Alberta STE Report

Islet Transplantation for the Treatment of Type 1 Diabetes

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ISLET TRANSPLANTATION FOR THE TREATMENT OF TYPE 1 DIABETES

Alberta STE Report: Policy-driven Health Technology Assessment reports that include an analysis of the social and system demographics, technological effectiveness and economic implications of a health technology. The reports are written under contract with the Alberta Health Technologies Decision Process and contextualized for use in Alberta.

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EXECUTIVE SUMMARY

Social and System Demographics Analysis

Type 1 diabetes mellitus, characterized by high blood glucose levels that require lifelong insulin therapy, can cause short- and long-term complications in different organs such as the heart, eyes, kidneys, and blood vessels. Although it accounts for only a minority (approximately 10%) of the total burden of diabetes in a population, it is the predominant form of the disease in younger age groups. It can develop at any age but usually appears in childhood or adolescence. Males and females tend to be equally vulnerable.

It is estimated that currently over 300,000 Canadians live with type 1 diabetes. In 2007 the estimated number of cases among Canadian youth (0 to 14 years) was 8400, and the incidence for this age group was estimated at 21.7 per 100,000 in 2010. According to data from Alberta Health, the total number of type 1 diabetes cases in Alberta increased in the 18 to 65 age group from 15,260 in 2006–2007 to 15,939 in 2008–2009.

Intensive management of type 1 diabetes using intensive insulin therapy delivered by multiple daily injections is the accepted standard of care for achieving and maintaining near-normal blood glucose in order to reduce the risk of complications. Guidelines for managing type 1 diabetes in adults recommend an individualized intensive insulin therapy regimen using either multiple daily injections or insulin pump therapy. Insulin pump therapy is usually considered after multiple daily injections regimens have been tried and have failed to optimize glycemic control safely. Despite recent advances in intensive insulin therapy, and regardless of the delivery method, intensive insulin therapy is still associated with an increased risk of developing recurrent and frequent severe hypoglycemic episodes and hypoglycemia unawareness, which can lead to disabling and potentially life-threatening outcomes. Fear of inducing hypoglycemia remains a major barrier in achieving optimal glycemic control safely in all age groups.

Approximately 10% of patients with type 1 diabetes are prone to disabling and life-threatening hypoglycemic episodes due to blood glucose instability. Satisfactory and safe control of blood glucose levels cannot be achieved in many of these patients who experience brittle/unstable type 1 diabetes despite optimized/appropriate intensive insulin therapy. Whole pancreas transplantation or islet transplantation may be an alternative to intensive insulin therapy for highly selected adults with unstable, uncontrolled type 1 diabetes. Whole pancreas transplantation or islet transplantation performed in combination with kidney transplantation (simultaneously or after) is considered for uremic patients. Pancreas transplantation alone or islet transplantation alone can be considered for non-uremic adults with severe hypoglycemia or uncontrolled diabetes.

Clinical islet transplantation is an attractive option because of its potential advantages over intensive insulin therapy and whole pancreas transplantation. In practice, however, there are still many technical and medical challenges to overcome before islet transplantation can be considered as a component of standard therapy for adults with type 1 diabetes.

In Alberta, most adults with type 1 diabetes are users of multiple daily injections. Clinical islet transplantation services for highly selected adults with unstable type 1 diabetes are provided only as part of the Clinical Islet Transplant Program in Edmonton within the Alberta Health Services budget. The program secured provincial funding for providing islet transplantation alone to manage

adults with type 1 diabetes who meet the program's eligibility criteria and serves 'non-research' patients from across Canada. Patients access the program through referral from their physicians/endocrinologists or can self-refer to the program. The waiting times for transplant vary from a few weeks to a year or more.

Technological Effects and Effectiveness

Intensive insulin therapy

Intensive insulin therapy, administered by multiple daily injections or continuous infusion through an insulin pump, remains the treatment of choice for the majority of patients with T1DM. Intensive insulin therapy can delay the onset or slow the progression of long-term diabetic complications; however it is associated with increased risk of severe hypoglycemic events and suboptimal glycemic control.

Pancreas transplantation

Whole organ pancreas transplantation is one of two means of beta cell replacement used currently to restore sustained normal glycemia without the associated risk of severe hypoglycemia. Since the first procedure was performed in 1966, pancreas transplantation (particularly simultaneous pancreas and kidney transplantation) has clearly demonstrated sustained, long-term glycemic control and prevention or stabilization of secondary complications of diabetes in T1DM patients with end-stage renal disease (ESRD). Pancreas transplantation, however, is a major surgical procedure and is associated with significant perioperative complications such as thrombosis, pancreatitis, or peritonitis.

Islet transplantation

Islet transplantation, another means of beta cell replacement, is a complex but less invasive procedure that consists of pancreas procurement and preservation, islet cell processing (islet isolation, purification, or culture), islet infusion, and an immunosuppressive regimen after transplantation.

Islet transplantation can be performed as:

1) islet transplantation alone (ITA) for patients without ESRD
2) islet after kidney transplantation (IAK)
3) simultaneous islet and kidney transplantation (SIK) for patients with ESRD

ITA has been the most commonly performed procedure since the publication of the Edmonton Protocol in 2000.

Because of the high risk of severe hypoglycemia events associated with intensive insulin therapy in a small group of T1DM patients, and because of the serious perioperative complications associated with whole organ pancreas transplantation, islet transplantation offers a less invasive alternative.

Evidence on safety and efficacy/effectiveness

The objective of this report is to address the following questions:

1) Is islet transplantation safe compared to whole organ pancreas transplantation or intensive insulin therapy, in terms of complications and side effects in the treatment of adult patients with T1DM?

2) Is islet transplantation effective compared to whole organ pancreas transplantation or intensive insulin therapy in terms of short-, intermediate-, and long-term outcomes in the treatment of adult patients with T1DM?
3) What sub-populations of adult patients are most appropriately treated with islet transplantation?

A comprehensive literature search identified six comparative studies (with eight publications) and 13 case series studies (with 20 publications) which included 10 or more patients and followed them for at least one year.

Comparative studies have demonstrated that islet transplantation is associated with a higher risk of procedure-related adverse events than occur with intensive insulin therapy, but with significantly fewer and less severe procedure-related complications than occur with whole organ pancreas transplantation.

Insulin independence achieved following islet transplantation was significantly lower than that achieved with pancreas transplantation and was usually not sustained over the long term. However, because of the reduced insulin requests that follow, islet transplantation can maintain levels of glycemic control similar to those provided by pancreas transplantation, and can prevent severe hypoglycemia in a small group of highly select patients. While no HrQoL outcomes were reported in any of the six comparative studies, four case series studies showed improved disease-specific QoL but not generic QoL scores. More sensitive tools, such as transplant-specific QoL measures, should be used to capture the full impact of islet transplantation on HrQoL and on patients' preferences and perceptions of islet transplantation.

Although limited data indicated positive impact of islet transplantation on some diabetic complications such as retinopathy, findings from the included studies are inconclusive. Larger controlled trials with better design are required to clarify the true impact of islet transplantation on long-term clinical outcomes.

No information is currently available comparing ITA with intensive insulin therapy in patients with severe hypoglycemia or hypoglycemia unawareness. No study directly compared ITA with pancreas transplantation alone (PTA) in non-uremic patients. No study was found that directly compared IAK with SPK (treatment of choice) for uremic patients. It seems that SPK remains the treatment of choice for T1DM patients with end-stage renal failure, while ITA is a treatment option for T1DM patients with a history of severe hypoglycemia under intensive insulin therapy and who experience unstable glycemic control but without end-stage renal failure.

Conclusion

The definition of success for islet transplantation remains controversial. Insulin independence may not be an appropriate clinical outcome for islet transplantation. Islet transplantation should aim at reducing the doses of required insulin therapy and the frequency of severe hypoglycemia events; these outcomes would improve patients' quality of life and would improve glycemic control to prevent long-term diabetic complications.

Islet transplantation is a complex procedure that has undergone continuous evolution over the past decade. It offers an alternative treatment option for a small group of patients with severe hypoglycemia, hypoglycemia unawareness, and brittle diabetes, who have failed to respond to standard treatment and management. Its safety and efficacy/effectiveness in these highly select

patients has been extensively investigated. The role of islet transplantation in the long-term treatment of T1DM has yet to be determined because of the potential risk of immunosuppression-related side effects, the absence of sustained long-term treatment effects, and the insufficient supply of donor pancreata**.**

Economics Analysis

Objective

The objective of the economic analysis was to estimate the costs and cost effectiveness of islet transplantation (IT) compared to intensive insulin therapy (IIT) alone and to estimate the potential economic impact of IT in Alberta.

Methods

A systematic review of economic studies and a primary economic evaluation using a decision analytic model were conducted to assess the cost effectiveness of IT compared to IIT. Analyses were also conducted to identify potential resource shifting (cost attribution analysis) and the budget impact of IT.

The clinical inputs for the model were based on data from the Clinical Islet Transplantation Program in Edmonton. Epidemiological, health service utilization, and cost data were obtained primarily from Alberta administrative databases. The analysis was conducted from a payer's perspective. Cost components included the physician, inpatient, and outpatient costs associated with diabetes management, associated secondary complications (amputation, blindness, renal failure, cardiovascular conditions, and neuropathy), and IT, including laboratory and program costs. Quality-adjusted life years (QALYs) were used as a measure of effectiveness. Each treatment will generate a difference in costs and outcomes, providing a basis for the comparative economic analysis.

Results

Value for money

Compared to IIT, IT generated an additional 2.06 years worth of perfect health at a 20-year horizon and 2.35 years worth of perfect health from a lifetime horizon if secondary complications such as amputation, blindness, renal failure, cardiovascular conditions, and neuropathy are prevented. The values decrease to 0.74 years worth of perfect health at a 20-year horizon and 0.78 at a lifetime horizon when assuming that IT does not prevent secondary complications. These differences are clinically significant and large in magnitude, given that a change of 0.03 years worth of perfect health is an indicator of clinical importance.

However, compared to IIT, IT was associated with an incremental cost of $374,604 at a 20-year horizon and $378,785 at a lifetime horizon if secondary complications are prevented, corresponding to a cost per additional year of perfect health of $181,847 and $161,185, respectively, if secondary complications are prevented. If secondary complications are not prevented the cost per additional year in perfect health is $506,429 at a 20-year time horizon and $380,850 at a lifetime horizon.

One study was identified in the review of the economic literature with which our results can be compared. Beckwith et al.[2] found that over a 20-year horizon, IIT was associated with $663,000 USD and 9.3 years worth of perfect health while IT was associated with $519,000 USD and 10.9 years worth of perfect health. Without performing an incremental analysis between IIT and IT, the

authors concluded that IIT is cost effective compared to IT. Both this study and our results show that IT is associated with clinically important improvements in health outcomes. The cost of IT is what drives the differences between these two analyses. In the study conducted by Beckwith et al.,[2] the costs of IT were assumed to be a one-time cost of $93,500 thousand with annual follow up costs of $19,000 per year. Over a 20-year time horizon, this is an underestimate of the total cost of IT, given that re-transplant has been common among IT recipients.

Cost attribution

Over a 20-year time horizon, there is a net cost increase of $14,463 per patient for physician services and $26,979 per patient for drugs (immunosuppressants). There was a net cost increase of $384 per patient for outpatient services but a cost saving of $1537 for inpatient services. This suggests that IT does have a small impact on reducing health service costs associated with general diabetes care (outpatient and inpatient categories account for costs associated with diabetes care and not those related to IT), but that the costs associated with IT including physician and immunosuppression offset any health system savings in diabetes management.

