76$) ($p=0.047$). These differences in diabetes-related complications appeared to be mediated by a difference in the prevalence of neuropathy between the cohorts (IPT: 10.9%, $n=19$ vs. control: 19.0%, $n=33$, $p=0.034$). The IPT cohort also had a significantly higher mean baseline number of CBG checks per day compared to the control cohort (IPT: 4.0 ± 0.8 vs. control: 3.7 ± 0.9 , $p=0.003$).

Table 6 – Baseline Clinical Characteristics of the Insulin Pump Therapy and Control Cohorts

	IPT Cohort n		Control Cohort n		p-value	Pairs included in analysis, n
Baseline A1C	0.078 ± 0.011	174	0.078 ± 0.013	174	0.586 [†]	174
% with optimal [*] baseline A1C – n (%)	44 (25.3)		43 (24.7)		1.000 [‡]	
Current smoking – n (%)	7 (4.0)		33 (19.0)		<0.001 [‡]	
At least 1 complication – n (%)	60 (34.5)		78 (44.8)		0.044 [‡]	
At least 1 glycaemic-responsive [§] complication – n (%)	58 (33.3)		76 (43.7)		0.047 [‡]	
Complications – n (%)	CVD		2 (1.2)		N/A	
	CAD		6 (3.5)		1.000 [‡]	
	PVD		0 (0)		N/A	
	Retinopathy		51 (29.3)		0.162 [‡]	
	Nephropathy		37 (21.3)		0.111 [‡]	
	Neuropathy		33 (19.0)		0.034 [‡]	
Baseline BMI (kg/m ²)	26.4 ± 4.7	156	27.3 ± 5.5	149	0.281 [†]	135
Baseline TDD (units)	52.2 ± 25.6	161	58.1 ± 33.7	170	0.101 [†]	157
Baseline # CBG/day	4.0 ± 0.8	163	3.7 ± 0.9	158	0.003 [†]	148
Baseline # insulin injections/day	4.2 ± 0.5	168	4.2 ± 0.7	168	0.794 [†]	162

IPT, insulin pump therapy; A1C, glycated hemoglobin; CVD, cerebrovascular disease; CAD, coronary artery disease; PVD, peripheral vascular disease; BMI, body mass index; kg, kilogram; m, meter; TDD, total daily insulin dose; CBG, capillary blood glucose

Data are mean values ± SD or number and frequency

Due to missing data, not all 174 pairs were compared for all variables

* Optimal A1C defined as ≤ 0.070

§ Glycaemic-responsive complications include retinopathy, nephropathy and neuropathy

Comparison between cohorts using [†]paired t-test or [‡]McNemar's test

A large number of subjects in both cohorts were missing data on the use of CGMS and the number of adverse events at baseline. Only 2 IPT subjects documented use of CGMS, while data on CGMS use was missing for the other 172 IPT subjects and all 174 control subjects. For adverse events at baseline, in those with available data, there were no documented episodes of DKA at baseline in either cohort (number of subjects with data for DKA: n=36 IPT cohort, n=48 control cohort) but there were 17 episodes of severe hypoglycaemia in 125 IPT cohort subjects at baseline and 15 episodes of severe hypoglycaemia in 115 control cohort subjects at baseline. The corresponding baseline incidences for severe hypoglycaemia were not significantly different between cohorts: 13.6 events per 100 patient-years in the IPT cohort and 13.0 events per 100 patient-years in the control cohort ($p=0.946$ negative binomial regression).

The pump therapy-related characteristics of the IPT cohort are shown in Table 7. The mean age at the start of IPT was 41.8 ± 12.7 years, and the mean duration of T1DM at the start of IPT was 22.0 ± 13.0 years. The majority (88.5%, n=154) of the IPT cohort used a Medtronic pump. The distribution of the timing of both ADP applications and ADP pump trial starts varied from 2008-2011 (though 2008 and 2011 were incomplete years). The mean wait time from referral to the SJHC DEC until the DEC appointment for the ADP process was 2.3 ± 2.4 months (wait time data available for only 69 subjects).

Table 7 – Pump Therapy-Related Characteristics of the Insulin Pump Therapy Cohort

		IPT Cohort n=174
Age at Pump Start (years)		41.8 ± 12.7
Duration of T1DM at Pump Start (years)		22.0 ± 13.0
Brand of Pump – n (%)		
	Medtronic	154 (88.5)
	Animas	20 (11.5)
Year of ADP application – n (%)		
	2008*	14 (8.1)
	2009	83 (47.7)
	2010	38 (21.8)
	2011*	21 (12.1)
	Missing	18 (10.3)
Year of ADP Pump trial start – n (%)		
	2008*	4 (2.3)
	2009	54 (31.0)
	2010	51 (29.3)
	2011*	36 (20.7)
	Missing	29 (16.7)

IPT, insulin pump therapy; T1DM, type 1 diabetes mellitus; ADP, Assistive Devices Program

Data are mean values ± standard deviation or number and frequency

* partial years – 2008 includes 4 months (September-December) and 2011 includes 8 months (January-August)

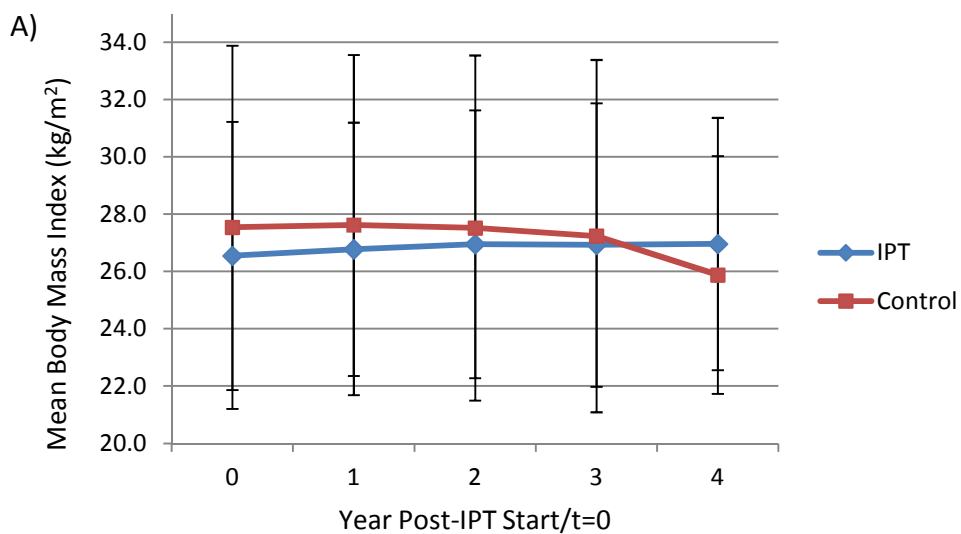
4.3 Cohort Characteristics at Follow-Up

The mean BMI and mean number of CBG per day in each year following IPT start (IPT cohort) or t=0 (control cohort) are shown in Figure 6A and B. The mean number of insulin injections per day in each year following t=0 for the control cohort is shown in Figure 7.

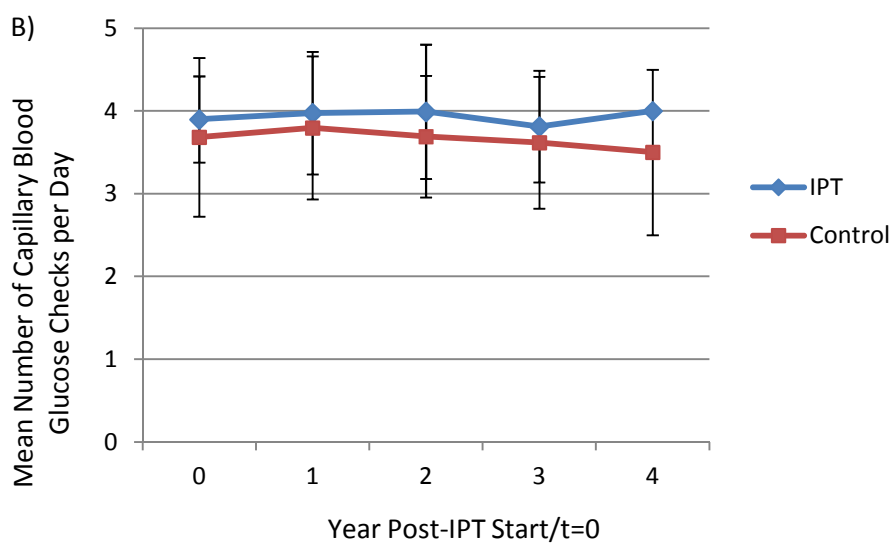
The mean BMI of the IPT cohort in the IPT start year was $26.5 \pm 4.7 \text{ kg/m}^2$ (n=154), and at t=0 year in the control cohort was $27.5 \pm 6.3 \text{ kg/m}^2$ (n=142). The mean BMI of the IPT cohort at year 4 post-IPT start was $27.0 \pm 4.4 \text{ kg/m}^2$ (n=5), while the mean BMI of the control cohort at year 4 post-t=0 was $25.9 \pm 4.2 \text{ kg/m}^2$ (n=5) (Figure 6A).

The mean number of CBG per day in the IPT cohort at IPT start year was 3.9 ± 0.5 (n=157), and at t=0 year in the control cohort was 3.7 ± 1.0 (n=152). At year 4 post-IPT start/t=0, the mean number of CBG per day was 4.0 ± 0.0 in the IPT cohort (n=4) and 3.5 ± 1.0 in the control cohort (n=4) (Figure 6B).

The mean number of insulin injections per day in the control cohort at t=0 year was 4.2 ± 0.6 (n=167), while the mean number of insulin injections per day at year 4 post-t=0 was 4.3 ± 0.5 (n=4) (Figure 7).



Number of Subjects					
IPT	154	158	119	54	5
Control	142	148	102	52	5



Number of Subjects					
IPT	157	161	115	48	4
Control	152	152	100	47	4

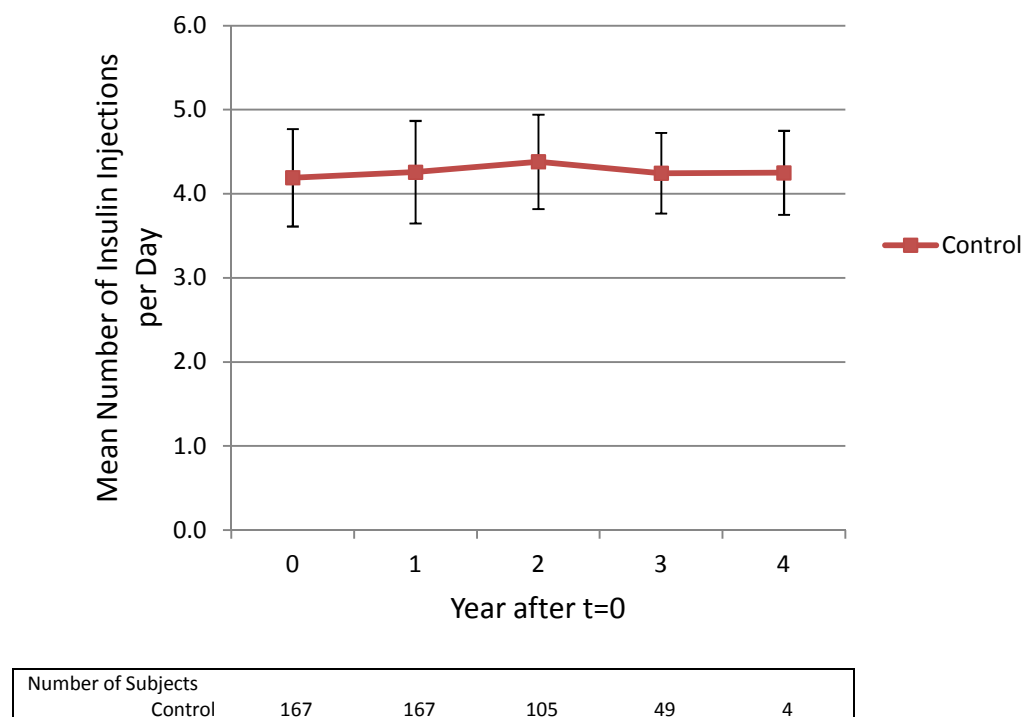
IPT, insulin pump therapy

Error bars represent standard deviation

Year 0 is the IPT start year (IPT cohort) or t=0 year (control cohort)

Data were classified as per calendar year, and length of follow-up was variable, thus not all subjects had data for each year (sample size at each year provided)

Figure 6 – Mean Body Mass Index and Mean Number of Capillary Blood Glucose Checks Per Day at Yearly Follow-Up for Insulin Pump Therapy and Control Cohorts



Error bars represent standard deviation

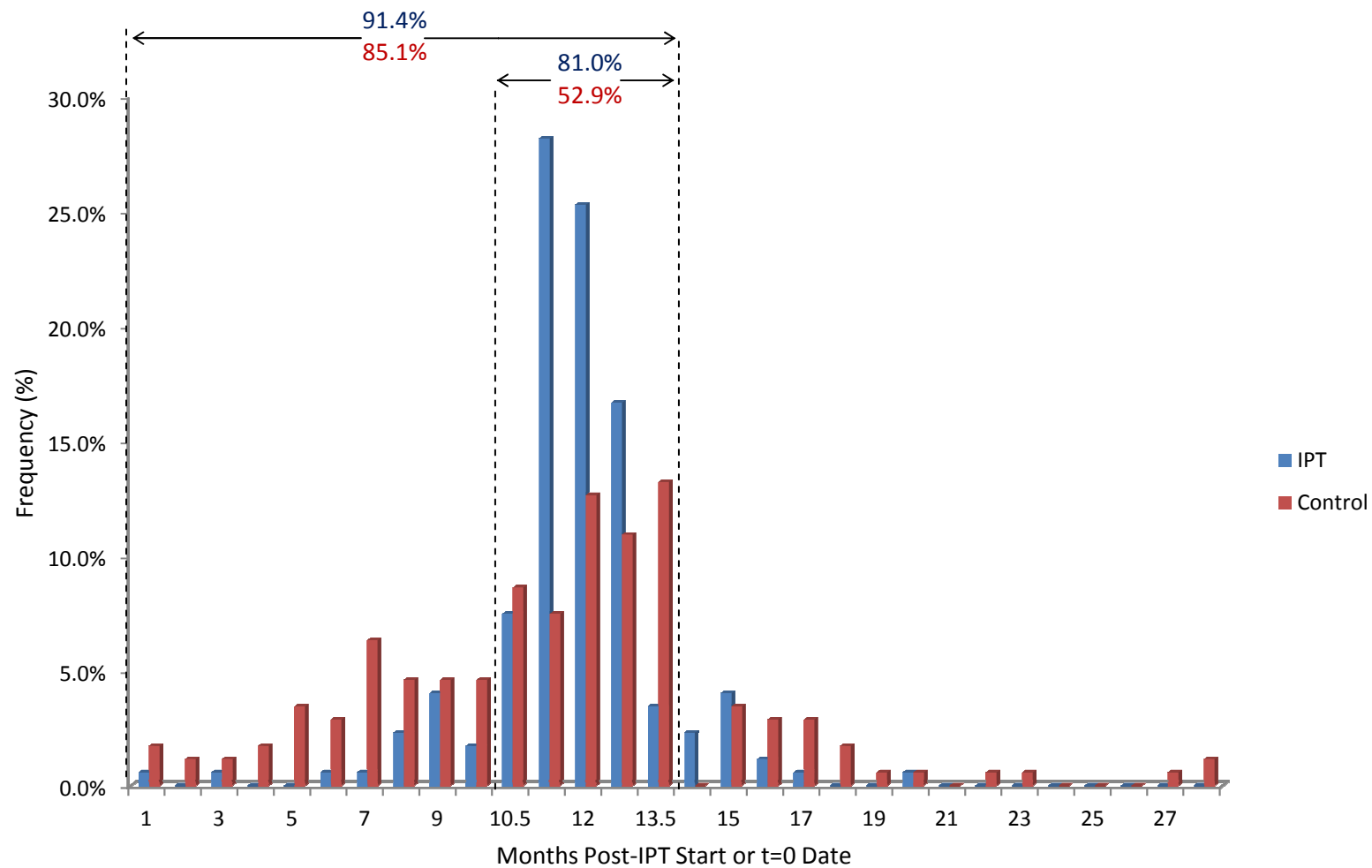
Year 0 is the t=0 year

Data were classified as per calendar year, and length of follow-up was variable, thus not all subjects had data for each year (sample size at each year provided)