Budget impact analysis

Given the current supply of available pancreata, the maximum number of IT procedures that can be performed annually is approximately 65. Excluding the 22 ITs currently being conducted per year, the budget impact for the additional 43 ITs is $3,450,784 for in-province patients and $2,439,347 for out-of-province procedures, for a total of $5,890,131. It is important to note that physicians in Alberta are not currently reimbursed for performing islet infusions. This would add $77,000 to the cost of performing the current 22 IT procedures and another $157,500 for the 43 additional procedures.

Conclusion

IT is associated with clinically significant improvements in health outcomes, but it is not cost-saving compared to IIT. Hence, IT does not dominate IIT (that is, IT is not less costly and more effective than IIT), and its cost-effectiveness depends on whether its associated health benefit is worth its additional cost. A prohibitive factor in the value of IT is the high associated cost per additional QALY gained. It is important to identify the services that have expanded, contracted, or been displaced in the health system to support IT (that is, the opportunity costs), and to evaluate the net impact of these actions in terms of their net health benefit. If the opportunity cost for the health system is greater than the value for money associated with IT (that is, greater than $181,847 per additional QALY gained), IT would be considered cost effective. While IT is associated with cost savings from reduced health service utilization for general diabetes management, savings are dominated by the cost increases associated with transplantation. The budget impact of IT is approximately $5.9 million per year.

Abbreviations

All abbreviations that have been used in this report are listed below unless the abbreviation is well known, has been used only once, or is a nonstandard abbreviation used only in figures, tables, or appendices (in which case the abbreviation is defined in the figure legend or below the table).

ACCS	Ambulatory Care Classification System
ACHORD	Alliance for Canadian Health Outcomes Research in Diabetes
ACR	albumin to creatinine ratio
ADA	American Diabetes Association
ADDQoL	Audit of Diabetes-Dependent Quality of Life
AHS	Alberta Health Services
ALT	alanine aminotransferase
AST	aspartate aminotransminase
ATG	antithymocyte globulin
AUD	Australian dollar
BG	blood glucose
BIA	budget impact analysis
BLA	biologics license application
BMI	body mass index
BT	blood transfusion
CCHS	Canadian Community Health Survey
CDA	Canadian Diabetes Association
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CGM	continuous glucose monitoring
CI	confidence interval
CIHI	Canadian Institute for Health Information
CIP	clinical islet program
CITR	Collaborative Ilset Transplantation Registry
CMV	cytomegalovirus
Cr	creatinine
CrCl	creatinine clearance

CRD	Centre for Reviews and Dissemination
CSII	continuous subcutaneous insulin infusion
CUA	cost-utility analysis
d(s)	day(s)
DAC	daclizumab
DAD	discharge abstracts database
DCCT	Diabetes Control and Complications Trial
DHCC	Diabetes, Hypertension & Cholesterol Centre
DKA	diabetes/diabetic ketoacidosis
dl	deciliter
DM	diabetes mellitus
DMS	data management software
DQoL	Diabetes Quality of Life
DSA	donor-specific antibodies
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
F	female
FDA	Food and Drug Administration
FF	fullgraft function
ft	feet
FU	follow-up
g	gram
GDM	gestational diabetes mellitus
GFR	glomerular filtration rate
GRAGIL	Groupe de Recherche Rhin Rhône Alpes Genèva pour la transplantation d'Ilots de Langerhans (In English: The Rhine Rhone Alpes Geneva Research Group for Islet Transplantation**)**
h(s)	hour(s)
HbA1C	glycosylated/glycated hemoglobin
HrQoL	health-related quality of life
HTA	health technology assessment

HTK	histidine-tryptophan-ketoglutarate
IAK	islet after kidney transplantation
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IDDM	insulin-dependent diabetes mellitus
IDF	International Diabetes Federation
IE	islet equivalent
IIT	intensive insulin therapy
IMT	intima media thickness
IND	investigational new drug
IQR	inter-quarter range
IS	immunosuppression
IPT	insulin pump therapy
IT	islet transplantation
ITA	islet transplantation alone
ITT	intention to treat
kg	kilogram
L	litre
LE	life expectancy
LFA-1	leukocyte functional antigen-1
LP	laparotomy
M	male
MAGE	mean amplitude of glycemic excursion
MBG	mean blood glucose
MDI	multiple daily injection
MeSH	Medical Subject Headings
mg	milligram
ml	milliliter
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
N	total number

NA	not available
NF	no graft function
ng	nanogram
NHS	National Health System
NICE	National Institute for Clinical Excellence
NIDDM	non–insulin-dependent diabetes mellitus
NPH	neutral protamine Hagedorn (a basal insulin)
NR	not reported
NS	not statistically significant
OFIA	operational and financing impact assessment
OGTT	oral glucose tolerance test
OR	odds ratio
PAK	pancreas after kidney (transplantation)
PCD	physician claims database
PF	partial graft function
PGF	primary graft function
PNE	perinephric edema
PSA	probabilistic sensitivity analysis
PTA	pancreas transplantation alone
PTLD	post-transplantation lymphoproliferative disorder
PVT	portal vein thrombosis
P-Y	person-years
QoL	quality of life
QALY	quality-adjusted life year
QHES	quality of health economics studies
RATG	rabbit antithymocyte globulin
RCT	randomized controlled trial
RR	relative risk
RT	real time
sCr	serum creatinine
SD	standard deviation

SE	standard error
SF-36	36-item Short Form Health Survey
SH	severe hypoglycemia
SHE	severe hypoglycemic event
SIK	simultaneous islet and kidney transplantation
SIR	sirolimus
SMBG	self-monitoring of blood glucose
SPK	simultaneous pancreas and kidney transplantation
SR	systematic review
SS	statistically significant
TAC	tacrolimus
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TDD	total daily dose
TEAE	treatment-emergent adverse event
U	unit
UK	United Kingdom
UKPDS	UK Prospective Diabetes Survey
ULN	upper limit of normal range
UPE	urinary protein excretion
US	United States
UW	University of Wisconsin
WHO	World Health Organization
wk(s)	week(s)
WMD	weighted mean difference
WOPT	whole organ pancreas transplantation or whole pancreas transplantation
WPT	whole organ pancreas transplantation or whole pancreas transplantation
WTP	willingness to pay
yr	year

Glossary/Dictionary

The glossary terms listed below were obtained and adapted from the following sources:

Guo B, Corabian P, Harstall C. *Islet transplantation for the treatment of Type 1 diabetes – an update.* Institute of Health Economics, Edmonton, AB, Canada; Report November 2008; pp i-65.

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Acidosis: Too much acid in the body. For a person with diabetes, this can lead to diabetic ketoacidosis.

Alpha cells: Cells, found in the islets of Langerhans in the pancreas, that are responsible for producing glucagon, a hormone that causes blood glucose to rise.

Antibodies: Proteins made by the body to protect itself from 'foreign' substances such as bacteria or viruses.

Autoimmune disease: Disorder of the body's immune system in which the immune system mistakenly attacks and destroys body tissue it believes to be foreign.

Autoimmune thyroid disease: An autoimmune disease that occurs when the body's immune system attacks its own thyroid cells, reducing or even destroying thyroid function.

Autonomic: Self-controlling; functionally independent.

Autonomic nervous system: The portion of the nervous system concerned with regulating the activity of cardiac muscle, smooth muscle, and glands.

Basal C-peptide: A protein that is attached to insulin produced in the body. When the pancreas secrets insulin, C-peptide is released in the blood stream. C-peptide blood levels can indicate whether a person is producing his/her own insulin. A test of C-peptide levels indicates how well the beta cells are functioning.

Beta cell: A cell in the pancreas that makes insulin. Beta cells are located in the islets of the pancreas (called the islets of Langerhans).

Blood glucose level: The amount or concentration of glucose in a given amount of blood. In Canada, blood glucose is measured in millimoles of glucose per litre of blood (mmol/L); the normal range before meals is 4.0 to 6.0 mmol/L; the normal range two hours after a meal is 5.0 to 8.0 mmol/L.

Bolus: An extra amount of insulin taken to cover an expected rise in blood glucose, often related to a meal or snack.

Brittle diabetes: A term used when a person's blood glucose level moves often from low to high and from high to low. It refers to type 1 diabetes mellitus that is very difficult to control (labile, unstable type 1 diabetes mellitus characterized by wide, unpredictable fluctuations of blood glucose values and difficult to control).

Calorie: A unit representing the energy provided by food; the sources of calories in a diet are carbohydrate, protein, alcohol, and fat.

Carbohydrate: One of the main nutrients in food and one of the main sources of calories. Sources of carbohydrates include the sugars naturally found in honey, fruits, vegetables, and milk; refined sugars such as table sugar and the sugars added to candies, jams, and soft drinks; and starches such as grains, rice, potatoes, corn, and legumes. All forms of carbohydrate are broken down into glucose during digestion.

Carbohydrate counting: A method of meal planning for people who have diabetes, which is based on counting the number of grams of carbohydrate in food.

Celiac disease: An autoimmune disease characterized by sensitivity to gluten, a protein found in wheat.

Cold ischemic time: The time measured from the point at which blood flow to the organ is stopped in the donor to the time at which blood flow to the organ is restored in the recipient.

Continuous glucose monitor: A blood glucose monitor with a small sensor that is inserted under the skin; this monitor automatically checks blood glucose levels every few minutes.

Conventional insulin therapy: Insulin therapy that consists of one or two daily insulin injections.

Conventional therapy: A system of diabetes management practiced by most people with diabetes, which consists of one or two insulin injections each day, daily self-monitoring of blood glucose levels, and a standard program of nutrition (meal planning) and exercise, along with regular visits to healthcare providers. The main objective in this form of treatment is to avoid very high and very low blood glucose levels. It is also called "standard therapy."

Creatinine: A waste product from protein in the diet and from the muscles of the body. Creatinine is removed from the body by the kidneys; as kidney disease progresses, the level of creatinine in the blood increases.

Dawn phenomenon: An increase in the blood sugar in the morning, possibly caused by the release of counterregulatory hormones such as cortisol, glucagon, and epinephrine, all of which can signal the liver to release glucose.

Diabetes: A disease in which the body either cannot produce insulin or cannot properly use the insulin it produces. This leads to high levels of glucose in the blood, which can damage organs, blood vessels, and nerves.

Diabetes Control and Complications Trial (DCCT): A multicentre randomized controlled trial, conducted between 1983 and 1993, that enrolled 1441 patients with type 1 diabetes from 29 centres and compared the effects of intensive insulin therapy (MDI or IPT) and conventional insulin therapy (defined as one or two daily insulin injections) on the long-term complications of diabetes.

Diabetic ketoacidosis (DKA): An acute and severe complication of diabetes in which extremely high blood glucose levels, along with a severe lack of insulin, result in the breakdown of body fat for energy and an accumulation of ketones (acids) in the blood and urine.

Diabetic retinopathy: A disease in which the small blood vessels (capillaries) in the back of the eye (retina) bleed or form new vessels.

Endocrine disease: Any disease of the endocrine system; diabetes is an endocrine disease because if affects the pancreas, a gland that produces the hormone insulin.

End-stage renal disease: A condition in which patients need dialysis treatment or a transplant due to the lost function of the kidney. Also known as chronic kidney failure.

Etanercept: A TNF-α antagonist.

Euglycemia: A blood glucose level within the normal range.

Exenatide: A glucagon-like peptide-1 (GLP-1) analogue.

Fasting blood glucose test: A test of a person's blood glucose level after the person has not eaten for 8 to 12 hours (usually overnight).

Glucagon: A hormone, produced by the alpha cells in the pancreas (in areas called the islets of Langerhans), which causes an increase in the blood glucose level.

Glycemic variability: The fluctuation in blood glucose levels throughout the day that is typically characterized by postprandial hyperglycemic spikes.

Glucose: A simple sugar found in the blood that serves as the body's main source of energy. Glucose is also known as dextrose.

Glycosuria: The presence of high levels of glucose in the urine, which can indicate abnormally high blood glucose levels.

Glycosylated hemoglobin (HbA1C): The amount of glucose-bound hemoglobin; a measure of blood glucose levels over the previous 120 days. Also called glycated hemoglobin.

Hepatic steatosis: In this condition, fat is deposited in liver cells, causing enlargement of, and sometimes damage to, the liver cells. Also known as fatty liver.

Honeymoon phase: The period of time after the diagnosis of type 1 diabetes when the dose of insulin may need to be reduced due to remaining or recovered insulin secretion from the pancreas; this period can last weeks, months, or years.

Human insulin: A synthetic form of insulin created in the 1990s using recombinant-DNA technology.

Hyperglycemia: Higher-than-normal blood glucose levels. Fasting hyperglycemia is blood glucose above a desirable level after a person has fasted for at least 8 hours; postprandial hyperglycemia is blood glucose above a desirable level between one and two hours after a person has eaten.

Hypoglycemia: A condition that occurs when the blood glucose level is lower than normal. Also called an insulin reaction.

Hypoglycemia unawareness: A state in which a person does not feel or recognize the symptoms of hypoglycemia.

Implantable insulin pump: A small pump placed inside the body to deliver insulin in response to remote control commands from the user.

Incidence: A measure of how often a disease occurs. It is the number of new cases of a disease among a certain group of people for a certain period of time.

Insulin: A hormone produced by the beta cells of the pancreas; it controls the amount of glucose in the blood.

Insulin analogue: Chemically-made insulin that is a modification of human insulin.

Insulin antagonist: Something that opposes or fights the action of insulin; glucagon is an antagonist of insulin.

Insulin-induced hypertrophy: Small lumps that form under the skin when a person repeatedly injects a needle in the same spot.

Insulin pen: An injection device the size of a pen that includes a needle and holds a vial of insulin.

Insulin pump: A portable, battery-operated device that delivers a specific amount of insulin through a small needle inserted under the skin. It can be programmed to deliver constant doses of insulin throughout the day, or to deliver extra insulin as required, or both. It is also called continuous subcutaneous insulin infusion (CSII).

Intensive insulin therapy: Therapy that consists of three or more daily insulin injections or of treatment with an insulin pump.

Intensive management: A treatment program for diabetes that uses intensive insulin therapy (that is, taking several doses of insulin throughout the day) with the goal of imitating the function of a healthy pancreas.

Intima media thickness: A measurement of the thickness of artery walls—usually performed by external ultrasound, occasionally by internal, invasive ultrasound catheters—to both detect the presence and track the progression of atherosclerotic disease in humans. Carotid intima media thickness is a measure shown to correlate with the likelihood of cardiovascular events (coronary artery disease, atherosclerotic vascular disease, mortality) in individuals with T1DM

Islet cells (islets): Groups of cells located in the pancreas that produce hormones to help the body break down and use food.

Islet transplantation: A procedure currently employed in human clinical trials, which involves taking beta (islet) cells from a donor pancreas and putting them into a person whose pancreas has stopped producing insulin.

Intermediate-acting insulin: A type of insulin that starts to lower blood glucose within 1 to 2 hours after injection and has its strongest effect 6 to 12 hours after injection, depending on the type used.

Lispro insulin: A rapid-acting insulin analogue in which the position of two amino acids are switched. The resulting insulin analog is faster-acting than regular (short-acting) insulin. On average, lispro insulin starts to lower blood glucose within 5 minutes after injection. It has its strongest effect 30 minutes to 1 hour after injection but keeps working for 3 hours after injection. It can be injected immediately before a meal, as opposed to regular, which should be injected 30 minutes or more before a meal.

Liver function test: A blood test that measures the levels of liver enzymes (alanine aminotransferase, aspartate aminotransminase) in the blood as a way of helping diagnose liver problems.

Long-acting insulin: A type of insulin that starts to lower blood glucose within 4 to 6 hours after injection and has its strongest effect 10 to 18 hours after injection.

Macrosomia: A condition in which a baby is considerably larger than normal (has a birth weight greater than 4000 grams).

Microalbuminuria: The appearance of low but abnormal levels (≥30 mg/day or 20 μg/min) of albumin in the urine. Patients having microalbuminuria are referred to as having incipient nephropathy.

Nephropathy: Diabetic kidney disease, a slow deterioration of the kidneys and kidney function that, in more severe cases, can eventually result in kidney failure. It is also known as end-stage renal disease, or ESRD.

Neuroglycopenia: Symptoms and signs of neurological dysfunction that are secondary to hypoglycemia. Prolonged neuroglycopenia can result in permanent brain damage.

Neuropathy: Progressive damage to the nervous system caused by diabetes, which leads to a loss of feeling in the hands and feet.

Nocturnal hypoglycemia: Hypoglycemia occurring while the patient is asleep (between the evening injection and getting up in the morning).

Noninvasive blood glucose monitoring: A way to measure blood glucose levels without having to prick the finger to obtain a blood sample.

Non-uremic: Without kidney failure.

NPH insulin: Neutral protamine Hagedorn, also called N insulin. On average, NPH insulin starts to lower blood glucose within 1 to 2 hours after injection. It has its strongest effect 6 to 10 hours after injection but keeps working for about 10 hours after injection.

Pancreas: An organ in the digestive system that produces several important hormones, including insulin and glucagon; it also produces pancreatic juice, which contains enzymes that help digestion.

Pancreas transplantation: A surgical procedure that involves taking a healthy whole or partial pancreas from a donor and placing it into a person whose pancreas is damaged (such as someone who has diabetes).

Pancreatic islets: Irregular microscopic structures scattered throughout the pancreas and comprising its endocrine portion. In humans, the pancreatic islets are composed of at least four types of cells: the *alpha cells*, which secrete the hyperglycemic factor glucagon; the *beta cells*, which are the most abundant, and which secrete insulin; the *delta cells*, which secrete somatostatin; and the *PP* (or *F*) *cells*, which secrete pancreatic polypeptide.

Prevalence: The number of people in a given group or population who are reported to have a disease.

Rapid-acting insulin: A type of insulin that starts to lower blood glucose within 5 to 10 minutes after injection and has its strongest effect 30 minutes to 3 hours after injection, depending on the type used.

Regular insulin: Short-acting insulin; on average, regular insulin starts to lower blood glucose within 30 minutes after injection; it has its strongest effect 2 to 5 hours after injection but keeps working for 5 to 8 hours after injection.

Secretagogue: A substance (such as a hormone) that stimulates secretion or that triggers release from the cells of another substance (a substance that stimulates cells to secrete or trigger the release of another substance).

Self-monitoring of blood glucose (SMBG): Blood testing done by a person with diabetes using a blood glucose meter or monitor to determine how much glucose is in the blood. SMBG helps people with diabetes and their healthcare professionals make decisions about their medications, diet, and exercise in order to achieve good blood glucose control.

Severe hypoglycemia: A hypoglycemia episode requiring assistance from another person, or that results in a seizure or coma.

Subcutaneous injection: Using a needle and syringe to put a fluid into the tissue under the skin.

Type 1 diabetes: An autoimmune disease that occurs when the pancreas no longer produces any insulin or produces very little insulin (previously called insulin-dependent diabetes or juvenile diabetes). Type 1 diabetes usually develops suddenly and most commonly in younger people under age 30 (in childhood or adolescence), and affects approximately 10% of people with diabetes. There is no cure for this disease. It is treated with lifelong daily insulin therapy, a planned diet and regular exercise, and daily self-monitoring of blood glucose levels.

Unit of insulin: The basic measure of insulin. U-100 insulin means 100 units of insulin per millilitre or cubic centimetre of solution. Most insulin made today in the United States is U-100.

Uremic: With kidney failure.

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SECTION ONE: SOCIAL AND SYSTEM DEMOGRAPHICS ANALYSIS APPROACH

Paula Corabian, BSc MPH

The social and system demographics approach to analysis (SSDA) summarizes available key information on the use of islet transplantation (IT) as a treatment option for adults with type 1 diabetes mellitus (T1DM) in Alberta, in Canada, and in other countries with developed market economies. This analysis was intended to describe the profile of T1DM (definition, progression, epidemiology, and population dynamics of affected adults in Alberta, in Canada, and worldwide) and patterns of care for this condition in adults (focusing on recommendations from evidence-based guidelines), as well as to identify potential inequities in health status or care across adult population groups. Social, ethical, and legal issues associated with the provision of IT as a treatment for adults with T1DM were also considered.

The SSDA report addressed the following questions:

- What is the prevalence and incidence of T1DM in Alberta, in Canada, and in other countries with developed market economies?
- How many adults in Alberta and in Canada have T1DM?
- What is the standard of care for adults with T1DM in Alberta, in Canada, and in other countries with developed market economies?
- What alternatives exist when standard of care for adults with T1DM fails?
- How many adults with T1DM would most benefit from IT in Alberta?
- What is the demand for IT as a therapy for T1DM in Alberta and in Canada?
- Are there any issues related to acceptability, adherence, or noncompliance when using IT for T1DM in Alberta compared to whole-pancreas transplantation (WPT, pancreas alone, or simultaneous pancreas and kidney transplantation) or to intensive insulin therapy (IIT) delivered by multiple daily injections (MDI) or by insulin pump therapy (IPT)?
- Are there any quality-of-life (QoL) issues when using IT for T1DM in Alberta compared to WPT or to IIT?
- Are there any social, ethical, and/or legal issues associated with the provision of IT for T1DM compared to WPT or to IIT?
- Are there any issues related to training and accreditation for, quality control of, and access to IT in Alberta, compared to WPT or to IIT?
- What are the utilization and waiting rates for IT as a therapy for T1DM in Alberta?
- What are the number and the distribution of health care practitioners and support staff providing IT in Alberta?
- What are the implications (on society, families and caregivers, and the affected individuals) for the provision of IT as a therapy for adults with T1DM in Alberta?

Data sources and data synthesis and analysis methods are described in Appendix S.A.

Profile of Illness

Diabetes mellitus is a chronic metabolic disorder characterized by the presence of hyperglycemia (higher than normal blood glucose levels) due to defective insulin secretion, defective insulin action, or both (www.diabetesatlas.org, www.diabetes.ca, www.diabetes.org, www.jdrf.ca).[1-9] Insulin is a hormone produced by the islet beta cells of the pancreas in response to rising blood glucose levels; it mainly regulates the metabolism of carbohydrates, but also of proteins and fats. Insulin deficiency leads to abnormal glucose metabolism and loss of control of blood glucose levels, which increases the risk of developing potentially devastating microvascular and macrovascular complications.

On the basis of etiology and clinical presentation of the disorder, diabetes mellitus is classified into: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus (GDM), and other specific types (www.diabetesatlas.org, www.diabetes.ca, www.jdrf.ca, www.diabetes.org).[1,2,4-9]This report addresses only T1DM.

Definition, classification, and description of T1DM

T1DM encompasses cases that are a result of pancreatic beta cell destruction, loss, or failure (which usually leads to absolute insulin deficiency) and are prone to diabetic ketoacidosis (DKA) (www.diabetesatlas.org, www.diabetes.ca, www.jdrf.ca, www.diabetes.org).[1,4–6,10–17] It is either immune mediated (in 85% to 90% of cases, when beta cell destruction is attributable to an autoimmune process) or idiopathic (in 10% to 15% of cases, when neither an etiology nor a pathogenesis is known).