Figure 7 – Mean Number of Insulin Injections Per Day at Yearly Follow-Up for Control Cohort

4.4 Glycaemic Control Outcomes

The timing of the follow-up A1C measurement varied by subject. The distribution of the timing of the follow-up A1C measurement for each cohort is shown in Figure 8. For both cohorts, the timing of the follow-up A1C measurements was normally distributed. The mean time for the follow-up A1C measurement was 11.7 ± 2.0 months post-IPT start (IPT cohort) and 11.4 ± 4.4 months post-t=0 date (control cohort); these were not significantly different ($p=0.369$ paired t-test).



A1C, glycated hemoglobin; IPT, insulin pump therapy

Figure 8 – Distribution of Timing of Follow-Up A1C Measurements for Insulin Pump Therapy and Control Cohorts

Analysis 1 required that the follow-up A1C be between 10.5 – 13.5 months post-IPT start/post-t=0 date—if no A1C was measured in this window, the subject was excluded from the analysis. As seen in Figure 8, 81.0% (n=141) of IPT subjects and 52.9% (n=92) of control subjects had follow-up A1C measurements between 10.5 – 13.5 months.

Analysis 2 required that the follow-up A1C be between 10.5 – 13.5 months post-IPT start/post-t=0 date. However, if no A1C was measured in this window, but an A1C measurement between 0 – 10.5 months post-IPT start/post-t=0 date was available, the subject was included and the follow-up A1C was imputed using LOCF. If no A1C measurement between 0 – 13.5 months post-IPT start/t=0 date was available for a subject, they were excluded from the analysis. As seen in Figure 8, 91.4% (n=159) of IPT subjects and 85.1% (n=148) of control subjects had follow-up A1C measurements between 0 – 13.5 months.

4.4.1 Change in A1C

The mean baseline A1C, mean follow-up A1C, and mean change in A1C from baseline to follow-up for each cohort are shown in Table 8.

Insulin Pump Therapy Cohort

The mean baseline A1C in the IPT cohort was 0.078 ± 0.011 . In Analysis 1, the mean follow-up A1C was 0.075 ± 0.009 , for a mean change in A1C of -0.002 ± 0.009 . In Analysis 2, the mean follow-up A1C was 0.075 ± 0.010 , for a mean change in A1C of -0.002 ± 0.009 . In both analyses, the change in A1C from baseline to follow-up was statistically significant (Analysis 1, $p=0.009$; Analysis 2, $p=0.002$).

Table 8 – Mean A1C at Baseline and Follow-Up, and Mean Change in A1C for Insulin Pump Therapy and Control Cohorts

Cohort	Analysis	Baseline A1C n=174	Follow-Up A1C n		Change in A1C (Follow-Up – Baseline)	p-value*
IPT	(1)	0.078 ± 0.011	0.075 ± 0.009	141	-0.002 ± 0.009	0.009
	(2)		0.075 ± 0.010	159	-0.002 ± 0.009	0.002
Control	(1)	0.078 ± 0.013	0.078 ± 0.014	92	0.000 ± 0.010	0.952
	(2)		0.080 ± 0.013	148	0.001 ± 0.010	0.487

A1C, glycated hemoglobin; IPT, insulin pump therapy

Data are presented as mean values ± standard deviation

*Comparison of baseline vs. follow-up A1C using paired t-test

Control Cohort

The mean baseline A1C in the control cohort was 0.078 ± 0.013. In Analysis 1, the mean follow-up A1C was 0.078 ± 0.014, for a mean change in A1C of 0.000 ± 0.010. In Analysis 2, the mean follow-up A1C was 0.080 ± 0.013, for a mean change in A1C of 0.001 ± 0.010. In both analyses, the change in A1C from baseline to follow-up was not statistically significant (Analysis 1, p=0.952; Analysis 2, p=0.487).

4.4.2 Paired Difference in A1C Change Score

The mean paired difference in A1C change scores between matched pairs of IPT and control subjects is shown in Table 9. In Analysis 1, the mean paired difference in the A1C change score was -0.003 ± 0.015, which was not statistically significant (p=0.126). However, in Analysis 2, the mean paired difference in the A1C change score was -0.003 ± 0.015, which was statistically significant (p=0.041).

Table 9 – Mean Paired Difference in A1C Change Score for Matched Pairs of Insulin Pump Therapy and Control Subjects

Analysis	Paired Difference in A1C Change Scores (IPT Change in A1C – Control Change in A1C)	p-value*	Pairs included in analysis, n
(1)	-0.003 ± 0.015	0.126	74
(2)	-0.003 ± 0.015	0.041	133

A1C, glycated hemoglobin; IPT, insulin pump therapy

Data are presented as mean values ± standard deviation

*Comparison of A1C change score for each matched IPT-control pair using paired t-test

4.4.3 Optimal A1C at Baseline and at Follow-Up

The proportions of subjects with an optimal A1C at baseline compared to follow-up in each cohort are shown in Table 10. “Optimal” A1C was defined as an A1C ≤ 0.070.

Insulin Pump Therapy Cohort

In Analysis 1, the proportion of IPT subjects with an optimal A1C at baseline was 27.0% (n=38), and at follow-up was 33.3% (n=47). These were not significantly different (p=0.163). In Analysis 2, the proportion of IPT subjects with an optimal A1C at baseline was 25.8% (n=41) and at follow-up was 32.1% (n=51), and these were also not significantly different (p=0.143).

Control Cohort

In Analysis 1, the proportion of control subjects with an optimal A1C at baseline and at follow-up were 22.8% (n=21) and 26.1% (n=24), respectively. These were not significantly different (p=0.607). In Analysis 2, the proportions of control subjects with an optimal A1C at baseline and follow-up were the same—both were 23.0% (n=34).

Table 10 – Difference in Proportion of Subjects with an Optimal A1C at Baseline vs. at Follow-Up in Insulin Pump Therapy and Control Cohorts

Cohort	Analysis	Optimal A1C at Baseline	Optimal A1C at Follow-Up	p-value*	Pairs included in analysis, n
IPT	(1)	38 (27.0)	47 (33.3)	0.163	141
	(2)	41 (25.8)	51 (32.1)	0.143	159
Control	(1)	21 (22.8)	24 (26.1)	0.607	92
	(2)	34 (23.0)	34 (23.0)	1.000	148

A1C, glycated hemoglobin; IPT, insulin pump therapy

Data are presented as number (percentage)

*Comparison of proportion at baseline vs. at follow-up using McNemar's test

However, given that the target “optimal” level of A1C should be individualized according to patient-specific factors, we repeated the analyses using pre-specified higher, but still clinically relevant, threshold levels ($A1C \leq 0.073$ and ≤ 0.075), and these results are shown in Tables 11A and 11B. In the IPT cohort in both Analysis 1 and 2, there was a significantly higher proportion of subjects with an $A1C \leq 0.073$ at follow-up (Analysis 1: 46.1%, n=65; Analysis 2: 45.3%, n=72) than at baseline (Analysis 1: 36.2%, n=51; Analysis 2: 35.2%, n=56) (Analysis 1: p=0.034, Analysis 2: p=0.023). Similarly, in both Analysis 1 and 2, there was a significantly higher proportion of subjects with an $A1C \leq 0.075$ at follow-up (Analysis 1: 55.3%, n=78; Analysis 2: 55.4%, n=88) than at baseline (Analysis 1: 44.0%, n=62; Analysis 2: 43.4%, n=69) (Analysis 1: p=0.014, Analysis 2, p=0.005).

Table 11 – Difference in the Proportion of Subjects with an A1C ≤ 0.073 and ≤ 0.075 at Baseline vs. at Follow-Up in Insulin Pump Therapy and Control Cohorts

A)

Cohort	Analysis	A1C ≤ 0.073 at Baseline	A1C ≤ 0.073 at Follow-Up	p-value *	Pairs included in analysis, n
IPT	(1)	51 (36.2)	65 (46.1)	0.034	141
	(2)	56 (35.2)	72 (45.3)	0.023	159
Control	(1)	33 (35.9)	36 (39.1)	0.581	92
	(2)	50 (33.8)	48 (32.4)	0.839	148

B)

Cohort	Analysis	A1C ≤ 0.075 at Baseline	A1C ≤ 0.075 At Follow-Up	p-value *	Pairs included in analysis, n
IPT	(1)	62 (44.0)	78 (55.3)	0.014	141
	(2)	69 (43.4)	88 (55.4)	0.005	159
Control	(1)	44 (47.8)	46 (50.0)	0.815	92
	(2)	63 (42.3)	66 (44.6)	0.701	148

A1C, glycated hemoglobin; IPT, insulin pump therapy

Data are presented as number (percentages)

*Comparison of proportion of subjects at baseline vs. at follow-up using McNemar's test

However, this pattern was not seen within the control cohort—there was no significant difference in the proportions of control subjects with an A1C ≤ 0.073 or an A1C ≤ 0.075 at follow-up compared to at baseline in either Analysis 1 or 2.

The proportions of subjects with an optimal A1C at follow-up (i.e. ≤ 0.070) were compared between the IPT and control cohorts, and the results are shown in Table 12. In Analysis 1, there were no significant differences between cohorts in the proportions of subjects with an optimal follow-up A1C. However, in Analysis 2, the IPT cohort had a significantly higher proportion of subjects with a follow-up A1C ≤ 0.070 (33.8%, n=45) compared to the control cohort (21.8%, n=29) ($p=0.044$).

Table 12 – Difference in the Proportion of Subjects with Follow-Up A1C ≤ 0.070 in Matched Pairs of Insulin Pump Therapy and Control Subjects

Analysis	IPT	Control	p-value*	Pairs included in analysis, n
(1)	23 (31.1)	18 (24.3)	0.487	74
(2)	45 (33.8)	29 (21.8)	0.044	133

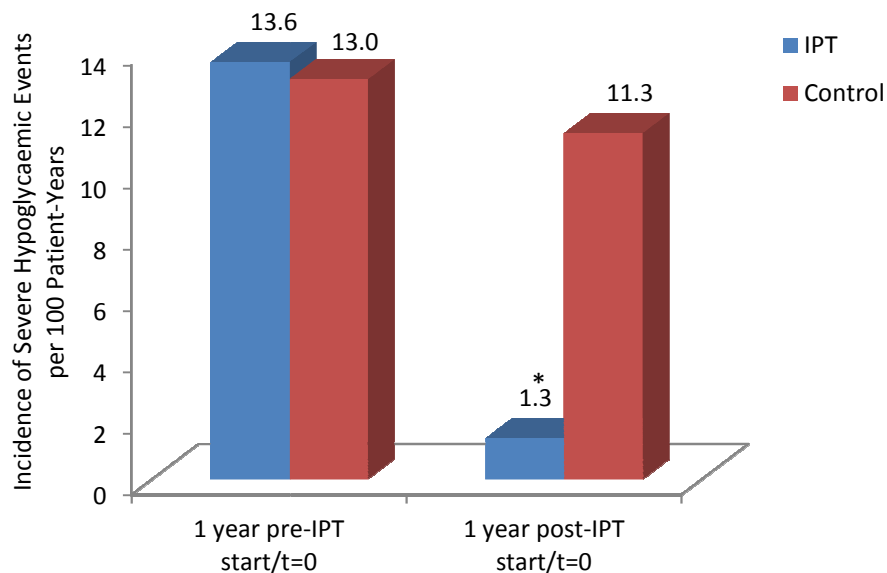
A1C, glycated hemoglobin; IPT, insulin pump therapy

Data are presented as number (percentage)

* Comparison of proportion of subjects in IPT vs. control cohorts using McNemar's test

4.5 Adverse Events

The number of episodes of DKA and severe hypoglycaemia per calendar year were collected for each subject in the 1 year prior to IPT start/t=0 year (baseline), the year of IPT start/t=0, and yearly thereafter. Due to varying length of follow-up and missing data, not all subjects had adverse event data for each follow-up year. There were no DKA episodes reported for either cohort at any follow-up year (number of subjects with data on DKA: IPT start/t=0 year n=23 (IPT), n=49 (control); year 1 n=30 (IPT), n=46 (control); year 2 n=18 (IPT), n=37 (control); year 3 n=10 (IPT), n=23 (control), year 4 n=3 (IPT), n=2 (control)). The incidence of severe hypoglycaemic events at baseline and after 1 year post-IPT start/t=0 is shown in Figure 9. As shown previously, there was no significant difference in the incidence of severe hypoglycaemia between cohorts in the 1 year prior to IPT start/t=0 (baseline). However, after 1 year post-IPT start/t=0, the IPT cohort had a significantly lower incidence of severe hypoglycaemia (2 events in 149 patients, for an incidence of 1.3 events per 100 patient-years) compared to the control cohort (14 events in 124 patients, for an incidence of 11.3 events per 100 patient years) ($p=0.016$). There was no significant difference in the incidence of severe hypoglycaemia between cohorts in year 2 (IPT: 2.9 per 100 patient-years vs. control: 3.8 per 100 patient-years, $p=0.743$) or year 3 (IPT: 2.6 per 100 patient-years vs. control: 7.3 per 100 patient years, $p=0.376$) post-IPT start/t=0. No episodes of severe hypoglycaemia were reported in either cohort in year 4 post-IPT start/t=0.