With respect to development, T1DM passes through the preclinical stage (characterized by progressive beta cell destruction or failure without symptoms), the clinical presentation with symptoms, the 'honeymoon stage' (a period of relative remission), and the chronic phase of severe or absolute insulin deficiency and lifelong dependence on insulin therapy for survival.[4,5,13–15,17–21] Progressive beta cell destruction or failure occurs at a variable rate and may last for months to years, during which the individual is asymptomatic. T1DM becomes clinically symptomatic when greater than 80% of the pancreatic beta cells are destroyed or fail to produce insulin.

Some individuals progress to clinical T1DM in infancy and others during late adulthood.[17,22,23] In young adults, there is evidence that the onset of T1DM may be characterised by a slower decline in beta-cell function compared with the decline in children and adolescents.[23]

After a diagnosis of T1DM and the start of insulin therapy, a transient (short-lasting) 'honeymoon stage'—characterized by an improvement in symptoms and even a reduction in insulin dosage—may develop due to production of insulin by the remaining surviving pancreatic beta cells (www.diabetes.ca, www.diabetes.org).[4,5,18,19] Although the progression from the relative remission stage into the chronic phase is usually gradual, it can be accelerated by inter-current illness.

Symptoms

The clinical onset of T1DM is often sudden and the condition is rarely diagnosed before symptoms develop (www.diabetesatlas.org, www.diabetes.ca, www.jdrf.ca, www.diabetes.org).[1,3–8,10,12,24–26] Warning signs and symptoms usually develop rapidly and may include increased thirst (polydipsia); increased frequency of urination (polyuria)—particularly urination at night (nocturia); tiredness or fatigue; increased hunger (polyphagia); sudden weight loss; recurrent infections; blurred vision or other eyesight changes; and symptoms of DKA (such as drowsiness, lethargy, decreased alertness,

rapid breathing, dehydration, abdominal pain, nausea, and vomiting). In severe cases, decreased consciousness or diabetic coma may be the first sign of T1DM.

Causes

It has yet to be determined what specifically prompts the autoimmune response that destroys the body's ability to produce insulin in T1DM (www.diabetes.ca, www.jdrf.ca, www.diabetes.org, www.diabetesatlas.org).[1,4,5,10–12,14,16–18,21,25,27–33] Available evidence suggests T1DM is a multifactorial condition that is likely prompted by the interplay between genetic susceptibility and immunological, environmental, and chemical factors.

Potential risk factors

Potential risk factors for T1DM include early fetal events (such as blood group incompatibility, maternal stress, and pre-eclampsia during pregnancy), viral and other pathogen exposure during gestation and early childhood, being ill in early infancy, early childhood stress, dietary factors (such as early exposure to cow's milk components and other nutritional factors), exposure to environmental toxins and contaminants, high birth weight and height, accelerated early growth, having a parent with T1DM, increasing maternal age at birth, and delivery by Cesarian section (www.diabetesatlas.org, www.diabetes.ca, www.diabetes.org, www.jdrf.ca, www.cdc.gov).[10-12,14,17,23,29,30,32-43] To date, none of these factors has been conclusively shown to influence the risk of developing T1DM.[11,12,17,33,42]

Reduced exposure to ultraviolet light and lower vitamin D levels, both of which are more likely found in the higher latitudes, have been associated with an increased risk of T1DM.[14,17,42–46]

Several studies have documented a seasonal pattern of T1DM onset, with increased incidence in the winter.[11,44,45] In both the northern and southern hemispheres, incidence declines during the summer months. The seasonal onset pattern of T1DM has been observed in both males and females and in all age groups; it appears to be more prominent in countries with large differences between summer and winter temperatures. The role climate plays in the development of T1DM is unclear.

Associated complications and comorbidities

T1DM can result in a variety of acute and chronic complications related to the disease itself, to its management, or to both (www.cdc.gov, www.diabetesatlas.org, www.jdrf.ca, www.diabetes.ca, www.diabetes.org).[1,4,5,8,10,20,33,47–52] The likelihood of developing complications appears to depend on the interaction of many factors, including poor metabolic control, genetic susceptibility, lifestyle, and gender.

T1DM can be complicated by the presence of some other diseases.[4,5,10,18,53]

Acute complications

T1DM and its management have two major and frequent acute complications: DKA and hypoglycemia (www.diabetes.ca, www.diabetes.org, www.jdrf.ca).[1,4,5,7,8,12,20,27,50-53,55,57-67] These acute complications reflect the difficulties of maintaining a balance between the recommended insulin therapy, dietary intake, and exercise.

DKA is a metabolic state resulting from acute hyperglycemia that can be life threatening (www.jdrf.ca, www.diabetes.ca, www.diabetes.org).[1,4,5,12,20,26,47,48,54,55] It occurs in individuals with newly diagnosed T1DM and in those with established T1DM. Risk factors include presence of infection, intercurrent illness, and noncompliance with insulin therapy (omission or under-use of insulin).

The most frequent acute complication of T1DM is ***hypoglycemia***, which is documented by symptoms and signs consistent with hypoglycemia and responding to the administration of carbohydrate, a low measured plasma glucose concentration (< 4.0 mmol/L for patients treated with insulin), and resolution of those symptoms and signs after the plasma glucose concentration is raised.[4,5,7,8,12,52,56–66] It can be further described by its degree of severity: mild (autonomic mediated symptoms; patient able to treat self), moderate (autonomic and neuroglycopenic mediated symptoms; patient able to treat self), and severe (patient may be unconscious; patient unable to treat self and requires assistance). The physical morbidity of a hypoglycemic event ranges from warning symptoms and signs (sweating, tremor, and tachycardia) to dizziness and blurred vision. In severe cases, uncontrolled hypoglycemia can lead to coma, seizure, or even death.

Risk factors for severe hypoglycemia include attempting tight blood glucose control, long-term diabetes, noncompliance with treatment, and infections (www.jdrf.ca, www.diabetes.ca, www.diabetes.org).[1,4,5,7,8,47,52,56,60,63–65,67]

It occurs frequently at night, during sleep, or in cases of hypoglycemia unawareness.[64] Asymptomatic nocturnal hypoglycemia is common. Increasing frequency of hypoglycemia can lead to impaired awareness of hypoglycemia and even to hypoglycemia unawareness.

Impaired awareness of hypoglycemia is the reduced ability to perceive the onset of hypoglycemia.[4,56,57,60–65,68] In clinical practice, the severity of this problem is variable; it affects 25% to 58% of patients with T1DM (depending on the cohort and the definition). Prevalence rises and severity increases with longer duration of diabetes; when hypoglycemia unawareness is present, the risk of severe hypoglycemia is increased six-fold. It may also be associated with strict glycemic control.

A major cause of hypoglycemia is iatrogenic, as a result of interplay between excess insulin administration and compromised glucose counterregulation.[4,5,7,8,52,56–66,69] Hypoglycemia can also be caused by insufficient food intake (missed meals), increased alcohol intake, excess exercise, or a combination of these. Iatrogenic hypoglycemia is a common complication of intensive insulin therapy and is the major factor limiting intensive management regimens that are aiming for near-normal glycemia. Approximately 10% of patients with T1DM are extremely sensitive to insulin therapy and lack counterregulatory measures, putting them at higher risk of neuroglycopenia.[2,25,60,70] These patients are prone to hypoglycemia unawareness and to recurrent, severe and life-threatening hypoglycemic episodes.

A small group of patients with T1DM is characterized by a severe instability of glycemic values, with frequent and unpredictable hypoglycemia or DKA episodes (www.citisletstudy.org).[25,64,65,69–72] This condition is known as brittle diabetes and affects three out of 1000 patients with T1DM, mainly young people (mean age 26±15 years), with a second frequency peak in people around 60 to 70 years of age.[64,65,69] Two thirds of affected patients are females with a shorter duration of diabetes than stable controls (13 ± 9 vs. 19 ± 11) associated with higher HbA1c levels and greater insulin requirements.[64] The health-related quality of life worsens significantly in these patients because of the frequency of acute events and hospital admissions and due to early occurrence of chronic complications. Among patients with unstable diabetes, for a small group (3% to 4%), glycemic instability leads to repeated hypoglycemic coma.[25,64,71]

Chronic complications

Chronic complications associated with T1DM arise from the damaging effects of prolonged (chronic) hyperglycemia and have been linked to poor glycemic control and the duration of the disease (www.diabetesatlas.org, www.diabetes.ca, www.diabetes.org, www.jdrf.ca).[1,4,5,10,12,20,33,48–50,54,73,74] These include microvascular complications (such as diabetic retinopathy, nephropathy, and neuropathy) and macrovascular complications (circulatory and cardiovascular events such as stroke and myocardial infarction).

T1DM is a strong risk factor for chronic kidney/renal disease, cardiovascular disease, and premature death in the adult population.[12,20,74–76] About 20% to 40% of patients with diabetes develop diabetic nephropathy within 10 to 25 years from disease onset, and 5% to 15% progress to chronic end stage renal disease (ESRD).[20,75,77] In patients with diabetes and chronic renal disease, the incidence of various cardiovascular complications and death is much higher than with either condition alone.[20,75,77] The relative risk of cardiovascular disease for individuals with T1DM can be as much as 10 times greater than for non-diabetic individuals.[20] Risk factors for cardiovascular disease in T1DM also include the presence of autonomic neuropathy.

A large study on microvascular complication in T1DM patients in the United States reported that affected females had double the risk for developing diabetic retinopathy and neuropathy than did affected males.[78]

Psychological morbidity

Psychological and psychiatric morbidity (including emotional and behavioural disorders and depression) is increased in individuals with T1DM (www.diabetes.ca, www.diabetes.org, www.jdrf.ca).[1,3–5,10,24,37,48,54,79–82] T1DM and its management impose a number of psychological stresses on both the affected individual and his or her family and caregivers. Fluctuations in blood glucose levels may contribute directly to alterations in behaviour and mood, with increased restlessness and irritability and reduced capacity to concentrate. Anxiety and depression, or both, are frequent consequences of T1DM and may be more severe in affected individuals than in general population. Difficulty evolves in T1DM management when psychological and psychiatric disorders contribute to poor self-care and glycemic control and a reduction in QoL.[3–5,79,81–83] Poor metabolic control may also exacerbate depression and diminish response to antidepressant regimens.[81]

Based on data from the Canadian Community Health Survey (CCHS) conducted in 2005, Fuller-Thomson et al.[83] found that the prevalence of "mood disorders such as depression, bipolar disorder, mania, or dysthymia" in people with T1DM was 7.9% as compared to 5.6% in people without T1DM. The difference did not reach statistical significance. These findings suggest that one in 13 Canadians with T1DM have a history of mood disorders. Age- and sex-adjusted odds of mood disorders are 56% higher in Canadians with T1DM than in those without the disease (OR = 1.56, 95% CI 1.04–2.34).

Fuller-Thomson and Sawyer used the 2005 CCHS data to compare lifetime prevalence of suicidal ideation among individuals (aged 12 or older) with and without T1DM.[79] The sample used for this study was restricted to 82,675 respondents in the four provinces where questions were included on the survey regarding suicidal ideation (Quebec, Ontario, Saskatchewan, and Alberta). The prevalence of suicidal ideation was estimated at 15.0% (95% CI = 7.1%, 22.9%) for those with T1DM (n = 190) and at 9.4% (95% CI = 9.0%, 9.8%) for those without T1DM (n = 82,485). Age- and sex-adjusted odds of suicidal ideation were 1.61 (95% CI = 1.08, 2.42) for individuals with T1DM (in

other words, those with T1DM had 61% higher odds of reporting suicidal thoughts than individuals without T1DM).

Epidemiology of T1DM and population dynamics of affected patients

T1DM accounts for 5% to 10% of all diabetes mellitus cases (www.diabetes.ca, www.diabetes.org, www.diabetesatlas.org, www.albertadiabetes.ca, www.jdrf.ca, www.cdc.gov/diabetes),[1,9,14,18,20,22,23,27,30,36,84–86] affecting 0.2% to 1% of the total population during a lifetime.[10,29,86] T1DM can develop at any age but usually appears between infancy and the late 30s.[5,10,12,20–22,49,87,88] Three-quarters of all cases are diagnosed in individuals younger than age 18.

The incidence and prevalence of T1DM vary based on age, gender, geography, and race or ethnicity (www.diabetesatlas.org).[1,12,16,30,34,42,50,89–93]

In areas with high prevalence, a bimodal variation in incidence showing a peak in early childhood and a second greater peak during early puberty has been reported.[1,12,16,30,34,42,50,89–93] A female excess is more commonly reported in countries with a low incidence, whereas a male excess occurs more often in countries with a high incidence—and almost exclusively in Europe and in populations of European descent. After the pubertal years, the incidence drops in young women but remains relatively high in young adult males up to age 29 to 35 years.[1,12,16,30,34,42,50,89–93]

T1DM has a wide geographic variation in incidence and prevalence (www.eatlas.idf.org, www.jdrf.ca).[1,12,34,39,42,90,93,94] Incidence is lowest in China and Venezuela (0.1 per 100,000 per year) and highest in Finland (40.9 per 100,000 per year).[34] Within the seven major insulin markets (the United States, Japan, France, Germany, Italy, Spain, and the United Kingdom) the prevalence of T1DM ranges from 0.2% (Japan) to 0.7% (Germany).[1] In these countries alone, more than 3.1 million people are affected.[1]

T1DM appears to be more common in Caucasians, in individuals of northern European descent, and in specific Mediterranean groups, and less common in people of Asian and African descent (www.cdc.gov, www.diabetesatlas.org, www.diabetes.org, www.diabetes.ca).[12,17,93,95] In North America it is more likely to develop in non-Hispanic white people than in American Indians, American Africans, Asians or Pacific Islanders, or Hispanics. There is evidence to suggest that when immigrants from an area with low incidence move to an area with a higher incidence, their T1DM rate tends to increase.

Trends in T1DM incidence and prevalence worldwide

According to the *Diabetes Atlas* produced by the International Diabetes Federation (IDF), among 246 million people affected by diabetes worldwide in 2006, approximately 22 million adults and 440,000 children were affected by T1DM (www.diabetesatlas.org). Although T1DM usually accounts for only a minority of the total burden of diabetes in a population, it is the predominant form of the disease in children and adolescents in most developed countries (www.cdc.gov, www.jdrf.ca, www.diabetes.org, www.diabetes.ca, www.diabetesatlas.org).[1,12,18,30,34,36,42,93,96–98] In 2006, of the world's 1.8 billion children (younger than age 14), approximately 440,000 suffered from T1DM, representing a prevalence of 0.02%, with about 70,000 new cases diagnosed annually and an average annual increment in incidence of 3% (www.diabetesatlas.org).

Data emerging from the WHO-sponsored Diabetes Mondiale (DiaMond) study[34,97] and from the IDF *Diabetes Atlas* (www.diabetesatlas.org) indicate that Asia, Africa, and South and Central America have relatively low rates of childhood (aged 0 to 14 years) T1DM, whereas northern Europe, North

America, New Zealand, and Australia have the highest rates. The reason for the north-south geographical gradient in T1DM incidence is unknown.[11] However, climate differences and increased prevalence of virus infections in children from the northern hemisphere as compared with children from the southern hemisphere may be involved in the variation seen between the northern and southern regions of Europe and North and South America.

In multinational comparisons conducted under the auspices of the WHO, the prevalence or cumulative incidence of long-term diabetic complications shows considerable geographic and ethnic variation.[12,51,99] Drawing on those findings, investigators have suggested that the performance of local healthcare systems and the local social distribution of wealth and purchasing power may play important roles in explaining the geographic variation of diabetes complications.[51] Most investigations on glycemic control in ethnic minorities have been conducted in adolescents, and it remains to be established whether the results can be extrapolated to adult populations.[12]

An increasing trend in T1DM incidence and prevalence has been reported in most regions of the world over the past few decades, by an average of 2% to 5% per year, mainly in young children, with clear indications of great geographic differences (www.diabetesatlas.org, www.cdc.gov).[12,16,20,25,30,31,34–36,39,42,93] Apart from the rise in incidence, factors contributing to a continued upward trend in global prevalence include better diagnosis of T1DM, improved availability of insulin and access to treatment, and increases in overall population. There are also indications of a decrease in mortality—from both unrecognized DKA in children and from late complications in young adults—in some developed countries, which could lead to an additional increase in T1DM prevalence.

Substantial variations are observed between geographically close countries with differing lifestyles, and between genetically similar but socio-economically disparate societies (www.diabetesatlas.org, www.cdc.gov).[12,20,30,31,34–36,42,93] Within-country incidence variations have also been observed in several countries (www.diabetesatlas.org).[12,30,34,42,89,90,93]

The increase in T1DM incidence has been shown in countries having both high and low prevalence, and the greatest increase is observed in children under age 5 (www.diabetesatlas.org).[12,14,20,34,36,42] However, there is an indication of a steeper increase in some of the low-prevalence countries and an association between the risk increase and gross national product estimates. These findings suggest that part of the increasing trend may be due to potentially preventable lifestyle factors. Comparisons between countries and regions with low and high incidence rates have suggested that higher socioeconomic status and degrees of urbanization may be among the environmental factors that play a role in the rising T1DM incidence.[12]

Patients with adult-onset T1DM differ from those with childhood-onset T1DM in terms of genetic, immunological, and clinical features.[12,17,22,23]

Information on mortality rates is difficult to ascertain without national or provincial registers on T1DM, and mortality in undiagnosed diabetes is probably a large hidden problem in the global perspective (www.diabetesatlas.org).

Trends in T1DM incidence in North America

In accordance with the European ancestry of much of their populations, both the United States (US) and Canada have high T1DM incidence rates (www.diabetesatlas.org).[12,42,93] The IDF *Diabetes Atlas* estimated the incidence rate for children (aged 0 to 14 years) at 20.8 per 100,000 and 21.7 per 100,000 in 2010 in the US and Canada, respectively (www.diabetesatlas.org).

T1DM in the United States

More than one million individuals (children and adults) in the United States have T1DM,[77,86,100,101] and more than 30,000 new cases are diagnosed every year.[70,94,100,102]

T1DM in Canada

In Canada, approximately three million people have diabetes (www.jdrf.ca, www.diabetes.ca, www.diabetesatlas.org).[103] Approximately 10% of the Canadians with diabetes have T1DM. According to the Juvenile Diabetes Research Foundation, currently over 300,000 Canadians live with T1DM (www.jdrf.ca).

Canada has one of the highest incidence rates of T1DM in children (aged 0 to 14 years) in the world (www.jdrf.ca, www.diabetesatlas.org).[34] The IDF *Diabetes Atlas* estimated the incidence for Canadian youth (aged 0 to 14) at 21.7 per 100,000 in 2010 (www.diabetesatlas.org). In 2007, the estimated number of prevalent cases of T1DM among Canadian youth (aged 0 to 14) was 8400.

Several studies reported recent estimates of T1DM rates in Newfoundland and Quebec.[30,42,89,90] The reported estimates showed geographical differences in incidence rates between the two provinces and between various regions within each province. Different ascertainment methods and case definitions were used in these studies, making comparisons across studies difficult.

Published results from two prospective cohort studies and one population-based study, conducted to determine the incidence of T1DM among children (aged 0 to 14 years) in Newfoundland and Labrador between 1987 and 2005, suggest that childhood T1DM is of particular importance in this province, where the incidence has been found to be the highest in North America and among the highest in the world.[36,42,89] It has been suggested that the high T1DM incidence in Newfoundland and Labrador might be caused by one or more environmental factors (such as early infant diet, vitamin D deficiency, and increased height, weight, and body mass index during early childhood), triggering the condition in genetically predisposed individuals (its population is unusual in the investigation of complex disease because of its settlement history, its subsequent founder effect, and its geographical isolation).[36,42,45] The incidence of T1DM in this province is temporarily related to exposure to ultraviolet B radiation.[44–46]

Legault and Polychronacos[90] gathered data through a government allocation program to determine the annual incidence of T1DM in Quebec in the pediatric population (aged 0 to 18) between 1989 and 2000. They found no evidence of an increase in the number of children diagnosed with T1DM in Quebec over the 12-year period, and reported a steady number of new diagnosed cases (approximately 240 per year).

T1DM in Alberta

According to data recently published by the Alberta Diabetes Surveillance System (ADSS), 19,324 new cases of diabetes were identified in 2009 and a total of 205,726 people of all ages (about one in 20) were living with diabetes in Alberta (www.albertadiabetes.ca). Increasingly, more men than women have been receiving new diagnoses of diabetes throughout the past decade. Men over the age of 55 years have significantly higher prevalence rates of diabetes than do women. Although the ADSS does not differentiate between T1DM and T2DM, it estimates that 5% to 10% of all people with diabetes have T1DM, which means that between 10,287 and 20,573 Albertans have T1DM.

Table S.1 and Table S. 2 provide information on the number of adults (aged 18 years and over) diagnosed with T1DM who accessed the healthcare system in Alberta in fiscal years 2006–2007,

2007–2008, and 2008–2009 (based on data from Alberta Health inpatient, outpatient, and physician claim datasets). For further details, see the section titled "Economic Evaluation" in this report.

Table S.1: Patients (aged 18 to 65 years) with T1DM, by Health Zone, in Alberta

	2006–2007			2007–2008			2008–2009		
Health Zone	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**
South zone	488	580	1068	535	634	1169	563	647	1211
Calgary zone	2044	2564	4608	2097	2674	4771	2232	2801	5032
Central zone	836	941	1777	893	1077	1970	868	996	1864
Edmonton zone	2840	3232	6073	2785	3333	6119	2720	3222	5942
North zone	743	991	1734	766	1047	1813	806	1086	1891
Province	**6950**	**8309**	**15,260**	**7075**	**8766**	**15,842**	**7189**	**8753**	**15,939**

Table S.2: Patients (aged >65 years) with T1DM, by Health Zone, in Alberta

	2006–2007			2007–2008			2008–2009		
Health Zone	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**	**Female**	**Male**	**Total**
South zone	346	382	729	356	415	772	392	427	820
Calgary zone	1038	1204	2244	987	1173	2162	1006	1205	2214
Central zone	556	579	1137	577	620	1199	519	576	1096
Edmonton zone	1453	1608	3066	1413	1596	3012	1285	1527	2816
North zone	337	395	733	335	435	771	336	422	759
Province	**3731**	**4169**	**7910**	**3668**	**4239**	**7917**	**3539**	**4158**	**7705**

Burden of T1DM

The burden of T1DM and associated complications includes nonmonetary and monetary elements (www.jdrf.ca, www.diabetes.ca, www.diabetes.org, www.diabetesatlas.org).[20,54,60,85,86,88,96,104–106] Affected individuals and their families bear the cost of T1DM through shorter length of life, deteriorating health, changes in quality of life (QoL) or disability, great out-of-pocket expenses, and inconvenience. Life expectancy for people with T1DM may be shortened by as much as 15 years (www.diabetes.ca).