Number of Subjects		
IPT	125	149
Control	115	124

IPT, insulin pump therapy

Data were classified as per calendar year, and length of follow-up was variable, thus not all subjects had data for each year (sample size at each year provided)

*p=0.016 IPT vs. control, negative binomial regression

Figure 9 – Incidence of Severe Hypoglycaemic Events in the 1 Year Pre-IPT Start/t=0 (baseline) and After 1 Year Post-IPT Start/t=0 for Insulin Pump Therapy and Control Cohorts

4.6 Missing Data – Follow-Up A1C Values

The proportion of subjects with missing follow-up A1C values in each analysis for each cohort was compared. In Analysis 1, 82 control subjects (47.1%) and 33 IPT subjects (19.0%) were missing follow-up A1C values in the pre-specified time window, and the proportion in the control cohort was significantly higher than the IPT cohort ($p < 0.001$). However, in Analysis 2, after using LOCF to impute missing values in 56 (32.2%) control and 18 (10.3%) IPT subjects, there was no significant difference between cohorts in the proportion of subjects missing follow-up A1C values (control: $n=26$, 14.9% vs. IPT: $n=15$, 8.6%, $p=0.117$).

The baseline characteristics between those with missing vs. non-missing follow-up A1C values were compared for each cohort (Appendices J and K).

Insulin Pump Therapy Cohort

In Analysis 1, there were 33 IPT subjects with missing follow-up A1C data. Compared to IPT subjects without missing A1C data, those with missing A1C data had a significantly lower mean baseline BMI ($25.2 \pm 3.6 \text{ kg/m}^2$, $n = 30$ vs. $26.8 \pm 4.9 \text{ kg/m}^2$, $n=126$, $p=0.049$) and lower mean baseline TDD (43.8 ± 18.4 units, $n=30$ vs. 54.1 ± 26.6 units, $n=131$, $p=0.014$). There were no differences in any other baseline characteristics between these two groups (Appendix J).

In Analysis 2, there were 15 IPT subjects with missing follow-up A1C data. There were no significant differences in baseline characteristics between these subjects and the 159 IPT subjects who were not missing A1C data (Appendix J).

Control Cohort

In Analysis 1, there were 82 control subjects with missing follow-up A1C data. Compared to control subjects without missing A1C data, those with missing A1C data had a significantly lower mean baseline TDD (52.8 ± 25.4 units, $n=81$ vs. 62.9 ± 39.4 units,

n=89; p=0.048) and were less likely to have a private drug plan (11.0%, n=9 vs. 22.8%, n=21; p=0.039). There were no differences in any other baseline characteristic between these two groups (Appendix K).

In Analysis 2, there were 26 control subjects with missing follow-up A1C data. There were no significant differences in baseline characteristics between these subjects and the 148 control subjects who were no missing A1C data (Appendix K).

4.7 Sensitivity Analyses

Effect of Wider Age Differences in Age-Matched Pairs

Of the 174 IPT-control pairs, 27 (15.5%) were not matched within a ± 5 year age difference. A sensitivity analysis including only the 147 pairs that were matched within this window of age differences showed similar results as presented above—a significant change in A1C was seen from baseline to follow-up in the IPT cohort but not in the control cohort (IPT: -0.002 ± 0.010 , p=0.006 (Analysis 1); -0.003 ± 0.010 , p=0.001 (Analysis 2); Control: 0.000 ± 0.011 , p=0.967 (Analysis 1); 0.001 ± 0.011 , p=0.369 (Analysis 2)) and a significant paired difference in change in A1C for matched IPT-control pairs was seen in Analysis 2 only (Analysis 1: -0.003 ± 0.016 , p=0.119; Analysis 2: -0.004 ± 0.016 , p=0.013).

Effect of Imputing Follow-Up A1C values from <6 Months Post-IPT Start/t=0

In Analysis 2, 18 (10.3%) IPT subjects and 56 (32.2%) control subjects had follow-up A1C values imputed using LOCF of values measured between 0-10 months post-IPT start/t=0. A sensitivity analysis imputing the follow-up values of only the 16 (9.2%) IPT subjects and 40 (26.4%) control subjects whose follow-up A1C were measured between 6-10 months post-IPT start/t=0 showed similar results as presented above—a significant change in A1C from baseline to follow-up was seen in the IPT cohort but not the control cohort

(IPT: -0.002 ± 0.010 , $p=0.002$; Control: 0.000 ± 0.011 , $p=0.616$) and a significant paired difference in change in A1C for matched IPT-control pairs was seen (-0.003 ± 0.015 , $p=0.049$).

4.8 Subgroup Analysis

The mean baseline and follow-up A1C, and the mean change in A1C from baseline to follow-up for both cohorts stratified by baseline A1C are shown in Tables 13 and 14. Three subgroups were defined according to the following A1C levels: ≤ 0.070 , 0.071 to 0.080 , and ≥ 0.081 . The baseline TDD was also compared between subgroups.

Insulin Pump Therapy Cohort

Analysis 1:

In the subgroup with baseline A1C ≤ 0.070 , the A1C significantly increased from baseline to follow-up (mean baseline A1C 0.065 ± 0.004 and mean follow-up A1C 0.069 ± 0.007) for a mean A1C change of 0.004 ± 0.008 ($p<0.01$). In the subgroup with baseline A1C ≥ 0.081 , the A1C significantly decreased from baseline to follow-up (mean baseline A1C 0.088 ± 0.009 and mean follow-up A1C 0.081 ± 0.009) for a mean A1C change of -0.007 ± 0.009 ($p<0.0001$). However, for the subgroup with baseline A1C 0.071 to 0.080 , there was no significant change in A1C from baseline to follow-up (Table 13A).

Analysis 2:

A similar pattern was seen for Analysis 2. In the subgroup with baseline A1C ≤ 0.070 , the A1C significantly increased from a mean baseline A1C of 0.065 ± 0.004 to a mean follow-up A1C of 0.069 ± 0.007 , for a mean A1C change of 0.004 ± 0.008 ($p=0.004$). In the subgroup with baseline A1C ≥ 0.081 , the A1C significantly decreased from a mean baseline A1C of 0.088 ± 0.009 to a mean follow-up A1C of 0.081 ± 0.010 , for a mean A1C change of -0.007 ± 0.009 ($p<0.0001$).

Table 13 – Subgroup Analysis: Mean A1C at Baseline and Follow-Up, Mean Change in A1C and Mean Baseline Total Daily Insulin Dose for Insulin Pump Therapy Cohort - Stratified by Baseline A1C

A)

Insulin Pump Therapy Cohort								
Analysis	Subgroup	Baseline A1C n		Follow-Up A1C n		Change in A1C (Follow-Up – Baseline)	p-value*	Pairs included in analysis, n
(1)	≤ 0.070	0.065 ± 0.004	44	0.069 ± 0.007	38	0.004 ± 0.008	<0.01	38
	0.071 – 0.080	0.076 ± 0.003	66	0.074 ± 0.008	49	-0.001 ± 0.008	0.249	49
	≥ 0.081	0.088 ± 0.009	64	0.081 ± 0.009	54	-0.007 ± 0.009	<0.0001	54
(2)	≤ 0.070	0.065 ± 0.004	44	0.069 ± 0.007	41	0.004 ± 0.008	0.004	41
	0.071 – 0.080	0.076 ± 0.003	66	0.074 ± 0.008	58	-0.002 ± 0.008	0.148	58
	≥ 0.081	0.088 ± 0.009	64	0.081 ± 0.010	60	-0.007 ± 0.009	<0.0001	60

B)

Subgroup	Baseline Total Daily Dose (units) n		p-value [†]
≤ 0.070	46.7 ± 24.1	42	0.229
0.071 – 0.080	52.8 ± 25.5	60	
≥ 0.081	55.5 ± 26.5	59	

A1C, glycated hemoglobin

Data are presented as mean ± standard deviation

* Comparison of baseline and follow-up A1C values within each subgroup by paired t-test

† Comparison of baseline total daily dose between subgroups by one-way ANOVA

Table 14 - Subgroup Analysis: Mean A1C at Baseline and Follow-Up, Mean Change in A1C and Mean Baseline Total Daily Insulin Dose for Control Cohort - Stratified by Baseline A1C

A)

Control Cohort								
Analysis	Subgroup	Baseline A1C		Follow-Up A1C		Change in A1C (Follow-Up – Baseline)	p-value *	Pairs included in analysis, n
(1)	≤ 0.070	0.064 ± 0.004	43	0.067 ± 0.007	21	0.003 ± 0.006	0.034	21
	0.071 – 0.080	0.076 ± 0.003	68	0.076 ± 0.007	40	0.001 ± 0.006	0.301	40
	≥ 0.081	0.091 ± 0.011	63	0.089 ± 0.017	31	-0.003 ± 0.016	0.310	31
(2)	≤ 0.070	0.064 ± 0.004	43	0.068 ± 0.008	34	0.004 ± 0.006	0.001	34
	0.071 – 0.080	0.076 ± 0.003	68	0.077 ± 0.007	58	0.001 ± 0.005	0.094	58
	≥ 0.081	0.091 ± 0.011	63	0.090 ± 0.014	56	-0.002 ± 0.015	0.346	56

B)

Subgroup	Baseline Total Daily Dose (units)		p-value [†]
	n		
≤ 0.070	44.3 ± 28.2	43	0.019[‡]
0.071 – 0.080	47.8 ± 24.4	66	
≥ 0.081	59.2 ± 33.4	62	

A1C, glycated hemoglobin

Data are presented as mean ± standard deviation

* Comparison of baseline and follow-up A1C values within each subgroup by paired t-test

† Comparison of baseline total daily dose between subgroups by one-way ANOVA

‡ As per the Tukey-Kramer test, the mean baseline total daily dose was significantly different between the subgroups with baseline A1C ≤0.070 and ≥0.081 (p<0.05)

However, in the subgroup with baseline A1C 0.071 to 0.080, there was again no significant change in A1C from baseline to follow-up (Table 13A). There was no significant difference in baseline TDD between subgroups (Table 13B).

Control Cohort

Analysis 1:

In the subgroup with baseline A1C ≤ 0.070 , the A1C significantly increased from baseline to follow-up (mean baseline A1C 0.064 ± 0.004 and mean follow-up A1C 0.067 ± 0.007) for a mean A1C change of 0.003 ± 0.006 ($p=0.034$). However, there was no significant change in A1C from baseline to follow-up in either the subgroup with baseline A1C 0.071 to 0.080 or the subgroup with baseline A1C ≥ 0.081 (Table 14A).

Analysis 2:

Similarly, in Analysis 2, only the subgroup with baseline A1C ≤ 0.070 showed a significant change in A1C from baseline to follow-up (mean baseline A1C 0.064 ± 0.004 and mean follow-up A1C 0.068 ± 0.008), for a mean A1C change of 0.004 ± 0.006 ($p=0.001$). The subgroups with baseline A1C 0.071 to 0.080 and baseline A1C ≥ 0.081 did not show any significant change in A1C from baseline to follow-up (Table 14A).

However, there was a significant difference in the baseline TDD among the 3 subgroups in the control cohort ($p=0.019$) (Table 14B). The subgroup with a baseline A1C ≤ 0.070 had a significantly lower baseline TDD than the subgroup with a baseline A1C ≥ 0.081 ($p<0.05$).

4.9 Summary of Results

This retrospective cohort study ascertained a group of adult IPT users funded by the MOHLTC ADP, and compared their glycaemic control at approximately 1 year after IPT start to a cohort of control subjects matched by T1DM duration and age. Data on adverse outcomes at baseline and follow-up (yearly up to 4 years post-IPT start/t=0) were also collected.

Subjects in the IPT cohort had a significant decrease in A1C from baseline to 1 year follow-up of 0.002 (or 0.2%), while the A1C level in the control cohort did not change. In the matched analysis, the mean paired difference in A1C change score between the IPT and control cohort subjects was -0.003, i.e. the mean improvement (decrease) in A1C was 0.003 (or 0.3%) more in the IPT cohort than in the control cohort. Subjects in the IPT cohort were more likely to have an optimal A1C at follow-up compared to those in the control cohort.

No subjects in either cohort had any episodes of DKA at baseline or at yearly follow-up. The baseline incidence of severe hypoglycaemic events was similar in both cohorts, but after 1 year post-IPT start/t=0, the IPT cohort had a significantly lower incidence of severe hypoglycaemia compared to the control cohort.

Exploratory subgroup analyses suggested that the effect of IPT use on the change in A1C differed according to baseline A1C where an improvement in A1C was seen in IPT subjects with baseline A1C levels ≥ 0.081 , but a worsening in A1C was seen in IPT subjects with baseline A1C levels ≤ 0.070 . No change was seen in those with baseline A1C levels 0.071 to 0.080.

Chapter 5: Discussion

5.1 Introduction

Insulin pump therapy is becoming an increasingly utilized method of insulin administration in T1DM, and as of September 2013, the provincial government funding program subsidizing its use in adults in Ontario has been in place for 5 years. In mid-2013, Alberta implemented an IPT funding program for residents of all ages, but otherwise, no other province in Canada provides financial support for IPT in adults with T1DM.

There are no Canadian studies that have examined the impact of a provincial funding program for IPT in adults. Despite RCT evidence³⁻¹¹ showing that IPT causes a small but significant improvement in glycaemic control, there is limited “real-world” evidence for the benefits of IPT on glycaemic control and adverse outcomes. Prior observational studies,⁶¹⁻⁷⁹ primarily in Europe, have been performed in small cohorts of adults with T1DM, but the majority of the studies did not have a control group, and most were in subjects with poor glycaemic control at baseline (i.e. baseline A1C values ≥ 0.080). Duration of IPT also varied widely between studies.⁶¹⁻⁷⁹

The objective of our study was to compare glycaemic control and adverse outcomes at 1 year between a cohort of adult IPT users funded by the ADP and a control cohort, matched by age and T1DM duration in order to determine the impact of ADP-funded IPT in adults with T1DM in Ontario under “real-world” conditions.

5.2 Summary of Key Findings & Comparison with Previous Research

5.2.1 Characterization of Insulin Pump Therapy Cohort

The IPT cohort included 174 adults with a mean current age of 45.0 years (mean age at IPT start 41.8 years), mean current duration of T1DM of 25.2 years (mean duration at IPT start 22.0 years), and approximately equal numbers of males and females (80/94). They were overweight, with a mean BMI of 26.4 kg/m², and very few (4%) were current smokers. Almost all (97.1%) were followed by an Endocrinologist, and slightly less than half (46%) lived in London. Their average yearly household income was \$70,922, and very few (6.9%) had access to private drug plan coverage. The subjects had fairly good glycaemic control prior to initiating IPT with a mean baseline A1C of 0.078, and with 25.3% of the cohort having a baseline A1C \leq 0.070. Approximately one third had at least 1 glycaemic-responsive complication (i.e. retinopathy, nephropathy or neuropathy) at baseline.