These personal burdens translate into significant costs for society as a whole (www.diabetes.ca, www.diabetes.org, www.jdrf.ca, www.diabetesatlas.org).[2,85,86,96,104,107,108] Although estimates of medical and social costs of T1DM appear less frequently in the literature, reports from England, Wales, Israel, Spain, and the United States demonstrated meaningful medical expenses connected to T1DM, both on a short-term and on a lifetime basis, related to the daily management of the disease and to the treatment of chronic complications.[85,86,107]

In terms of social costs of T1DM, several studies noted higher rates of disability and work-related absenteeism in persons with T1DM, particularly in those with chronic complications.[85,86,107,108] The impact of T1DM may also be felt in ways that are less easily quantifiable, such as the influence it may have on the employment experiences of affected individuals.[107–109] In addition, health, life, and sometimes even automobile insurance may be more difficult to obtain for a person with T1DM.

Individuals may face limitations in the types of jobs available for them (for example, employment in commercial driving is limited because of concerns about hypoglycemia).[107]

Iatrogenic hypoglycemia is a common problem for individuals with T1DM and can affect all aspects of life including personal relationships, employment, driving, acceptability for insurance and the premiums demanded, physical activity, and travel.[4,7,17,23,52,56,57,60–65,68,106,107,110] Fear of hypoglycemia can have a major impact on QoL. Iatrogenic hypoglycemia also adds significant costs to the management of T1DM.[23,26]

In summary, T1DM places a considerable burden (which is associated with the treatment of the disease and its complications) on the affected individuals and their families, on the healthcare system as well as on the economy and society.

Patterns of Care

Diagnosis of T1DM

Diagnosis of diabetes is based on patient history, physical examination, and appropriate laboratory findings (www.diabetes.org, www.diabetes.ca), as when:[3–7,9,10,22,26,24,27,73,111]

- the fasting venous plasma (blood) glucose concentration is greater than or equal to 7.0 mmol/L (126 mg/dL), or
- characteristic symptoms and signs are present and the casual (random) venous plasma glucose concentration is greater than or equal to 11.1 mmol/L (200 mg/dL), or
- the plasma glucose concentration taken at least 2 hours after eating is greater than or equal to 11.1 mmol/L (200 mg/dL) in a 75 g oral glucose tolerance test (OGTT)

Generally, individuals with T1DM present with acute symptoms and elevated blood glucose levels, and most cases are diagnosed soon after the onset of hyperglycemia.[3,5–10,22,26,67,111] In the absence of symptoms, it is recommended that both aforementioned plasma glucose criteria be met and repeated on another day in order for a diagnosis of diabetes to be made.

Recently, the measurement of HbA1c levels has been considered as a diagnostic test for diabetes[5,6,9,112,113] and in January 2010 the HbA1c measurement was endorsed by the American Diabetes Association (ADA) as a diagnostic and screening tool for diabetes.[5,6,9] According to the ADA, an HbA1c level of greater than 6.5% (measured on two separate occasions) is diagnostic of diabetes.[5] The HbA1c measurements should be performed by a clinical laboratory because of the lack of standardization of point-of-care testing.[5] An HbA1c test may not be appropriate for patients who are pregnant or who have hemoglobinopathy or abnormal erythrocyte turnover.[5]

Differentiating T1DM from T2DM is based on patient characteristics, history, and laboratory tests, if appropriate.[4,5,9,14,22,24,26,67,111] In young to middle-aged patients, it is often difficult to distinguish between T1DM and T2DM, especially in the absence of family history. In borderline diagnostic situations the presence of autoimmune markers is helpful in differentiating between T1DM and T2DM.

Management of T1DM in adults

Successful management of T1DM is currently based on appropriate and effective diabetes and nutritional education (adapted to each individual's age, maturity, lifestyle, culture, and the stage of their diabetes), insulin replacement therapy, blood glucose monitoring, nutritional planning, physical

activity and exercise, and the psychological adjustment and wellbeing of the whole family (www.diabetes.ca, www.diabetes.org).[1,3,5,7,8,23,24,27,47,48,110,114–118] The subcutaneous administration of exogenous insulin is the basis of therapy for T1DM, and given the availability of numerous and various formulations and mixtures, a wide range of possible regimens exist, from a frequency of up to two injections per day (conventional insulin therapy) to intensive insulin therapy (IIT) involving three or more injections per day.

Results from various clinical studies published during the past two decades prompted the development of a consensus statement on intensive glycemic control by intensive diabetes management as a therapeutic standard of care for T1DM, regardless of the patient's age (www.diabetes.ca, www.diabetes.org).[1,3–5,7,8,20,24,27,59,114,116,119] This position was confirmed by the Diabetes Control and Complications Trial (DCCT), the Epidemiology of Diabetes Interventions and Complications (EDIC) study, the Epidemiology of Diabetes Complications (EDC) study, and other long-term follow-up studies, which showed that intensive glycemic control approaching near-normal glycemia prevents, postpones, or slows the progression of retinal, renal, and neurological complications.[12,20,23,23,52,69,74,87,88,117,118,120,121]

Intensive diabetes management is an attempt to achieve and maintain near-normal glycemia (blood glucose levels) by using IIT and by adjusting for other important factors to approximate normal physiology.[1,4,5,7,8,20,23,24,27,52,67,87,114,117,122] IIT aims to mimic physiological insulin secretion by providing incremental prandial insulin (short- and rapid-acting formulations) coinciding with each meal or snack and continuous basal insulin (intermediate- and long-acting formulations) overnight and between meals or snacks. It involves flexible, multiple-component insulin regimens tailored to the patient's medical needs and lifestyle and guided by frequent blood glucose monitoring. Patients need to follow action plans that guide them in daily self-management, altering insulin doses and timing, food intake, physical activity, or a combination of these in an attempt to achieve their glycemic goals and targets. Patient education, motivation, and dedication are critical to the successful implementation of this therapy. Also very important are strong family support and the availability of healthcare professionals experienced in diabetes care.

Currently the main goals of intensive T1DM management include:

1) achievement of near-normal blood glucose and HbA1c levels to avoid hyperglycemia and prevent the development or progression of diabetes complications over time
2) prevention/avoidance of DKA and hypoglycemia
3) maintenance of QoL, or achievement of the highest QoL compatible with daily demands of T1DM (self-management)[20,52,59,74,87,117,118,120,122,123]

These can be reached if patients are adequately selected and educated.

Current IIT practice

Currently, the treatment of choice for achieving and maintaining normoglycemia in adults with T1DM is IIT using flexible basal-bolus regimens, delivered by MDI or IPT.[3–5,7,8,63,70,124] This approach has been proven to provide greater glycemic control, reduce the risk of developing diabetic complications, and delay the progression of chronic complications when compared with conventional insulin therapy using fixed-dose regimens. However, a large gap remains between reported research evidence and practice remains, which may be attributed to the disease itself (insulin hypersensitivity and glucose counterregulatory failure), lack of more physiological insulin

replacement approaches, the patient (external control locus, denial of disease, and difficulties in self-management), and the multiple and various barriers that patients and healthcare providers face in the day-to-day management of T1DM (related to the complexity and demands of IIT, the presence of psychosocial barriers, the presence of hypoglycemia unawareness and repeated severe hypoglycemic events, and the fear of hypoglycemia).[12,20,23,52,56–60,62–64,69,71,74,87,102,117,118,120,121,123–125]

The risks of hypoglycemia unawareness and recurrent and frequent severe hypoglycemic episodes, which can lead to potential life-threatening outcomes, remain major obstacles for appropriate intensive management of T1DM.[4,5,7,8,12,17,23,52,56–58,60,61,63,64,68–72,74,110,117,118,121,123,124,126] Even under strict conditions, despite using optimized IIT regimens, nearly 50% of patients do not reach the optimal target of HbA1C level without repeated episodes of severe hypoglycemia and/or hypoglycemia unawareness.[71,117,123] The current challenge is to reach sustained normoglycemia to prevent long-term complications with no significant increase in the incidence of severe hypoglycemia and/or hypoglycemia unawareness.

Despite substantial improvements in insulin therapy and the care of patients with T1DM, a subset of people with T1DM (~10%) have great difficulty in achieving overall glycemic control without disabling hypoglycemia as they are especially prone to develop hypoglycemia unawareness and severe hypoglycemia due to blood glucose instability.[1,50,70,77,127–133] Once optimized IIT has failed for these patients, a more physiological glycemic control may be provided by beta-cell replacement therapy, as a means of restoring endogenous insulin secretion.[50,70,72,75,77,88,130,131,134,135]

Alternative therapy for adults with T1DM: Beta cell replacement therapy

Beta-cell replacement therapy is a potential alternative therapy for adults with brittle T1DM who, despite optimal IIT, cannot reach and sustain normoglycemia without repeated episodes of severe hypoglycemia and/or hypoglycemia unawareness.[4,25,50,52,63,64,69,70,76,88,101,121,126,128,130,131,134–144] Restoring beta cell function can be achieved either by whole organ pancreas transplantation (WPT) or by isolated allogeneic islet transplantation (IT). The major benefit of restoring beta cell function by WPT or IT is that it allows more physiologic control of glucose metabolism, that is, glucose-dependent insulin secretion, than does IIT. However, both transplant procedures require recipients to follow an immunosuppressive medication regimen as long as the graft is functioning, to have regular blood tests, and to remain vigilant for symptoms/signs of organ rejection or infection. Any of their advantages must be weighed against the risks and adverse effects associated with each procedure and with the chronic (lifetime) immunosuppressive therapy that accompanies these treatments.

Whole pancreas transplantation (WPT)

The first successful whole pancreas transplantation (WPT) in two patients with T1DM was reported in 1967, demonstrating that a euglycemic state could be obtained without the need for exogenous insulin.[2,25,50,63,69,70,72,76,77,88,100,101,126,129,130,133,134,137,138,141–143,145–148] Since then, WPT has been performed in more than 30,000 patients and has been reported to be effective in restoring normal endogenous insulin secretion, maintaining long-term glucose homeostasis, controlling or reverting acute and chronic complications of diabetes, and improving QoL. QoL improvement appears to be particularly evident in patients with hypoglycemic unawareness, brittle diabetes, or gastroparesis.[63,142] However, WPT is a technically demanding procedure and is associated with serious surgical risks and post-transplant adverse effects, despite refined surgical techniques, effective immunosuppression modalities, anti-viral prophylaxis, and post-transplant monitoring. Other limitations include organ availability and poorer graft survival if retransplantation is needed.

There are three circumstances when WPT is considered as a treatment for adults with T1DM.[2,4,26,53,67,72,92,104-106,117,132,135,146,148,149,151-155] For select medically suitable patients with ESRD (uremic patients) who are good candidates for kidney transplantation, simultaneous pancreas and kidney transplantation (SPK) is used. For those patients who suffered from renal failure and had a successful kidney transplant (with good renal allograft function) and are immunosuppressed, pancreas after kidney (PAK) is an option if they meet the criteria for WPT. Pancreas transplantation alone (PTA) is considered for non-uremic patients (those with preserved native renal function) with very unstable T1DM who had a history of frequent and severe metabolic complications (hypoglycemia, DKA) and severe and incapacitating clinical and emotional problems with using exogenous insulin therapy, or consistent failure of insulin-based management to prevent acute complications. SPK is most commonly performed, followed by PAK and PTA. The usual and most persuasive indications for PTA are very poor glucose control and dangerous episodes of hypoglycemic unawareness.[26,72,153]

Isolated allogeneic islet transplantation (IT)

Isolated allogeneic islet transplantation (IT) has been proposed as an alternative to WPT for adults with brittle T1DM (www.citisletstudy.org).[50,52,63,70,76,88,121,126,130,134,135,137,138,138,142,150] When compared to WPT, which requires major surgery, the potential advantage of IT stems from the relative simplicity of the procedure, its low invasiveness, and its increased safety in terms of post-transplant complications. IT can be performed on an outpatient basis under local anesthesia and can be repeated several times without major discomfort to the patient. Islet cells can be isolated from organs otherwise deemed unsuitable for WPT. IT avoids the surgical and postoperative complications associated with WPT and the possible complications related to enzyme production by the exocrine cells, as experienced in WPT.

However, IT requires complex and expensive procedures, including pancreas procurement and preservation, pancreas digestion, islet purification and culture, transplantation/infusion of islets, and immunosuppressive therapy (www.citisletstudy.org).[2,25,50,52,70,72,88,121,126,127,130,130,134–138,141,142,151–156] Islet isolation, purification and preparation requires expertise and assessment of the quality and quantity of islets before being deemed suitable for donation. Most IT recipients require at least two islet infusions to achieve sufficient functioning islet mass.

Successful IT can achieve long-term improved/nearly normal glycemic control with reduced incidence or prevention of hypoglycemic episodes, and offers the promise of insulin independence (www.citisletstudy.org).[2,25,50,52,70,72,88,121,126,127,130,134–138,141,142,151,155,156] However, currently insulin independence after successful IT is not sustainable over the long term in all patients and IT is associated with a number of serious side effects, mainly related to the procedure itself and to the toxicity of the immunosuppression regimens. There is also the risk of immune sensitization, particularly when immunosuppressive drugs are discontinued in patients who have lost their graft function, which limits their access to future kidney transplantation should that be required.

Indications for IT in T1DM patients has expanded over the past decade due to advances in islet processing procedures and immunosuppressive protocols.[4,50,52,64,70,72,75,88,102,121,126,127,130,133–138,142,145,146,148,151,155,157–159] As with WPT, establishing an optimal indication of IT is difficult because transplantation is a point of no return, particularly when compared to optimized IIT.[151,155,157–159]

Currently, the generally accepted indications for IT alone (ITA) are based on those described by the Edmonton group in 2000.[4,50,52,64,70,72,75,88,102,121,126,127,130,133–138,142,145,146,148,151,155,157,158] ITA offers an alternative to PTA and it has been considered for adults with brittle T1DM and hypoglycemic

unawareness and/or repeated severe hypoglycemic episodes who present unsatisfactory glycemic control despite optimized IIT and who have a history of severe clinical and emotional problems with exogenous insulin therapy. Exclusion criteria include: diabetes duration < 5 years; age < 18 years or > 65 years; body mass index (BMI) >28kg/m^2 (BMI > 30kg/m^2 in some centres) or insulin need/requirements > 1U/Kg/day; desire for pregnancy; addictions or psychiatric disorders; hepatic abnormalities; and progressive microvascular diabetic complications. Renal function appears to decline after ITA in patients with significant preexisting renal dysfunction.[4]

IT performed simultaneously with or after a kidney transplant may be an alternative to WPT in unstable adults with uncontrolled T1DM and ESRD, especially for those with contraindications to major surgery.[4,50,72,75,88,126,129,130,133,136,137,142,144,146,148,149,151,155,160] IT performed simultaneously with a kidney transplant (SIK) has been considered for uremic adults with unstable and uncontrolled T1DM who either are not optimal WPT candidates because of age, cardiovascular disease, or other complications or who choose not to undergo a major surgical procedure. Islet after kidney transplantation (IAK) has slowly emerged as an alternative to PAK for adults with a reasonably well functioning kidney graft, who would most likely benefit from better metabolic control without taking high risks in terms of patient or kidney graft survival.

Recommended Management of T1DM in Adults

Evidence-based guidance recommends case management provided by a multidisciplinary team of healthcare providers with skills in diabetes management as an efficient and effective means of healthcare delivery for patients with diabetes.[3–5,7,8] Such teams may include, but are not limited to, physicians, nurse practitioners, physicians' assistants, nurses, dietitians, pharmacists, and mental health professionals with expertise and a special interest in diabetes. The patient and/or family member must be part of the team and it is essential in this collaborative and integrated approach that individuals with diabetes assume an active role in their care. To be successful, the multidisciplinary team must recognize and adapt to the patient's priorities, diabetes knowledge, and readiness to implement the treatment plan. A common environment (such as a diabetes centre) is considered an important resource in allowing a diabetes multidisciplinary team to work and communicate efficiently while providing consistent advice.[8]

According to the reviewed, evidence-based guidance, IIT remains the primary component of standard care for individuals of all ages with T1DM.[3–5,7,8,70] Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, presence of nocturnal or severe hypoglycemic episodes, and hypoglycemia awareness status, as well as their ability for self-management. Although both MDI and IPT are recommended for the delivery of various IIT regimens, to achieve glycemic targets and avoid acute complications, IPT is recommended when MDI is considered to be impractical or inappropriate. Because both delivery methods are viewed as strongly dependent on patient discipline, skill, and adherence, it is recommended that they be offered only as part of a package of care that involves continuing education, dietary management, instruction on the use of insulin delivery and blood glucose monitoring systems, emotional and behavioural support, and expertise in diabetes care.

The use of basal-bolus regimens delivered by MDI as part of an intensive diabetes management program is the treatment of choice for all adults, and IPT is considered when MDI has failed (adequate glycemic control is not obtained by MDI without disabling hypoglycemia), provided that those receiving the treatment have the commitment and competence to use the therapy effectively.[3–5,8,24,114]

For individuals with hypoglycemia unawareness, the available guidance recommends insulin replacement therapy characterized by increased frequency of glucose monitoring (SMBG), less stringent glycemic targets with avoidance of hypoglycemia, and consideration of a psychobehavioural intervention program (blood glucose awareness training), if available.[4,5,8]

For individuals with T1DM and ESRD who have had or plan to have a kidney transplant, WPT (done simultaneous or subsequent to the kidney transplant) is recommended as an acceptable alternative to insulin therapy (Table S.3).[4,140] According to the 2006 ADA position statement, these patients should meet the medical indications and criteria for kidney transplantation and not have excessive surgical risk for the dual-transplant procedure.[140] In the absence of indications for kidney transplantation, pancreas transplantation should only be considered in patients who exhibit:

1) a history of frequent, acute, and severe metabolic complications (hypoglycemia, marked hyperglycemia, DKA) requiring medical attention
2) clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating
3) consistent failure of insulin-based management to prevent acute complications[140]

Program guidelines for ensuring an objective multidisciplinary evaluation of the patient's condition and eligibility for transplantation should be established and followed.[140] In their 2006 position statement, ADA states that IT is an experimental procedure, only to be performed in the setting of controlled research studies.[140]

Table S.3: Recommended management of T1DM in highly selected adults

Country (Specialty body/Agency)	Transplantation (whole-pancreas or islet transplantation)
Canada (2008 CPG on management of diabetes by CDA)[4]	1. Pancreas transplant should be considered for individuals with T1DM and ESRD who are undergoing or had undergone a successful KT. 2. Pancreas transplant or IT may be considered for individuals with T1DM and preserved renal function, but with persistent metabolic instability characterized by severe glycemic lability and/or severe hypoglycemia unawareness despite best efforts to optimize glycemic control.
US (2006 position statement of ADA on PT and IT)[140]	1. Pancreas transplantation is an acceptable alternative to insulin therapy in patients with imminent/established ESRD who have had or plan to have a KT. Patients must meet KT indications and not have excessive surgical risk. 2. In absence of indications for KT, pancreas transplantation should only be considered in patients with: (a) a history of frequent, acute, and severe complications requiring medical attention (b) severe clinical and emotional problems with exogenous insulin therapy that are incapacitating (c) consistent failure of insulin-based management to prevent acute complications. 3. IT should be performed only within the setting of controlled research studies.
UK (2008 guidance on IT by NICE)[139]	IT is indicated for T1DM patients with hypoglycemia unawareness and/or those already on immunosuppressive therapy because of renal transplantation. Patient selection should involve a multidisciplinary team.

ADA – American Diabetes Association; CPG – Clinical Practice Guidelines; ESRD – end stage renal disease; IT – (allogeneic pancreatic) islet transplant/transplantation; KT – kidney transplant/transplantation; NICE – National Institute for Health and Clinical Excellence; NHS – National Health Service; T1DM – type 1 diabetes mellitus; UK – United Kingdom; US –United States

According to the Clinical Practice Guidelines issued in 2008 by the Canadian Diabetes Association (CDA), either WPT or IT may be considered for individuals with T1DM and preserved renal function, who also present with persistent metabolic instability characterized by severe glycemic lability and/or severe hypoglycemia unawareness despite best efforts to optimize glycemic control.[4]

The interventional procedure guidance issued in 2008 by the National Institute for Health and Clinical Excellence (NICE) states that the evidence on the use of IT for T1DM shows short-term efficacy with some evidence of long-term efficacy.[139] However, the evidence on its safety shows that serious complications may occur as a result of the procedure. According to NICE guidance, patient selection for IT should involve a multidisciplinary team and selection criteria should take into account that this procedure is particularly indicated for patients with hypoglycemia unawareness and/or those already on immunosuppressive therapy because of renal transplantation.

History and Characteristics of IT

The adoption of IT has experienced bursts of enthusiasm followed by skepticism since the first reported clinical case in 1980s (www.citisletstudy.org).[2,25,72,76,77,88,101,127,131,134,138,144,150,159–163] Initial results were disappointing, with an immediate success rate in terms of insulin independence of only 10%. In 2000, Shapiro and colleagues from the IT program/centre in Edmonton reported on seven patients rendered insulin independent for 1 year after being treated with an infusion of an adequate mass of freshly prepared islets from two or more deceased donor pancreases combined with glucocorticoid-free immunosuppressive therapy. This approach (known as the Edmonton protocol) addressed several drawbacks of previously used ITA approaches and represented a groundbreaking innovation in this emerging field.

Within the next few years, the number of clinical IT centers and IT recipients increased worldwide (www.citisletstudy.org).[2,25,70–72,74,75,76,77,88,101,127,131,134,136,138,144,150,159–163] However, a multicentre trial conducted to evaluate the reproducibility of the Edmonton protocol reported variable rates of success (only centres with greatest experience in IT achieved insulin independence in approximately 80% of recipients within the first year post-transplantation). A 5-year follow-up of the Edmonton protocol indicated that the graft function is lost or significantly reduced over time (< 10% of patients remained insulin independent 5 years post-transplantation). In addition to the problem of graft durability, both the procedure itself and the immunosuppressive therapy were associated with a number of serious adverse effects. These data indicated the need of further advances in the preservation of the graft function.

The Edmonton group's success has led to acceptance that IT is a clinically feasible therapy and may be considered for the treatment of highly selected adults with unstable and uncontrolled T1DM despite optimal IIT (www.citisletstudy.org).[2,4,25,72,76,77,88,101,127,131,134,136,138,139,144,150–152,154–165] However, experience from other IT centres worldwide, and the long-term follow-up of the Edmonton protocol, have noted several technical and medical challenges associated with IT that have limited its utilization.