The age and duration of T1DM of published observational cohorts of IPT users have varied. In general, the mean age and duration of T1DM at the time of IPT start in our IPT cohort (mean age 41.8 years, mean duration 22 years) was similar to that of IPT users in previous studies (mean age range 29 to 50.5 years, mean duration range 9.3-29 years).⁶¹⁻⁷⁹

Of note, the duration of IPT use in previous observational studies was markedly different compared to our cohort. We characterized our IPT cohort from 1 year pre-IPT start until up to 4 years post-IPT start, though length of follow-up varied by subject based on year of IPT start (the mean available follow-up was 2.2 ± 0.8 years post-IPT start). To assess the change in glycaemic control while on IPT, we specifically examined the time period between 1 year pre- and 1 year post-IPT start. In previous studies⁶¹⁻⁷⁹, the mean duration of IPT use ranged from 6 months to 13.1 years.

Furthermore, the cohorts of IPT users in previous observational studies⁶¹⁻⁷⁹ had poorer glycaemic control at baseline compared to our IPT cohort—the mean baseline A1C of the IPT cohorts in the previous 19 studies was 0.085 (range 0.077-0.106), whereas our IPT cohort had fairly good glycaemic control at baseline (mean baseline A1C 0.078).

5.2.2 Comparison of Insulin Pump Therapy and Control Cohorts

The matched control cohort in our study included 174 adults who had similar baseline characteristics to the IPT subjects with some exceptions: fewer control subjects were followed by an Endocrinologist, more control subjects had private drug plan coverage, more control subjects were current smokers, and more control subjects had at least 1 glycaemic-responsive complication (specifically neuropathy). The control cohort also performed a lower mean number of CBG checks per day at baseline.

Taken together, except for the difference in private drug plan coverage, these baseline clinical differences between the control and IPT cohorts suggest that our control cohort was less invested in their health and T1DM self-care relative to our IPT cohort. It is interesting to note that, despite these differences, there was no difference in baseline glycaemic control between the IPT and control cohorts, with the same mean baseline A1C of 0.078 and a similar proportion (24.7%) with a baseline A1C \leq 0.070.

5.2.3 Glycaemic Control Outcomes

Change in A1C from Baseline to Follow-Up

At approximately 1 year post-IPT start, our IPT subjects had a significant decrease in A1C compared to baseline. The mean follow-up A1C in the IPT cohort was 0.075, which, while still suboptimal, represented a mean change in A1C of -0.002 from baseline in the IPT users (Analysis 1 and 2). At the same time, a similar decrease in A1C from baseline was not seen in our control subjects—their mean follow-up A1C ranged from 0.078 (Analysis 1) to 0.080 (Analysis 2) which yielded a statistically and clinically non-significant mean change in A1C over 1 year of 0 to +0.001 from baseline.

Of the prior 19 observational studies evaluating the association between IPT and glycaemic control, 18 also showed a significant decrease in A1C with IPT use.^{61,62,64-79} Four studies^{67,77-79} also reported a mean change in A1C from baseline to follow-up in IPT users, and showed slightly greater changes in A1C (range -0.0054 to -0.0115) as compared to our study. However, these studies defined their follow-up A1C differently than our study. Two of these studies^{77,78} also examined the change in A1C in a control group of non-IPT users. A summary comparing our results with the results of those studies reporting changes in A1C in the IPT group from baseline to follow-up and the difference in change in A1C between the IPT and control groups is shown in Table 15.

Table 15 – Comparison of Results: Current Study and Prior Studies Reporting Change in A1C from Baseline to Follow-Up in Patients on Insulin Pump Therapy and Difference in Change in A1C Between Insulin Pump Therapy and Control Group

Author (Year)	Country (Data Source)	Change in A1C from Baseline to Follow-up (mean \pm SD)	n	Timing of Follow-Up	Difference between groups for change in A1C at Follow-up (mean \pm SD)
Liu (current study)	Canada (3 ^o care centre)	IPT: -0.002 \pm 0.009 Control: 0.001 \pm 0.010	159 148	1 year	-0.003 \pm 0.015 (unadjusted paired difference, n=133 pairs)
Carlsson ⁷⁷ (2013)	Sweden (EMR from 10 clinics)	IPT: -0.0054 \pm 0.0111 Control: -0.0003 \pm 0.0086	260 2,213	1 year	-0.0051 (unadjusted) -0.0042 (adjusted)
Cohen ⁷⁸ (2013)	Australia (3 ^o care centre)	IPT: -0.006 Control: -0.001	102 105	1 year	not reported
Grant ⁷⁹ (2013)	United Kingdom (3 ^o care centre)	IPT: -0.010 (no control group)	171	6-12 months	N/A
Lepore ⁶⁷ (2005)	Italy (3 ^o care centre)	IPT: -0.0115 \pm 0.0084 (no control group)	82	3 months	N/A

A1C, glycated hemoglobin; SD, standard deviation; IPT, insulin pump therapy; 3^o, tertiary; EMR, electronic medical record; N/A, not applicable

Carlsson et al.⁷⁷ performed a retrospective cohort study in 272 subjects on IPT, measuring A1C at 1, 2 and 5 years of IPT use (the primary outcome was at 5 years). The mean change in A1C at 1 year in the IPT subjects was -0.0054, which was statistically significant. For their primary outcome determination at 5 years, they used a large time window (5 years \pm 6 months) for A1C measurement. As well, they defined A1C at 1 year as the first A1C value after 1 year, but did not specify the time window for measurement, making it unclear whether the 1 year value also was subject to the same large time window. In our study, our pre-specified window for follow-up A1C was relatively narrow (12 \pm 1.5 months); this difference may partly explain why we observed a smaller mean change in A1C in our IPT cohort. Carlsson et al.⁷⁷ also studied a matched control group of non-IPT users (matched by the IPT start date \pm 182 days), with an average of 9 matched controls per IPT user and a total control group of 2437 subjects. Similar to what we observed in our control cohort, their control group did not have a significant change in A1C from baseline to 1 year (mean change -0.00033).

Grant et al.⁷⁹ retrospectively examined the impact of mental health problems on glycaemic control in 350 patients with T1DM on IPT. In the subgroup of IPT users without a history of mental health problems (n=171), the mean change in A1C from baseline to follow-up was -0.010, which was statistically significant. However, in this study, the time window for the follow-up A1C used for analysis was again relatively large being between 6-12 months post-IPT start. This difference may explain why we observed a smaller mean change in A1C.

Cohen et al.⁷⁸ performed a retrospective cohort study of 126 subjects newly started on IPT, and examined the change in A1C from baseline at 6 and 12 months, and then yearly from 2 until 5 years. The peak A1C reduction in the IPT group was -0.0064 at 6 months, with a statistically significant reduction of -0.0060 persisting at 1 year. However, the A1C values used in their analyses were the means of all A1C measurements in that time period (i.e. in the first 6 months, 12 months, and the mean for each subsequent year), which may contribute to the greater change in A1C as compared to what we saw in our

study. In addition, unlike our study, the control cohort in Cohen et al. had a significant reduction in A1C of -0.0015 (at 6 months), but their control subjects participated in a structured 5 week education program (including 2.5 hour group meetings per week), similar to the DAFNE (Dose Adjustment For Normal Eating) program.⁸⁹ This education program may explain why the control subjects in their study experienced a small but significant change in A1C at 6 months. However, at 1 year, the change in A1C in their control group was not significant.

Lepore et al.⁶⁷ conducted a retrospective cohort study in 82 subjects on IPT in which they examined A1C values which were measured every 3 months while subjects were on IPT (with mean IPT duration 31.9 ± 14.5 months). They showed a significant mean change in A1C of -0.0115 over this time, but, as in Cohen et al.,⁷⁸ the follow-up A1C value used in the analysis was the mean of all follow-up A1C measurements. Thus, their longer duration of follow-up with multiple A1C determinations may have allowed for detection of a greater change in A1C.

In the current study, it was felt that the use of a single A1C value measured within the defined follow-up period was a more clinically relevant outcome measure, as opposed to the mean of all A1C values measured within that time. Using a mean of all measured A1C values may provide a broad reflection of the overall glycemic control in a time period, but it may not clearly illustrate the magnitude of change in A1C. For example, in 2 subjects both with baseline A1C values of 0.080 and each with 2 subsequent follow-up A1C values—subject one with follow-up values of 0.090 then 0.070, and subject two with follow-up values of 0.100 then 0.060—their mean follow-up A1C would be the same (0.080), giving a 0% change compared to baseline for both subjects, when in actuality both had a significant improvement in A1C compared to baseline, as per their second follow-up A1C values of 0.070 and 0.060, respectively.

One study⁶³ did not demonstrate a significant decrease in A1C from baseline to follow-up in IPT users. Bode et al. performed a prospective cohort study in which 55 patients with T1DM with severe recurrent hypoglycaemia and/or suboptimal glycaemic control

(A1C ≥ 0.080) after ≥ 12 months of an intensive therapy program on an MDI regimen were crossed-over to IPT and followed for at least 12 more months.⁶³ No significant change in A1C was observed from baseline on MDI to follow-up on IPT. However, due to the intensive therapy program that was offered while on both MDI or IPT (including quarterly routine visits, 24-hour access to telephone support, and close phone and fax contact throughout), the glycaemic control of the subjects was fairly good at baseline on MDI (mean A1C 0.077 ± 0.015). Given that Bode et al. included subjects with recurrent severe hypoglycaemia, this may have limited the subjects' ability to safely further tighten their glycaemic control on IPT. The baseline incidence of severe hypoglycaemia on MDI in Bode et al. was high (138 events per 100 patient-years), which is 10-fold higher than the baseline incidence of severe hypoglycaemia in our IPT cohort (13.6 events per 100 patient-years). This difference in severe hypoglycaemia may explain why a significant decrease in A1C was observed in our IPT cohort, but not in that of Bode et al., despite similar glycaemic control at baseline.

Paired Difference in Change in A1C

In the matched analyses, a statistically significant paired difference in change in A1C from baseline to follow-up between the IPT and control subjects was not seen in Analysis 1. Possible reasons for why Analysis 1 did not show a significant difference are: there was, in fact, no true difference in the change in A1C between matched pairs of IPT and control subjects; the greater proportion of missing follow-up A1C values in the control cohort (47.1%) than in the IPT cohort (19.0%) masked the presence of a significant difference in the change in A1C; or the differences in baseline characteristics between those with vs. without missing follow-up A1C values influenced the ability to detect a significant paired difference in change in A1C. For example, IPT subjects with missing follow-up A1C values had lower BMI and lower TDD than those without missing values, while control subjects with missing follow-up A1C values had lower TDD and were less likely to have a private drug plan than those without missing values. As per the *a priori* power calculations (Table 3), the small sample size in Analysis 1 ($n=74$ pairs) was

less likely to be a reason for the lack of statistical significance (as even a sample size of $n=50$ per group would have been powered to detect a difference as small as 0.00027, or 0.027%, between groups).

However, a statistically significant mean paired difference in change in A1C between matched pairs of IPT and control subjects of -0.003 (or -0.3%) was seen in Analysis 2. The definition of a clinically meaningful change in A1C may be somewhat subjective, and to our knowledge, no studies have examined what constitutes a clinically meaningful difference in change in A1C (i.e. the clinically significant difference of a difference), but we believe that our observed paired difference in change in A1C is clinically significant. A 2009 report by the Canadian Agency for Drugs and Technologies in Health⁹⁰ noted that data on the minimally clinically important difference (MCID) in A1C for patients with T1DM is lacking, but prior studies^{91,92} comparing the effect of different types of insulin in lowering A1C in patients with T1DM have used a change in A1C of 0.3% as the MCID in power analyses. In addition, in their 2008 Guidance for Industry,⁹³ the US Food and Drug Administration also defined a “clinically meaningful reduction” in A1C as 0.3%. Moreover, given that this mean paired difference in change in A1C of -0.3% between the IPT and control cohorts was seen in the context of fairly good baseline glycaemic control and was also accompanied by a decrease in the incidence of severe hypoglycaemia in the IPT cohort only further underscores the clinical significance of the results.

The only previous observational study to report the difference in change in A1C from baseline to follow-up between matched IPT and control subjects was Carlsson et al.⁷⁷ In their study, they found an unadjusted difference between groups for change in A1C from baseline to follow-up at 1 year of -0.00507, which is similar to (though slightly greater than) what we observed in our study. However, they also performed analysis of covariance adjusting for the baseline A1C, and the adjusted difference between groups at 1 year was -0.0042 (Table 14). We did not do an adjusted analysis in our study for the purpose of this thesis, but an adjusted analysis using multivariable regression to account for potential confounding factors is planned.

Proportion with Optimal A1C

a) Comparison of Proportions at Baseline vs. at Follow-Up in each cohort

Optimal glycaemic control is a key component in the management of T1DM. According to the 2013 CDA Clinical Practice Guidelines, the target A1C should be ≤ 0.070 for most patients with T1DM.² However, it is also recommended that the target A1C level may be less strict (i.e. 0.071 - 0.085) in the presence of risk factors that make it unsafe to achieve tight glycaemic control (i.e. recurrent severe hypoglycaemia, hypoglycaemia unawareness, severe coronary artery disease, multiple comorbidities) or other situations in which the potential benefits of tight glycaemic control may not be outweighed by its risks (i.e. limited life expectancy, high level of functional dependency).²

In our study, the proportion of subjects with an A1C of ≤ 0.070 increased from baseline to follow-up in the IPT cohort in both analyses (Analysis 1: from 27.0% to 33.3%, Analysis 2: from 25.8% to 32.1%), but these increases were not statistically significant. In the control cohort, the proportion of subjects with an A1C of ≤ 0.070 increased from baseline to follow-up only in Analysis 1 (from 22.8% to 26.1%), but this was also not statistically significant. However, the proportions of IPT subjects with an A1C ≤ 0.073 or ≤ 0.075 did significantly increase from baseline to follow-up (in both Analysis 1 and 2), yet this was not seen in control subjects. Taken together, this suggests that IPT may help improve glycaemic control to a certain level, but that there may be a threshold below which it is difficult to further improve glycaemic control—for example, due to limitations from hypoglycaemia. Once a patient has reached target optimal glycaemic control (i.e. ≤ 0.070) it may be difficult to further lower the A1C, regardless of the method of insulin delivery. This likely reflects the larger problem of failure to recreate true physiological insulin delivery in patients with longstanding T1DM.

Mecklenburg et al.⁶¹ examined the proportions of subjects with a “normal” A1C at baseline and while on IPT. In contrast to our study, the proportion of subjects that achieved a target (i.e. normal) A1C was statistically significantly higher during the first

year on IPT (26%, n=33) than that at baseline (9%, n=11) ($p=0.0001$). However, in Mecklenburg et al.,⁶¹ the A1C was “...calculated as a percentage of the mean in a normal population and converted to the comparable absolute values in our present assay....” and the normal range of their assay was 0.0045 - 0.0080 (4.5-8.0%). Thus, the threshold for their target A1C was higher than what was defined as “optimal” in our study. Furthermore, 8 of the 33 subjects in their study who achieved the target A1C during the first year on IPT were pregnant, while pregnancy was an exclusion in our study.

Reda et al.⁶⁹ also compared the proportions of subjects achieving an $A1C \leq 0.070$ pre- and post-IPT start in their study of 105 subjects. In contrast to our study, they found that a higher proportion of subjects achieved an $A1C \leq 0.070$ after IPT start (17.1%, n=18) compared to before the IPT start (8.6%, n=9). However, they followed subjects up to 6 years after initiation of IPT, but did not specify at what time point after IPT start the subjects achieved the target A1C. Similarly, Sudhakaran et al.⁷² showed an increase in the proportion of subjects achieving an $A1C < 0.070$ on IPT compared to pre-IPT (from 0% to 17.6%). However, their number of subjects with T1DM was small (n=17). Marmolin et al.⁷⁵ also showed an increase in the proportion of subjects who attained an $A1C \leq 0.070$ on IPT compared to pre-IPT, from 13% (n=8) to 24% (n=14). In none of these 3 studies was it stated whether the increase in proportion of IPT users achieving their target A1C was statistically significant.^{69,72,75}

b) Comparison of Proportions at Follow-Up between IPT vs. Control Cohorts

Since both the IPT and control cohorts had comparable glycaemic control at baseline, the proportion of subjects who achieved an optimal A1C value at follow-up was compared between the IPT and control cohorts. In both Analysis 1 and 2, there was a higher proportion of subjects with an $A1C \leq 0.070$ at follow-up in the IPT cohort than in the control cohort, though only Analysis 2 showed that this difference was statistically significant. The differing results between Analysis 1 and 2 may again be a function of sample size, as Analysis 1 included only 74 pairs, while Analysis 2 included almost double the sample size. (Other potential reasons for the differing results are as stated

previously above). No prior study compared this proportion at follow-up between an IPT and control cohort.

5.2.4 Adverse Events

In our study, there were no episodes of DKA at baseline or at follow-up in either cohort. This is similar to 2 prior retrospective cohort studies, where the incidence of DKA was negligible in subjects pre- or post-IPT start.^{67,72} Several other studies did observe episodes of DKA but did not note any significant change in the incidence of DKA before or after IPT use.^{63,70} Reda et al. reported an incidence of 20 episodes per 100 patient-years in the year prior to IPT start and an incidence of 5 episodes per 100 patient-years during IPT use, but it was not stated whether this was a statistically significant decrease.⁶⁹

In our study, there was no significant difference in the baseline incidence of severe hypoglycaemia between cohorts, but after 1 year post-IPT/ $t=0$, the IPT cohort had a significantly lower incidence of severe hypoglycaemia compared to the control cohort. Other studies have also shown a decrease in the incidence of severe hypoglycaemia with the initiation of IPT use.^{63,65,67,69-72} Bode et al. reported a decrease in incidence from 138 events per 100 patient-years while on MDI to 22 events per 100 patient-years while on IPT⁶³. However, this study was conducted specifically in subjects with recurrent severe hypoglycaemia, which is why the baseline incidence was so high. Similarly, the other studies^{65,67,69-72,75} which showed a significant decrease in incidence of severe hypoglycaemia with IPT use all had higher incidences at baseline than our study—we observed an incidence of only 13.6 events per 100 patient-years (IPT cohort) and 13.0 events per 100 patient-years (control cohort) at baseline. This compares to the other 6 studies that had baseline incidences of severe hypoglycaemia at least 2-fold greater than ours. The low baseline incidence of severe hypoglycaemia seen in our subjects is likely related to the amount of missing adverse event data in both cohorts. In turn, this likely contributed to our limited ability to detect any differences from baseline to follow-up within each cohort, and between cohorts.

5.2.5 Subgroup Analysis

In our study, subgroup analysis showed that IPT subjects with a baseline A1C ≥ 0.081 had a mean change in A1C of -0.007 from baseline to follow-up, while IPT subjects with a baseline A1C 0.071 to 0.080 showed no change, and those with a baseline A1C ≤ 0.070 had a mean 0.004 increase in A1C from baseline to follow-up. In the control cohort, subjects with a baseline A1C ≤ 0.070 also had an increase in A1C from baseline to follow-up (mean 0.003 to 0.004 increase), but no significant change in A1C was seen in the control subjects with a baseline A1C 0.071 to 0.080 or ≥ 0.081 . Of note, severe hypoglycaemia was not the reason for why the subgroup with baseline A1C ≤ 0.070 in both cohorts showed a significant increase in A1C from baseline to follow-up. In fact, the majority of severe hypoglycaemic episodes at baseline were seen in the subgroup with baseline A1C ≥ 0.081 in both cohorts—82.3% (n=14) in the IPT cohort and 66.7% (n=10) in the control cohort. However, even though the highest baseline severe hypoglycaemia incidence was in the subgroup with baseline A1C ≥ 0.081 in both cohorts, this subgroup in the IPT cohort was still able to show a significant reduction in A1C at follow-up, yet this subgroup in the control cohort was not.

Our results are similar to other studies which showed a differential effect of IPT use on glycaemic control depending on baseline A1C.^{63,67,71} Bode et al.⁶³ demonstrated that those with a baseline A1C ≥ 0.080 had a significant decrease in A1C with IPT use, whereas those with a baseline A1C < 0.080 did not have any change in A1C with IPT use. Lepore et al.⁶⁷ found that those subjects with a baseline A1C > 0.100 had a greater A1C reduction (-0.015 ± 0.006) with IPT use vs. those with a baseline A1C < 0.080 (-0.006 ± 0.005). Riveline et al.⁷¹ also showed a significant (-0.090) improvement in A1C in subjects with a baseline A1C ≥ 0.090 . However, Giménez et al.⁷⁰ did not find any difference in glycaemic control in subgroups of subjects divided by baseline A1C ≤ 0.070 or > 0.070 , though given that the mean baseline A1C in their study was 0.079 ± 0.013 , the subgroup with baseline A1C > 0.070 likely had too few numbers to show a difference in subgroup analysis.

5.3 Use of WebDR as a Researchable Database

WebDR was a convenient tool which was used to: a) identify all patients with T1DM followed by the Diabetes Clinics at SJHC, b) assemble a cohort of IPT users and c) construct a cohort of non-IPT users from which we could select matched controls. This was the first use of WebDR for research, and the process allowed us to identify both its strengths and weaknesses as a researchable database.

5.3.1 Identification of Insulin Pump Therapy Cohort and Matched Controls

There are no data fields in WebDR to specifically identify ADP-funded adult IPT users. Instead, adults with T1DM on IPT were identified via a WebDR query of medication lists for insulin pump-compatible insulins and insulin doses, and review of their physician paper chart was performed to confirm ADP coverage. However, to ensure that all eligible IPT users followed by the Diabetes Clinics at SJHC were identified, IPT use was also independently verified by comparison to the list of adults started on IPT maintained by the St. Joseph's Hospital DEC. Comparing those IPT users identified by WebDR to those identified by the DEC list showed a 46% concordance between the two data sources (i.e. of the 229 IPT users identified by WebDR, only 105 were also identified by the DEC list, while the other 124 were not identified by the DEC list). An additional 119 IPT users on the DEC list were not identified by WebDR. Possible reasons for why patients were listed as IPT users on WebDR but not on the DEC list are: IPT use was initiated at another DEC (instead of the St. Joseph's Hospital DEC); IPT was started when the patient was under the care of the pediatric program; the patient was on IPT but not funded by the ADP; or IPT was started prior to September 2008 or after August 2011 and the IPT start date was not documented on WebDR. Possible reasons for why patients were listed as IPT users on the DEC list but not on WebDR are: IPT doses were not entered in the patient's WebDR record; IPT was started during pregnancy (the Endocrine Pregnancy Clinic is the only clinic at SJHC that sees adult patients with T1DM but that does not use WebDR); or the patient was no longer followed by a physician at the

Diabetes Clinics at SJHC and so they were not entered into WebDR or their WebDR record was inactivated.

In our study, use of both WebDR and the DEC list allowed us to be confident that all eligible adults with T1DM on IPT followed by the Diabetes Clinics at SJHC were identified. However, it does highlight that the use of WebDR as the sole data source to identify patients who started IPT between September 2008 and August 2011 would not have captured all IPT users at SJHC during that time. Of note, at the time of manual data entry of clinical data from physician paper charts (in 2010-2011), documentation of IPT use was not the highest priority. However, WebDR has now been in routine clinical use for over 2 years with ongoing updates of patient records at each clinic visit (including medication lists). We expect that the accuracy of WebDR in identifying IPT users will have improved, and thus may be used in future studies involving patients on IPT. To confirm this, a paper chart review of all adult patients with T1DM followed by the Diabetes Clinics at SJHC is planned, with cross-reference to WebDR to ensure electronic documentation of IPT use and ADP coverage.

5.3.2 Validation of A1C Dates and Values

Validation of the baseline and follow-up A1C levels and dates was performed. It showed that WebDR had fair to good (69.4% to 80.6%) accuracy for these variables. Of note, there were no instances where the WebDR value was incorrect compared to the reference standard, but rather, the inaccuracy observed was due to missing values in WebDR. This is related to our study data collection period and the protocol for manual data entry for data from physician paper charts that was performed in 2010-2011. Given that the ADP started in September 2008, we required A1C values as early as March 2007. However, when manual data entry was performed, for most physician charts, only the most recent A1C few values would be entered (and the number of values could range depending on the data entry clerk).

The accuracy of historical A1C data of our study cohort should now be improved compared to when our validation was performed, since missing data was entered into

WebDR at the time of data extraction. As well, WebDR data from 2011 onwards will likely also be more accurate than what we observed in our validation, given that WebDR is now being used routinely for clinic visits at almost all of the Diabetes Clinics at SJHC. The use of WebDR in this study allowed us the opportunity to assess the accuracy of the glycaemic control data within WebDR, and will help improve its accuracy for use in future research studies.

5.4 Study Strengths

This study is one of only a few observational cohort studies that has evaluated the effect of IPT on glycaemic control in a large cohort of adults with T1DM on IPT as compared to a control cohort of adults with T1DM not on IPT in a “real-world” setting.

In addition, this study is the largest descriptive cohort of adults with T1DM on IPT in Canada to date. It is also the only study to describe a population of IPT users who are funded by the Ontario MOHLTC ADP, which has provided IPT funding for adults with T1DM for the past 5 years. The subjects in our study were all followed by the Diabetes Clinics of SJHC, a major tertiary care centre with a large geographic catchment area in Southwestern Ontario, and thus they are likely representative of adults with T1DM both provincially and nationwide. We judge that our cohort can be used in future studies evaluating the impact of ADP-funded IPT on adults with T1DM in Ontario. This should provide valuable information to health policy makers in at least Ontario, if not across Canada, where funding programs for adults using IPT are varied, or may not exist at all.

Another strength is in the design and analysis of our study. We used 1:1 matching in the selection of our control cohort and purposefully chose change in A1C as our primary outcome in an attempt to control for bias due to confounding by 3 important factors: baseline A1C, age, and duration of T1DM. Prior observational studies^{67,68,71, 94,95} and meta-analyses of before-after studies and/or RCTs^{5,6} have shown that the baseline A1C is one of the most (if not the most) important factor predictive of improved glycaemic

control on IPT. Other observational studies have also found that age^{67,94-96} and duration of T1DM⁹⁵ are related to glycaemic control on IPT.

5.5 Study Limitations

Our study had several limitations. As a retrospective observational study, it was limited to the data available on WebDR and in the physician paper charts. This reduced our ability to control for known confounding factors. Despite ensuring that the cohorts were well-matched for age and duration of T1DM, it is possible that other differences between the IPT and control cohorts may have contributed to the results seen. We also attempted to control for differences in baseline A1C by selecting the change in A1C as our primary outcome, but other potentially important factors exist that could confound the association between IPT use and glycaemic control.

For example, the greater decrease in A1C seen in the IPT cohort compared to the control cohort could be due not to IPT per se, but rather to the intensive training and education that is required prior to initiation of IPT. Further, the patients who are willing to go on IPT may be inherently more motivated to manage their T1DM in comparison to those who do not. However, our study does reflect “real-world” conditions in which there are patients with a wide range of ability for self-management of their T1DM, and in which some choose to pursue IPT and others do not.

Other factors shown to have been associated with improved glycaemic control on IPT include blood glucose variability while on an MDI regimen^{68,76} and the use of a bolus dose calculator for at least 50% of boluses.⁹⁷ As data on these factors were not collected routinely in WebDR or in physician paper charts, we were not able to include these variables in our study.

Confounding by indication may also be a limitation in our study, as we did not collect information on the indication for IPT use. It is possible that those patients who were

started on IPT were recommended to do so by their physicians if their glycaemic control was persistently suboptimal on MDI, as compared to those patients who were maintained on MDI, and subsequently be more motivated to improve their glycaemic control. However, it is somewhat reassuring that the mean A1C in the IPT and control cohorts was similar at baseline, which would not be expected if the main indication for IPT in our IPT cohort was suboptimal glycaemic control.

We did measure other clinical variables at baseline that have been shown to be associated with glycaemic control in adults with T1DM (higher income or educational status⁹⁸ and frequency of CBG monitoring⁹⁹) and in those with T1DM specifically on an MDI regimen (BMI and insulin dose)⁶⁸ or on IPT (frequency of CBG monitoring⁷¹ and presence of complications).⁹⁵ There was no difference in average household income, mean BMI, or mean TDD at baseline between the cohorts. The IPT cohort did perform more CBG monitoring at baseline, which may have contributed to the difference in glycaemic control seen between the IPT and control cohorts. However, the IPT cohort had a smaller proportion of subjects with at least 1 glycaemic-responsive complication (i.e. neuropathy), and a prior study⁹⁵ found that the presence of complications was predictive of better glycaemic control on IPT. We did not yet perform an analysis adjusting for these factors; however, this is planned.

Another limitation of our study was the amount of missing outcome data (follow-up A1C and adverse events) in both cohorts. To address this, 2 analyses were performed for our primary outcome—Analysis 1 (no imputation) and Analysis 2 (imputation using LOCF for the missing follow-up A1C values). The proportion of missing values between the IPT and control cohorts differed significantly in Analysis 1, but there was no significant difference between cohorts in Analysis 2. Differences in the proportion of missing follow-up A1C values may explain why Analysis 1 did not show a statistically significant difference in the paired difference in A1C change score, while Analysis 2 did show a statistically significant difference.

Of note, an important assumption for use of LOCF in our study was that the follow-up, but missing, A1C did not significantly change from the last available A1C level. In Analysis 2, 18/174 (10.3%) of IPT subjects and 55/174 (31.6%) of control subjects had their follow-up A1C imputed. However, of these imputed values, a large proportion of them, in both cohorts (14/18, 77.8% in IPT cohort; 24/55, 43.6% in control cohort) were carried forward from measurements taken between 8-10 months post IPT start/t=0 (i.e. relatively close to the pre-specified window for follow-up A1C). We think it improbable that the A1C changed significantly from 8-10 months until 10.5 months. Furthermore, a prior study by Cohen et al.⁷⁸ showed that the greatest A1C reduction while on IPT occurred in the first 6 months, with significant decreases in A1C persisting up until 3 years. Similarly, Lepore et al.⁶⁷ showed a significant A1C reduction in patients on IPT within 3 months that persisted until 2 years. Together, this supports our use of LOCF to impute follow-up A1C values prior to 1 year in our study.

Another limitation in our study is selection bias and its effect on the generalizability of our results. Since we excluded adults with < 1 year duration of T1DM, IPT patients with < 1 year of IPT use, and pregnant women, our results may not be generalizable to these populations.

Another potential source of selection bias was the exclusion of patients who did not have a post-IPT start/t=0 follow-up A1C documented, and those no longer followed (i.e. with an inactive WebDR record), because they did not return to the Diabetes Clinics for follow-up. These patients may represent a less motivated population whose glycaemic control may have worsened during follow-up. In our study, only 1 IPT patient did not have a follow-up A1C. This is not unexpected, as at least 2 A1C measurements per year are required for renewal of ADP funding so this ensures that patients return for follow-up to the Diabetes Clinics. However, 10 control patients with baseline A1C values available were not selected due to not having a follow-up A1C (either not documented in WebDR/physician paper chart, or else were no longer followed/inactive record), so given the higher number of control patients excluded for this reason, there is a concern

that the control subjects in our study are a selected sample of more motivated patients. However, if this was the case, it would bias the results toward the null, as the difference in A1C change score between the IPT and control cohorts would be smaller. However, given that we did observe a significant difference (in Analysis 2), then it may be inferred that, had it been possible to include those control subjects excluded for no follow-up A1C, the difference in A1C change score would have been even larger than what was observed.

5.6 Future Directions

The results of this study provide evidence to support a beneficial effect of IPT use in improving glycaemic control in adults with T1DM. We used matching in the design and analysis to help limit bias due to confounding by age and duration of T1DM, and selected the change in A1C as our primary outcome to take baseline A1C into account. However, this study did not use multivariable analysis to adjust for other potential confounding variables, such as the differences in baseline characteristics seen between the control and IPT cohorts. Therefore, the next step will be to perform multiple linear regression analyses to adjust for these baseline differences between the cohorts to obtain a potentially less-confounded estimate of the association between IPT and glycaemic control in adults with T1DM.

This study was the first to characterize patients on IPT who are funded by the Ontario MOHLTC ADP. Future planned studies building on these results include a validation study with our IPT cohort to validate the Ontario-wide data of all adults on ADP-funded IPT, and a health care utilization study. We plan to link our cohort data to provincial healthcare administrative databases to examine the effect of IPT use on important diabetes-related health care utilization outcomes (i.e. physician outpatient visits, eye examinations, diabetes-related emergency room visits and hospitalizations).

Data from our IPT cohort may also be used in a future cost-effectiveness analysis of IPT therapy in Ontario. A prior health economic comparison study¹⁰⁰ in 2009 showed that IPT may be cost-effective as compared to MDI in adults with T1DM in Canada, but the study used a theoretical sample with demographic and clinical characteristics based on those from subjects in the DCCT.²⁶ However, it would be interesting to determine whether similar results would be obtained if the analysis was done using data from our real-world IPT cohort.

Lastly, this study was the first to use WebDR, the EMR system of the Diabetes Clinics at SJHC, for clinical research, and this was the first step in establishing its utility as a comprehensive researchable database for use in the future to examine other important clinical research questions in patients with diabetes.

5.7 Conclusions

Prior meta-analyses of RCTs have shown that IPT can cause a small but significant improvement in glycaemic control as compared to an MDI regimen. However, there is more limited evidence for the benefits of IPT in improving glycaemic control and adverse events under “real-world” conditions, and no studies have been performed in Canada.

Ontario was the first province in Canada to implement a government funding program supporting the use of IPT in adults, and the program has been in place for 5 years. This study is the first to characterize a population of ADP-funded IPT users, and to assess the clinical impact of this funding program in adults. Our findings suggest that ADP-funded IPT is associated with a clinically relevant improvement in glycaemic control and a significant decrease in severe hypoglycaemia in adults with T1DM as compared to a matched control population. This is consistent with findings from prior RCTs, and provides “real-world” evidence in support of the clinical benefits afforded by the MOHLTC ADP funding for IPT in Ontario. The results of this study should help inform health policy makers in Ontario, and encourage continued government support of IPT in adults with T1DM.

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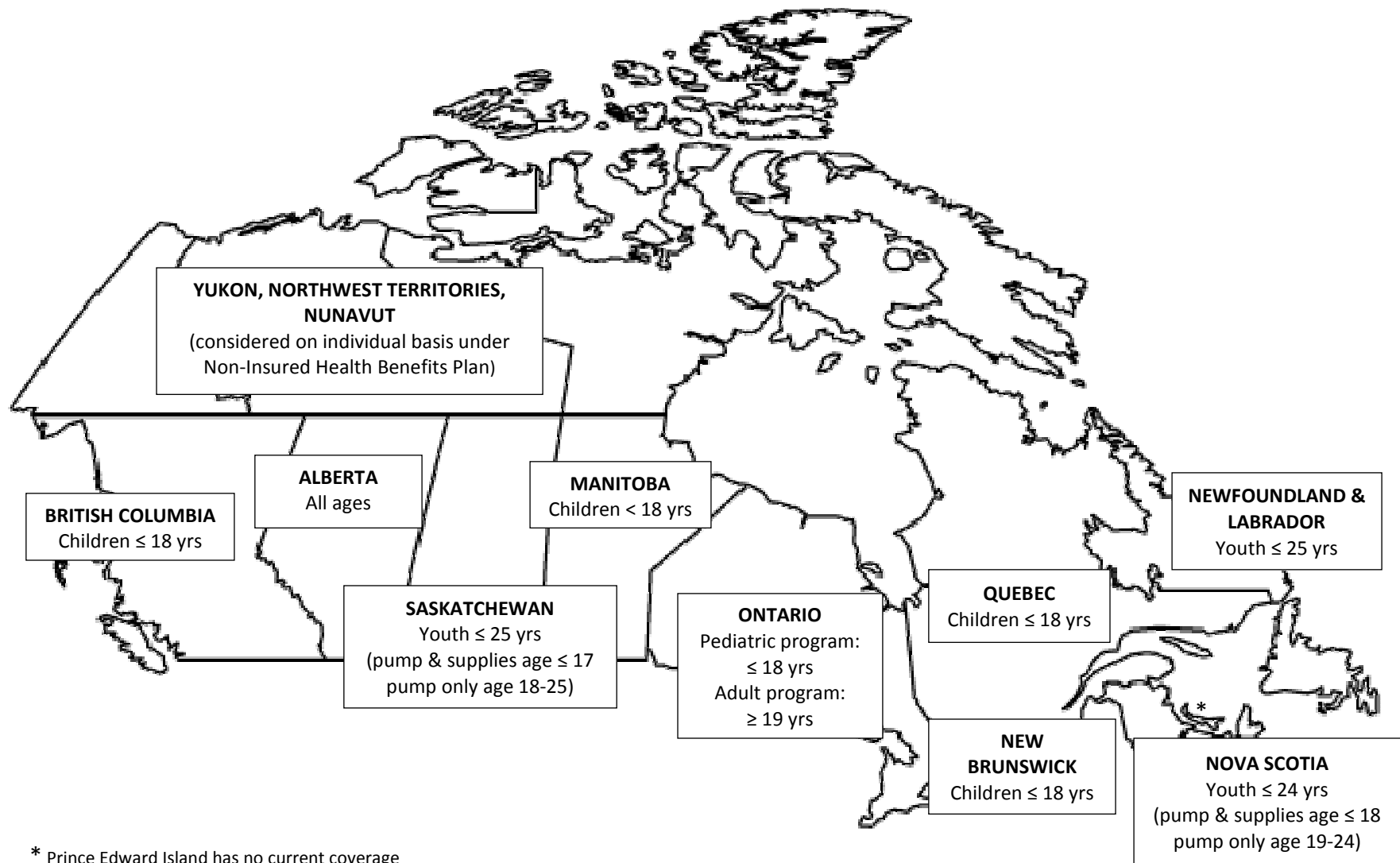
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Appendices

Appendix A – Summary of Existing Funding Programs for Insulin Pump Therapy in Canada



Appendix B – Adult Assistive Devices Program Insulin Pump Therapy Clinics in the Ontario South West Local Health Integration Network



- ★ London
- Owen Sound, Stratford, St. Thomas, Woodstock

Appendix C – Assistive Devices Program – Adult Eligibility Criteria for Initial Application and for Yearly Renewal

Initial Application

1. Applicant has Type 1 diabetes
2. Applicant has demonstrated experience with a basal/bolus insulin regimen for at least one year
3. Applicant demonstrates the ability to self-assess and take action based on blood glucose results by: carbohydrate counting, correction bolus & sick day management
4. Applicant demonstrates a commitment to long-term diabetes follow-up through regular assessments by diabetes educators and physicians at least 3 times a year or as deemed appropriate by the diabetes team
5. Applicant has participated in a pre-assessment for insulin pump therapy according to ADP requirements

Yearly Renewal

1. Applicant continues to demonstrate an ongoing commitment to blood glucose monitoring a minimum of four times daily
2. Applicant demonstrates the ability to self-assess and take action based on blood glucose results by: carbohydrate counting, correction bolus & sick day management
3. Applicant has demonstrated that they have benefited from pump therapy through one of the following results:
 - a. Improved quality of life
 - b. Improved A1C results
 - c. Reduction in the number of hypoglycaemic events
 - d. Reduction in the number of diabetic ketoacidosis episodes
 - e. Improved management of the “dawn phenomenon”
4. Applicant demonstrates a commitment to long-term diabetes follow-up through regular assessments by diabetes educators and physicians at intervals deemed appropriate by the ADP Registered Adult Diabetes Program

Appendix D – Assistive Devices Program – Adult Application Form



Ministry of Health
and Long-Term Care
Assistive Devices Program (ADP)

Application for Funding Insulin Pumps and Supplies for Adults



Clear Form

Section 1 – Applicant's Biographical Information

PLEASE PRINT

Last Name	First Name	Middle Initial
Health Number (10 digits)	Version	Date of Birth (yy/mm/dd)
		Gender <input type="checkbox"/> Male <input type="checkbox"/> Female
Name of Long-Term Care Home (LTC) (if applicable)		

Address

Building Number	Street Name	Suite/Apt Number
Lot/Concession/Rural Route	City/Town	Postal Code
Home Telephone (include area code)		Business Telephone (include area code)
		Ext

Confirmation of Benefits

I am receiving social assistance benefits ☐ Yes ☐ No
 If yes, check ☒ one only:
☐ Ontario Works Program (OWP) ☐ Ontario Disability Support Program (ODSP)
☐ Assistance to Children with Severe Disabilities (ACSD)
 I am eligible to receive coverage for Insulin Pumps or Supplies from:
 Workplace Safety & Insurance Board (WSIB) ☐ Yes ☐ No
 Veterans Affairs Canada (VAC) – Group A ☐ Yes ☐ No

Section 2 – Devices and Eligibility (to be completed by Physician)

Devices/Supplies Required (check all that apply)

☐ Insulin Pump ☐ Supplies for ADP listed Insulin Pump

Reason for Application (only required for Insulin Pump funding request)

☐ First access for Insulin Pump & Supplies category ☐ Replacement of Previously ADP Funded Device(s)

Replacement Pump Required Due To (check as appropriate)

☐ Current device no longer meeting applicant's need ☐ Normal wear and applicant confirms that it is no longer under warranty

Confirmation of Applicant's Eligibility: answers required to all the statements

To be completed by an Endocrinologist or another Specialist Physician who is associated with one of the adult diabetes programs.

Please confirm that the following Eligibility Criteria have been met: (criterion #2 not required if applying for Insulin Supplies only)

1. Applicant has Type1 diabetes	<input type="checkbox"/> Yes <input type="checkbox"/> No
2. Applicant has demonstrated experience with a basal/bolus insulin regimen for at least one year	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Applicant demonstrates the ability to self-assess and take action based on blood glucose results by: carbohydrate counting, correction bolus & sick day management	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Applicant demonstrates a commitment to long-term diabetes follow-up through regular assessments by diabetes educators and physicians at least 3 times a year or as deemed appropriate by the diabetes team	<input type="checkbox"/> Yes <input type="checkbox"/> No
5. Applicant has participated in a pre-assessment for insulin pump therapy according to ADP requirements	<input type="checkbox"/> Yes <input type="checkbox"/> No

Number of episodes of DKA in the last 6 months

Number of severe episodes of hypoglycaemia in last 12 months

Date Insulin pump therapy 90 day trial initiated (yy/mm/dd)	Date of referral to the Adult Diabetes Educational Program (yy/mm/dd)	Date of first appointment with Adult Diabetes Educational Program (yy/mm/dd)	Wait time in days (from referral to first appointment) FOR ADP USE ONLY
/ /	/ /	/ /	

Provide the last three A1c results

1. Date (yy/mm/dd)	A1c	2. Date (yy/mm/dd)	A1c	3. Date (yy/mm/dd)	A1c
/ /		/ /		/ /	

Applicant's Last Name, First Name (PLEASE PRINT)	Health Number (10 digits)	Version
--	---------------------------	---------

Section 3 – Applicant's Consent & Signature

NOTE: This section of the form may be signed only by the applicant or his or her agent

I consent to the Ministry of Health and Long-Term Care (the Ministry) collecting the information I provide on this form for the purpose of assessing and verifying my eligibility to receive benefits under the Ministry's Assistive Devices Program (the "Program"). In addition, I consent to the Ministry and the Workplace Safety and Insurance Board (WSIB) collecting, using and disclosing personal information about me, including the information on this form and information related to my entitlement to health care benefits under the Workplace Safety and Insurance Act ("WSIA"), for the purpose of assessing and verifying my eligibility to receive benefits under the Program and WSIA.

The Ministry and WSIB will limit the information that they exchange about me to only that information that is necessary for the purpose above.

The Ministry will only use and disclose my personal health information in accordance with the Personal Health Information Protection Act, 2004, and the Ministry's "Statement of Information Practices" which is accessible at: www.health.gov.on.ca. In addition, the WSIB will collect, use and disclose personal information about me from the Ministry for the purpose of administering and enforcing the WSIA.

I understand that if I choose to withhold or withdraw my consent to the collection, use and disclosure of this information by the Ministry or WSIB, I may be denied coverage under the Program.

I have read the Applicant Information Sheet, understand the rules of eligibility for ADP and am eligible for the equipment specified. I certify that the information I have provided on this form is true, correct and complete to the best of my knowledge. I understand that this information is subject to audit.

Please indicate the payee and authorize by signature below:

☐ Payment to Applicant ☐ Payment to Agent (provide contact info below) ☐ Payment to LTCH (see Section 1)

Signature

X

☐ Applicant ☐ Agent Date (yyyy/mm/dd)

If the above signature is not that of the applicant, specify relationship and complete contact information below

☐ Spouse ☐ Parent ☐ Legal Guardian ☐ Public Trustee ☐ Power of Attorney

PLEASE PRINT

Last Name		First Name		Middle Initial
Address				
Building Number	Street Name			Suite/Apt Number
Lot/Concession/Rural Route		City/Town	Province	Postal Code
Home Telephone (include area code)		Business Telephone (include area code)		Ext.

Section 4 – Signatures

Physician's Signature

I certify that the applicant has Type 1 diabetes and has demonstrated a clinical need for insulin pump therapy and has participated in a diabetes education program.

PLEASE PRINT

Physician's Last Name		Physician's First Name	
Business Telephone (include area code)		Ext.	Ontario Health Insurance Billing No. (8 digits)
Physician's Signature		Date Signed (yyyy/mm/dd)	

X

Name of Diabetes Program providing education

PLEASE PRINT

Program/Team Name	ADP Clinic Number	Business Telephone (include area code)	Ext.
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Applicant's Last Name, First Name (PLEASE PRINT)		Health Number (10 digits)		Version	
Section 4 – Signatures (continued) Vendor Information (for pump only)					
I hereby certify that the applicant named above has received the items as authorized.					
Vendor Business Name				ADP Vendor Registration Number	
PLEASE PRINT Vendor Representative's Last Name			Vendor Representative's First Name		
Position Title		Business Telephone (include area code)		Ext	
Vendor Location					
Vendor Representative's Signature X		Date (yy/mm/dd) / /		Vendor Invoice Number	
Equipment Specifications (for pump only)					
ADP Device Code		Description of Item (Make & Model)		Serial Number	
Proof of Delivery (for pump only)					
To be completed and signed by the applicant, parent or agent					
I confirm that I have received the insulin pump described in Section 4 and that I agree to participate in a 90 day trial. If at the end of the 90 day trial period, it is determined that I am not a suitable candidate for insulin pump therapy at this time, I agree to return the insulin pump to the vendor indicated in Section 4. On receipt of the returned insulin pump the vendor must credit ADP the full amount of the ADP price in order to ensure that I may reapply at a later date.					
Signature X		<input type="checkbox"/> Applicant <input type="checkbox"/> Agent		Date (yy/mm/dd) / /	

Note: Attachments will not be considered by the Assistive Devices Program

It is an offence punishable by fine and/or imprisonment to knowingly provide false information to obtain funding.

[Print Form](#)

Appendix E – Assistive Devices Program – Adult Renewal Form

Ministry of Health
and Long-Term Care
Assistive Devices Program

Ministère de la Santé
et des Soins de longue durée
Programme d'appareils et accessoires fonctionnels



RE: Insulin Pump Supplies for Adults Funding Renewal Letter

Claim No:

The Assistive Devices Program (ADP) provides you with an annual grant of \$2,400.00 to assist you with the purchase of insulin pump supplies. Every year you are required to renew your application.

In order to confirm your ongoing eligibility for the grant, this form must be signed and dated by your Adult Diabetes Program and returned (not a fax or copy) to the ADP address shown above. If approved, you will continue to receive your insulin pump supplies grant payment on a quarterly basis for the next year.

Ongoing Eligibility Confirmation:

To be completed by an Endocrinologist or another Specialist Physician who is associated with one of the registered Adult Diabetes Programs.

1. Applicant continues to demonstrate an ongoing commitment to blood glucose (BG) monitoring a minimum of four times daily ☐ Yes ☐ No
2. Applicant demonstrates the ability to self-assess and take action based on blood glucose results by: Carbohydrate counting, correction bolus & sick day management ☐ Yes ☐ No
3. Applicant has demonstrated that they have benefited from pump therapy through one of the following results:
 - Improved quality of life;
 - Improved A1c results;
 - Reduction in the number of hypoglycaemic events;
 - Reduction in the number of diabetic ketoacidosis (DKA) episodes; and
 - Improved management of the "dawn phenomenon"☐ Yes ☐ No
4. Applicant demonstrates a commitment to long-term diabetes follow-up through regular assessments by diabetes educators and physicians at intervals deemed appropriate by the ADP Registered Adult Diabetes Program ☐ Yes ☐ No

Provide the last 2 A1c results	1 st A1c	_____	Date:	(yyyy/mm/dd)
	2 nd A1c	_____	Date:	(yyyy/mm/dd)
Number of incidents requiring third party intervention by a family member:				_____
Number of incidents requiring third party intervention by Emergency Medical Services:				_____

<input type="checkbox"/>	I certify that the above named person has type 1 diabetes, continues to demonstrate a clinical need for insulin pump therapy, meets the above-listed criteria, and is in compliance with the requirements of our local diabetes education program.
<input type="checkbox"/>	I certify that the above named person does not meet all of the above listed criteria for ongoing funding of their pump supplies through the Assistive Devices Program.
Physician's Name _____ Ontario Health Insurance Billing Number _____ Physician's Signature _____ Date (yyyy/mm/dd): _____ ADP Clinic Number _____ Name of Adult Diabetes Program _____	
Please allow six weeks for processing. Additional payments of the same amount will be made about every three months for the next year. If your current banking information has changed since your last application or you now wish to have your grant payment deposited directly into your bank account, please call _____ to obtain a direct deposit application form.	
The collection of the information on this form is authorized under the Ministry of Health Act, R.S.O. 1990, c.M.26, section 6(1) to determine eligibility for financial assistance under the Assistive Devices Program. For further details concerning this collection, please contact the Program Manager, Assistive Devices Program,	

Appendix F – Western University Health Sciences Research Ethics Board Approval



Use of Human Participants - Ethics Approval Notice

Research Ethics

Principal Investigator: Dr. Stewart Harris

File Number: 103103

Review Level: Delegated

Approved Local Adult Participants: 500

Approved Local Minor Participants: 0

Protocol Title: Provincially-Funded Insulin Pump Therapy and Glycemic Control: Real World Experience in London, Ontario

Department & Institution: Schulich School of Medicine and Dentistry/Epidemiology & Biostatistics, Western University

Sponsor:

Ethics Approval Date: November 06, 2012 **Expiry Date:** October 30, 2013

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Other	Appendix 2 - Sample Size and Power Calculations	2012/09/29
Other	Appendix 1 - List of Data Elements to be extracted from WebDR and paper chart	2012/09/21
Western University Protocol		

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer to Contact for Further Information

Janice Sutherland	Grace Kelly	Shantel Walcott
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This is an official document. Please retain the original in your files.

Western University,

Appendix G – Western University Health Sciences Research Ethics Board Revision Approval



Research Ethics

Use of Human Participants - Revision Ethics Approval Notice

Principal Investigator: Dr. Stewart Harris

File Number: 103103

Review Level: Delegated

Protocol Title: Provincially-Funded Insulin Pump Therapy and Glycemic Control: Real World Experience in London, Ontario

Department & Institution: Schulich School of Medicine and Dentistry/Epidemiology & Biostatistics, Western University

Sponsor:

Ethics Approval Date: October 15, 2013 Expiry Date: October 31, 2014

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Study End Date	The study end date has been extended to October 31, 2014 to allow for continuation of the study.	

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

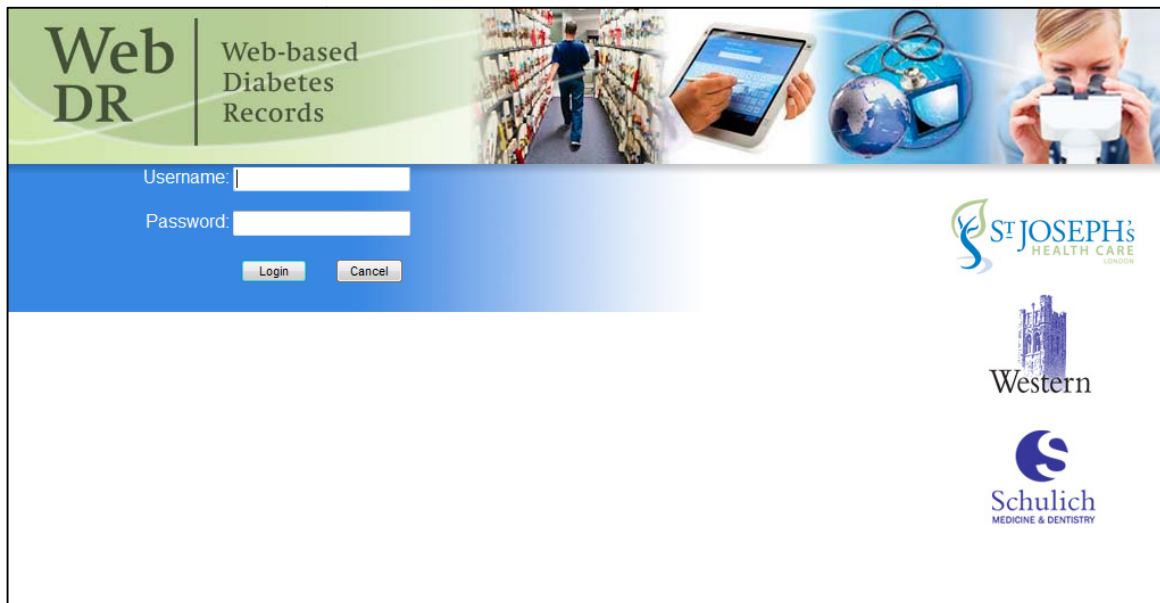
Ethics Officer to Contact for Further Information

<input type="checkbox"/> Erika Basile	<input checked="" type="checkbox"/> Grace Kelly	<input type="checkbox"/> Vikki Tran
---------------------------------------	---	-------------------------------------

This is an official document. Please retain the original in your files.

Western University,




Appendix H – Screenshots of WebDR

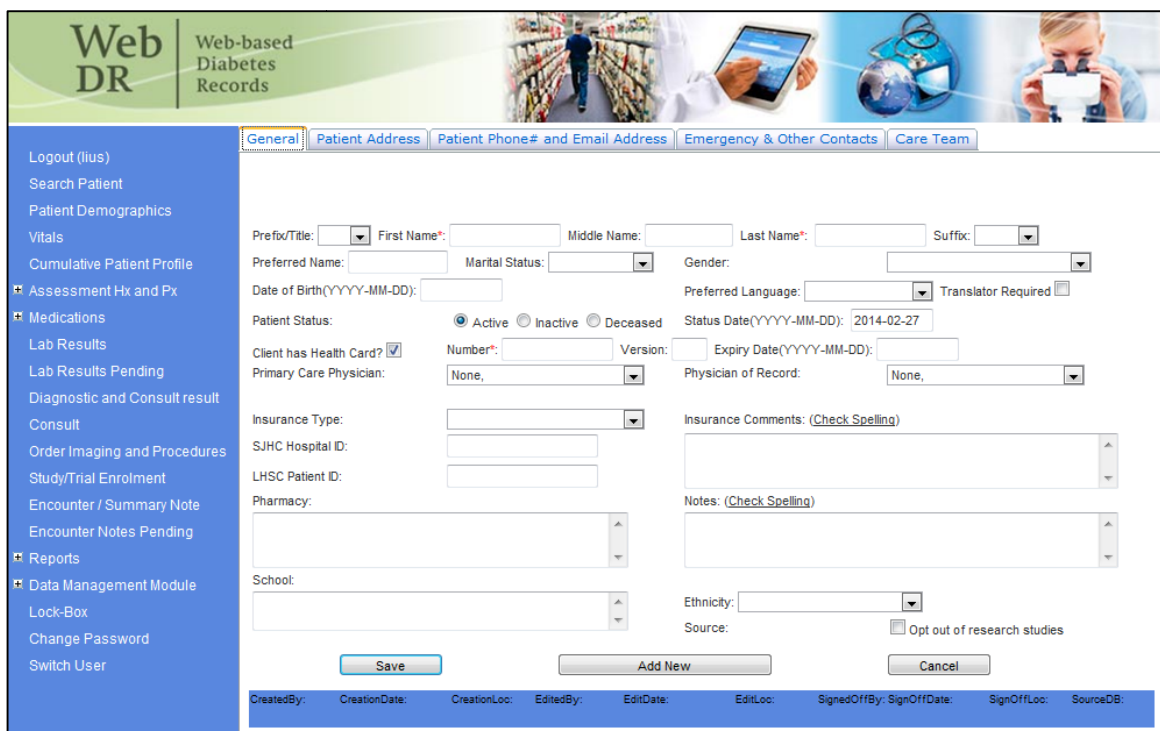


Web DR | Web-based Diabetes Records

Username:

Password:



Web DR | Web-based Diabetes Records

[General](#) | [Patient Address](#) | [Patient Phone# and Email Address](#) | [Emergency & Other Contacts](#) | [Care Team](#)

[Logout \(lius\)](#)
[Search Patient](#)
[Patient Demographics](#)
[Vitals](#)
[Cumulative Patient Profile](#)
[Assessment Hx and Px](#)
[Medications](#)
[Lab Results](#)
[Lab Results Pending](#)
[Diagnostic and Consult result](#)
[Consult](#)
[Order Imaging and Procedures](#)
[Study/Trial Enrolment](#)
[Encounter / Summary Note](#)
[Encounter Notes Pending](#)
[Reports](#)
[Data Management Module](#)
[Lock-Box](#)
[Change Password](#)
[Switch User](#)

Prefix/Title: First Name*: Middle Name: Last Name*: Suffix:
 Preferred Name: Marital Status: Gender:
 Date of Birth(YYYY-MM-DD): Preferred Language: Translator Required ☐
 Patient Status: ☒ Active ☐ Inactive ☐ Deceased Status Date(YYYY-MM-DD): 2014-02-27
 Client has Health Card? ☒ Number*: Version: Expiry Date(YYYY-MM-DD):
 Primary Care Physician: Physician of Record:
 Insurance Type: Insurance Comments: (Check Spelling)
 SJHC Hospital ID:
 LHSC Patient ID:
 Pharmacy:
 School:
 Ethnicity:
 Source: ☐ Opt out of research studies

CreatedBy: CreationDate: CreationLoc: EditedBy: EditDate: EditLoc: SignedOffBy: SignOffDate: SignOffLoc: SourceDB:

Appendix I – Validation of WebDR Data

The accuracy of WebDR was assessed as compared to the physician paper chart, which was used as the reference standard for comparison. A computer-generated random sample of 36 patient records (i.e. 10% of the total sample size) was selected for the validation. Four variables were validated for accuracy: baseline (i.e. pre-IPT start/t=0) A1C value, baseline A1C date, follow-up (i.e. post-IPT start/t=0) A1C value, and follow-up A1C date. If the WebDR value matched the physician paper chart value, it was coded as a “match”, but if the WebDR value and the physician paper chart value did not match, it was coded as “no match”. If there was no WebDR value recorded but a value was present in the physician paper chart, it was coded as “not recorded”.

The results of the validation are presented below:

Variable	Match (%)	No Match (%)	Not Recorded (%)
Baseline A1C value	25 (69.4%)	0 (0%)	11 (30.6%)
Baseline A1C date	25 (69.4%)	0 (0%)	11 (30.6%)
Follow-Up A1C value	29 (80.6%)	0 (0%)	7 (19.4%)
Follow-Up A1C date	28 (77.8%)	0 (0%)	8 (22.2%)

Therefore, the accuracy of WebDR for the baseline and follow-up A1C levels and dates in our study could be considered fair to good, with accuracy ranging from 69.4% - 80.6%. The inaccuracy present was due to missing values in WebDR, as opposed to incorrect values in WebDR.

Appendix J – Baseline Characteristics of those with Missing vs. Non-Missing Follow-Up A1C Values – Insulin Pump Therapy Cohort

	Analysis 1					Analysis 2				
	IPT Non-Missing		IPT Missing		p-value	IPT Non-Missing		IPT Missing		p-value
	n		n			n		n		
Age (years)	45.4 ± 12.3	141	43.3 ± 14.7	33	0.465 [†]	45.4 ± 12.8	159	41.0 ± 11.9	15	0.194 [†]
Duration of T1DM (years)	25.2 ± 12.8		25.2 ± 14.8		0.984 [†]	25.2 ± 13.2		25.0 ± 12.9		0.952 [†]
Gender (Male) – n (%)	62 (44.0)		18 (54.6)		0.273 [‡]	74 (46.5)		6 (40.0)		0.627 [‡]
Private Drug Plan - n (%)	9 (6.4)		3 (9.1)		0.701 ^{**}	10 (6.3)		2 (13.3)		0.276 ^{**}
City (London) - n (%)	63 (44.7)		17 (51.5)		0.478 [‡]	72(45.3)		8 (53.3)		0.550 [‡]
Physician (Endocrinologist) – n (%)	137 (97.2)		32 (97.0)		1.000 ^{**}	155 (97.5)		14 (93.3)		0.366 ^{**}
Average Yearly Household Income	\$70,976 ± \$12,897		\$70,695 ± \$12,845		0.911 [†]	\$70,869 ± \$12,662		\$71,491 ± \$15,191		0.880 [†]
Baseline A1C	0.077 ± 0.010		0.079 ±0.013		0.562 [†]	0.078 ± 0.011		0.077 ± 0.010		0.693 [†]
Optimal [*] baseline A1C – n (%)	38 (27.0)		6 (18.2)		0.297 [‡]	41 (25.8)		3 (20.0)		0.763 ^{**}
Current smoking – n (%)	7 (5.0)		0 (0.0)		0.349 ^{**}	7 (4.4)		0 (0.0)		1.000 ^{**}
At least 1 complication – n (%)	49 (34.8)		11 (33.3)		0.877 [‡]	55 (34.6)		5 (33.3)		0.992 [‡]
At least 1 glycaemic-responsive [§] complication – n (%)	48 (34.0)		10 (30.3)		0.682 [‡]	53 (33.3)		5 (33.3)		1.000 [‡]
Complications – n (%)	CVD	0 (0)	0 (0)	N/A	0 (0.0)	0 (0.0)	N/A			
	CAD	4 (2.8)	2 (6.1)	0.319 ^{**}	5 (3.1)	1 (6.7)	0.423 ^{**}			
	PVD	1 (0.7)	0 (0)	1.000 ^{**}	1 (0.6)	0 (0.0)	1.000 ^{**}			
	Retinopathy	30 (21.3)	9 (27.3)	0.457 [‡]	34 (21.4)	5 (33.3)	0.331 ^{**}			
	Nephropathy	18 (12.8)	7 (21.2)	0.268 ^{**}	22 (13.8)	3 (20.0)	0.456 ^{**}			
	Neuropathy	16 (11.4)	3 (9.1)	1.000 ^{**}	18 (11.3)	1 (6.7)	1.000 ^{**}			
Baseline BMI (kg/m ²)	26.8 ± 4.9	126	25.2 ± 3.6	30	0.049[†]	26.5 ± 4.7	142	25.9 ± 4.6	14	0.664 [†]
Baseline TDD (units)	54.1 ± 26.6	131	43.8 ± 18.4	30	0.014[†]	53.0 ± 26.0	147	43.6 ± 19.4	14	0.110 [†]
Baseline # CBG/day	4.0 ± 0.7	130	4.1 ± 0.9	33	0.797 [†]	4.0 ± 0.8	148	4.0 ± 0.8	15	0.907 [†]
Baseline # injections/day	4.2 ± 0.5	135	4.2 ± 0.6	33	0.538 [†]	4.2 ± 0.6	153	4.1 ± 0.4	15	0.585 [†]

*Optimal defined as ≤ 0.070; § glycaemic-responsive complications defined as retinopathy, nephropathy, neuropathy

IPT, insulin pump therapy; A1C, glycated hemoglobin; T1DM, type 1 diabetes mellitus; CVD, cerebrovascular disease; CAD, coronary artery disease; PVD, peripheral vascular disease; BMI, body mass index; kg, kilogram, m, meter; TDD, total daily insulin dose; CBG, capillary blood glucose

Comparisons between missing and non-missing groups using [†] two sample t-test, [†] Chi-square test, or ^{**} Fisher's Exact test

Appendix K – Baseline Characteristics of those with Missing vs. Non-Missing Follow-Up A1C Values – Control Cohort

	Analysis 1					Analysis 2					
	Control Non-Missing		Control Missing		p-value	Control Non-Missing		Control Missing		p-value	
	n		n			n		n			
Age (years)	45.7 ± 14.0	92	44.9 ± 12.3	82	0.675 [†]	45.4 ± 13.5	148	44.6 ± 11.8	26	0.748 [†]	
Duration of T1DM (years)	26.8 ± 12.9		23.4 ± 13.3		0.092 [†]	25.4 ± 13.1		24.2 ± 13.4		0.693 [†]	
Gender (Male) – n (%)	52 (56.5)		45 (54.9)		0.828 [‡]	84 (56.8)		13 (50.0)		0.522 [‡]	
Private Drug Plan - n (%)	21 (22.8)		9 (11.0)		0.039[†]	26 (17.6)		4 (15.4)		1.000 ^{**}	
City (London) - n (%)	47 (51.1)		43 (52.4)		0.859 [‡]	77 (52.0)		13 (50.0)		0.849 [‡]	
Physician (Endocrinologist) – n (%)	85 (92.4)		74 (90.2)		0.614 [‡]	136 (91.9)		23 (88.5)		0.473 ^{**}	
Average Yearly Household Income	\$71,909 ± \$13,993		\$68,979 ± \$13,806		0.167 [†]	\$70,396 ± \$13,892		\$71,285 ± \$14,480		0.773 [†]	
Baseline A1C	0.078 ± 0.013		0.078 ± 0.012		0.933 [†]	0.079 ± 0.013		0.075 ± 0.010		0.078 [†]	
Optimal* baseline A1C – n (%)	21 (22.8)		22 (26.8)		0.541 [‡]	34 (23.0)		9 (34.6)		0.204 [‡]	
Current smoking – n (%)	15 (16.3)		18 (22.0)		0.343 [‡]	26 (17.6)		7 (26.9)		0.281 ^{**}	
At least 1 complication – n (%)	45 (48.9)		33 (40.2)		0.251 [‡]	69 (46.6)		9 (34.6)		0.256 [‡]	
At least 1 glycaemic-responsive [§] complication – n (%)	43 (46.7)		33 (40.2)		0.389 [‡]	67 (45.3)		9 (34.6)		0.312 [‡]	
Complications – n (%)	CVD		1 (1.1)		1 (1.2)	1.000 ^{**}		2 (1.4)		0 (0)	1.000 ^{**}
	CAD		4 (4.4)		2 (2.4)	0.685 ^{**}		6 (4.1)		0 (0)	0.593 ^{**}
	PVD		0 (0)		0 (0)	N/A		0 (0)		0 (0)	N/A
	Retinopathy	29 (31.5)	22 (26.8)	0.497 [‡]	47 (31.8)	4 (15.4)	0.091 [‡]				
	Nephropathy	18 (19.6)	19 (23.2)	0.562 [‡]	33 (22.3)	4 (15.4)	0.427 [‡]				
	Neuropathy	18 (19.6)	15 (18.3)	0.831 [‡]	27 (18.2)	6 (23.1)	0.590 ^{**}				
Baseline BMI (kg/m ²)	27.4 ± 5.4	79	27.0 ± 5.6	70	0.660 [†]	27.1 ± 5.3	126	28.1 ± 6.2	23	0.453 [†]	
Baseline TDD (units)	62.9 ± 39.4	89	52.8 ± 25.4	81	0.048[†]	59.2 ± 35.5	144	51.8 ± 20.6	26	0.147 [†]	
Baseline # CBG/day	3.6 ± 0.9	84	3.9 ± 0.8	74	0.089 [†]	3.7 ± 0.9	136	3.7 ± 0.6	22	0.712 [†]	
Baseline # injections/day	4.2 ± 0.6	88	4.2 ± 0.8	80	0.859 [†]	4.2 ± 0.7	142	4.2 ± 0.9	26	0.702 [†]	

*Optimal defined as ≤ 0.070, §glycaemic-responsive complications defined as retinopathy, nephropathy, neuropathy

A1C, glycated hemoglobin; T1DM, type 1 diabetes mellitus; CVD, cerebrovascular disease; CAD, coronary artery disease; PVD, peripheral vascular disease; BMI, body mass index; kg, kilogram, m, meter; TDD, total daily insulin dose; CBG, capillary blood glucose

Comparisons between missing and non-missing groups using [†]two sample t-test, [‡]Chi-square test, or ^{**}Fisher's Exact test

Vita

Name: Selina Laura Liu

Post-Secondary Education, Degrees and Certifications Bachelor of Science (Honours), Life Sciences
Queen's University
Kingston, Ontario, Canada
1996-2000

Master of Science, Pharmacology & Toxicology
University of Western Ontario
London, Ontario, Canada
2000-2004

Doctor of Medicine
Queen's University
Kingston, Ontario, Canada
2002-2006

Royal College of Physicians and Surgeons of Canada
Fellowship in Internal Medicine 2010
Certification in Endocrinology and Metabolism 2011

Master of Science, Epidemiology & Biostatistics
University of Western Ontario
London, Ontario, Canada
2011-2014

Post Graduate Training: Internal Medicine Residency Training
University of Western Ontario
London, Ontario, Canada
2006-2009

Endocrinology Subspecialty Training
University of Western Ontario
London, Ontario, Canada
2009-2011

Research Fellow, Resident Research Career Development Program
Schulich School of Medicine & Dentistry
University of Western Ontario
London, Ontario, Canada
2011-2013

Honours and Awards:	Postgraduate Medical Education Resident/Fellow Travel Award Schulich School of Medicine & Dentistry University of Western Ontario 2009
	Resident Research Career Development Program Schulich School of Medicine & Dentistry University of Western Ontario 2011
	2 nd Prize, Best Clinical Research Presentation Second Annual Diabetes Research Day Schulich School of Medicine & Dentistry 2011
	CIHR-NIHCHD Summer Institute in Reproductive & Perinatal Epidemiology Participant 2012
	Western Graduate Research Scholarship – Epidemiology Schulich School of Medicine & Dentistry University of Western Ontario 2011-2014
Academic and Clinical Appointments:	Assistant Professor Division of Endocrinology & Metabolism, Department of Medicine University of Western Ontario 2014-present

Research and Publications:

Peer-Reviewed Publications:

1. Liu SL, Shah BR, Naqshbandi M, Tran V, Harris SB. Increased rates of adverse outcomes for gestational diabetes and pre-pregnancy diabetes in on-reserve First Nations women in Ontario, Canada. *Diabetic Medicine* 2012 29(8):e180-3. doi: 10.1111/j.1464-5491.2012.03691.x

2. Liu SL, McDonald CG, Yoo J, Myers KA. What's Old is New Again: A Now Unusual Presentation of Primary Hyperparathyroidism. *Canadian Journal of General Internal Medicine*. 2011; 6(2):39-42.
3. Liu SL, Lebrun CM. The Effect of Oral Contraceptives and Hormonal Replacement Therapy on Bone Mineral Density in Pre- and Peri-Menopausal Women: A Systematic Review. *British Journal of Sports Medicine*. 2006, 40(1):11-24.
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2. Liu SL, Shah BR, Naqshbandi M, Tran V, Harris SB. High Prevalence of Diabetes in Pregnancy in First Nations Women in Ontario. CDA/CSEM Canadian Diabetes Association Professional Conference & Annual Meeting, October 26-29, 2011, Toronto, ON. *Canadian Journal of Diabetes*. 2011 Sept; 35(4) (Suppl 1): 430. (Abstract)
3. Liu SL, Paul TL, Van Uum SH. Central Adrenal Insufficiency due to Epidural and Facet Joint Injections and Chronic Opioid Use. The Endocrine Society Annual Meeting – ENDO 11, June 4-7, 2011, Boston, MA. (Abstract)
4. Liu SL, McManus R. Research Proposal: Effects of an Acute Short-Term Fast on Glucose, Insulin, and Markers of Inflammation in Patients with Type 2 Diabetes Requiring more than 100 units of Insulin Daily. The Endocrine Society Clinical Investigator Workshop, November 5-7, 2010, San Francisco, CA.
5. Liu SL, Wyllie B, Van Uum SH. Graves' Disease Presenting as Hypokalemic Thyrotoxic Periodic Paralysis in a Canadian First Nations Person. The Endocrine Society Annual Meeting – ENDO 10, June 19-22, 2010, San Diego, CA. *Endocrine Reviews*. 2010 June; 31(3) (Suppl 1): S1502. (Abstract)

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12. Liu SL, Schmuck S, Parker S, Chorzyczewski J, Dixon J, Sims S, Feldman RD. Aldosterone Regulation of Vascular Tone via Immediate Effects on Endothelial Function. 17th Annual Meeting of the American Hypertension Society, May 14-18, 2002, New York, NY. American Journal of Hypertension. 2002, 15(4) Part 2:212A. (Abstract)

Non Peer-Reviewed Publications:

1. Liu SL. Aldosterone Regulation of Vascular Tone. M.Sc. Thesis - Pharmacology & Toxicology, University of Western Ontario, October 2003.