The focus of IT's primary goals has shifted to: the achievement of stable, normalized glycemic control without hypoglycemic episodes, QoL improvement, and regression of and/or prevention of progressive diabetes complications (www.citisletstudy.org)[2,4,25,72,76,77,88,101,127,131,134,136,138,139,144,150–152,154,156–165]

The safety of the patient remains one of the main priorities and the overall risks and benefits need to be carefully addressed for each IT candidate. Insulin independence is still desirable and remains the ultimate goal of the ongoing research in this area.

The Collaborative Islet Transplant Registry (CITR) is the largest registry of IT data and collects data since 1999 mainly from medical institutions in the United States and Canada that have an identified IT program or an interest in starting one (www:citregistry.org).[25,72,141,155,166,167] According to CITR annual reports, predictors of better islet graft function were a higher number of islet infusions, a greater number of total infused islet equivalent, whether the islet processing centre was affiliated with the IT centre, higher islet viability, larger islet size, and the use of daclizumab, etanercept, or calcineurin inhibitors in the immunosuppressive regimens. The accumulated experience in IT indicates that the best candidates for IT are older recipients with better glycemic control (with lower pre-transplant HbA1c levels). Related processing and infusion centres substantially reduce the chances of losing the last graft. In-hospital administration of steroids was associated with a negative outcome.

Challenges of clinical IT centres/programs

An effective and successful clinical IT program depends on several financial, administrative, and medical issues that need to be considered.[2,76,88,126,127,130,135,136,138,140,151–156,165,168–170] Clinical IT is associated with relatively high costs necessary to cover infrastructure costs, need for specialized equipment, supplies, staff/personnel salaries, organ acquisition, islet isolation and preparation, and patient care costs (including follow-up and monitoring). However, IT is still considered an experimental procedure in most countries, which affects the funding streams available to existing IT programs and influences the way IT is perceived, the infrastructure available to such programs, and the interrelationships with other key specialties. Clinical IT programs have to deal with unique regulatory aspects and must follow current Good Manufacturing Practice (GMP) guidelines and biological product standards. The deceased donor pancreas, islet isolation, and islet preparation must meet pre-established quality criteria.

The medical issues can be divided into pre-transplant-related, procedure-related, and post-transplant-related.[2,2,88,100,126,127,130,135,136,138,146,148,152–155,159,164,168–171] Two important issues associated with better outcomes are related to organ pool (the availability of deceased donor pancreases from donors with specific characteristics) and islet isolation and preparation procedure. Successful islet isolation and preparation has been correlated with several donor variables including donor age, body mass index, and retrieval by the local surgical team. Optimal islet isolation is also dependent on optimal retrieval and transportation of donor pancreases. The isolation and preparation of good/high-quality islets is expensive, technically demanding, labour-intensive, and time-consuming, with many different factors influencing successful outcome. The process is complex and difficult to control, requires considerable expertise and experience, has a steep learning curve, and has yet to be standardized. International experience has shown that islet isolation and preparation procedure should be performed in significant numbers (high volume) so the required highly specialized skills can be maintained and further developed.

Because of the limitation of islet yield from donors, supplemental transplants are required in many cases to provide an adequate islet engraftment.[88,127,130,135,151,152,154–156,159,161,172] For a single IT recipient, two or more deceased donor pancreases may be required for successful IT, which is a major limitation given the shortage of human islet cells.

Effective immunosuppressive management is one of the most important factors in the prevention of acute graft rejection and for the improvement of long-term graft survival.[63,88,130,134,135,155,159,163,171–173] Close monitoring of maintenance immunosuppressive drugs and monthly toxicity assessments are currently an important part of the follow-up and care of IT recipients. However, the ability to detect rejection in IT recipients is currently limited.

Recipient assessment and selection is key to the success of IT and critical for its best utilization, and it is recommended that it be performed by a multidisciplinary team.[2,4,138–140,143] Project management and regulatory compliance are also critical.

An effective and successful clinical IT program is dependent on a multidisciplinary approach that covers all aspects of IT.[2,76,76,88,102,126,127,130,135,136,138,139,144,151–156,168–170,174] International experience suggests that patient assessment and care before, during, and after transplantation should be performed by a highly specialized and experienced multidisciplinary team with all the necessary skills (including skills in metabolic assessment, islet isolation and preparation, radiologic interventions, management of immunosuppressive therapy-related complications, infection prevention, and treatment of post-transplant complications), knowledge, and motivation. Strict selection criteria, close clinical monitoring, and prompt management of emerging complications can maximize the IT benefits while minimizing its risks. A well-structured administrative team is also essential to guarantee that technical and medical activities related to the transplant are organized and unhindered.

Training in the IT procedure involves training organ donor surgeons, the development of highly trained laboratory staff in the specialized procedure of islet isolation and preparation, and the training of medical and nursing staff involved in pre- and post-transplant patient care.[49,155] Specialized training is required to cover the clinical aspects of the procedure as well as the technical training surrounding islet isolation, preparation procedures, and GMP guidelines.

Utilization of, access to, and demand for IT

The results reported with the Edmonton protocol in 2000 led to an increase in clinical IT activity at existing research centres and the opening of other IT centres worldwide (www.citregistry.org).[2,25,50,64,72,100,126,127,141,148,150,155,156,166,168,175] Seventy-six centres around the world were performing IT in 2005[168] and, as of May 2011, there were 730 IT recipients worldwide.[176] Currently, however, IT is not widely available to all potential candidates and it is not reimbursed by insurance plans in most countries.[2,64,127,150,155,168]

IT is currently restricted to highly selected adults with T1DM (www.citisletstudy.org) (http://chitbr.med.ubc.ca; www.jdrf.ca, www.islet.ca).[2,50,72,130,133,138,140,142,151,157–159,168] Because of the technical and medical challenges and limitations currently associated with IT, to improve the likelihood of success, most programs and clinical trials restrict access to patients who meet strict criteria. Children (< 18 years of age), elderly patients (> 65 years of age) and female candidates who desire to become pregnant in the future are currently excluded from the protocols due to unknown safety issues. From an IT program's perspective, the greatest chances for success have those slim and insulin sensitive candidates who are committed to transplantation and have good diabetes control and self-management skills and who have realistic expectations (whose goal is to avoid hypoglycemia and who view insulin independence as a bonus), reliable psychosocial support, and adequate financial resources.

In Canada, two programs currently provide IT services: the Clinical Islet Transplant Program (CITP) in Edmonton and the Centre for Human Islet Transplantation and Beta-cell Regeneration

(CHITBR) in Vancouver (http://chitbr.med.ubc.ca, www.islet.ca).[155,156] The CITP continues to have the largest single-centre experience in the world.[70,163,172,176] The first IT for T1DM performed at CHITBR occurred in 2003, and since then 70 IT procedures have been performed in 31 patients.[156] The CHITBR is currently conducting the first study that compares IT to standard medical care.

A Canadian study was recently conducted to quantify the demand for IT among adults (18 years and older) with T1DM if IT was widely available, to identify potential demographic or health variables that may influence the decision and to explore perceptions of IT.[177] A total of 1664 surveys were mailed to patients with T1DM from two centres: one with an IT program (Vancouver) and another without a program (Halifax). Of the 1499 eligible surveys (Halifax 631 and Vancouver 868), 588 were returned (Halifax 307 and Vancouver 281). There was no difference between the respondents from the two centres in terms of marital status, education level, or household income. There were significantly more males among the Vancouver respondents ($p < 0.05$). Equal numbers of respondents from both centres were familiar with IT. Halifax respondents were more likely to be on IPT than Vancouver respondents (22.2% vs. 8.5%; $p < 0.0001$) and less likely to have micro-vascular complications (47.5% vs. 56.4%; $p < 0.05$). There was no difference in the likelihood of discussing IT with their family doctor or in hypoglycemia awareness, macrovascular complications, knowledge of their most recent HbA1C, perceived diabetes control, or perceived general health.

The main outcome of this study was the rate of acceptance of IT by adults with T1DM after learning about its potential risks and benefits.[177] The overall acceptance rate ('yes' or 'probably yes') among responders was 76.7%. Acceptance rates were lower in Vancouver than in Halifax ($p < 0.05$). The most common expectations of respondents who would accept IT were hope for fewer diabetes-related complications (92.7%), less hypoglycemia (78.5%), no insulin injections (75.0%), and potential increased life expectancy (72.3%). Among those who would not accept IT ('no' or 'probably no'), the most frequently cited reasons were daily immunosuppressant medications (90.6%) and risks not yet identified (58.8%). As well, 43.8% of patients indicated that they would not or probably would not accept IT because of the possibility of not being insulin-free.

Acceptance was higher among those of younger age and with less formal education and was not associated with other demographic characteristics, such as sex or marital status.[177] Patients most likely to accept IT were from households with lower income**.** Overall, there were no differences in rates of hypoglycemia unawareness, hypoglycemia frequency, macrovascular or microvascular complications, and IPT usage between those accepting and not accepting IT. Patients who would accept IT had a higher recalled HbA1C, used higher daily doses of insulin, and had worse perceived diabetes control and worse perceived general health than patients who would not accept IT. Most of them indicated that they would not consider IT a failure if insulin was required post-transplant.

Ethical and Legal Issues Related to IT

The following commentary used information contained in several documents located through the Internet searches conducted for the SSDA section of this report (http://webdoc.sub.gwdg.de/univerlag/2010/schicktanz.pdf) (www.ualberta.ca/~pflaman/organtr.htm) (www.articlesbase.com/medicine-articles/legal-and-ethical-issues-of-organ-transplants-141140.html) (www.who.int/ethics/topics/human_transplant/en/) (www.who.int/ethics/Tissue%20and%20Organ%20Transplantation.pdf) (www.ahc.umn.edu/img/assets/26104/Organ_Transplantation.pdf) (www.ethicsforschools.org/transplantation/orgtnp.htm).[178–180]

The ethical and legal issues related to IT concern the donor, the recipient, the allocation of limited resources, and the means of procuring human islets, and are similar to those generated by current advances in clinical organ and tissue transplantation, the problem of organ/tissue supply versus organ/tissue demand, and the appropriate allocation of available organs/tissue. The field of clinical organ and tissue transplantation has generated many predictable and unpredictable issues including: definition of death; organ recovery; consent for organ/tissue donation; care of deceased donors in intensive care units; waiting list criteria for potential transplant recipients; and "transplant tourism".

The most important ethical issue that arises when considering the IT procedure is the risk-to-benefit ratio for patients who trade off unstable and poorly controlled T1DM with immunosuppression therapy for life. If it cannot be considered a life-saving procedure, its advantages in the long-term should be carefully considered and balanced with the morbidity and mortality associated with the procedure and the side effects of immunosuppression.

Because balancing the risk-to-benefit ratio remains central to selecting appropriate candidates for IT, informed consent is very important. Patients selected as appropriate candidates need to be informed that they will likely not remain insulin independent in the long-term and must accept the risks of immunosuppression so that they may have the endogenous insulin production to facilitate more stable and safer glucose control.

Another important ethical issue surrounding IT arises from the shortage of available donor pancreases.

The issues of whether expensive procedures such as IT are cost-effective and whether public funds should cover its costs for everyone who could benefit from it are also important. IT is a highly complex and labour-intense procedure, the planning and execution of which require a high degree of specialization and expertise. Experience in the islet isolation and preparation procedure and in the management of immunosuppressive medication is very important for the success of IT.

Management of adults with T1DM in Alberta

The literature search conducted for this analysis did not reveal any published reports on the current practice of managing adults with T1DM in Alberta and/or any issues related to the provision of appropriate treatments for this population in Alberta. None of the retrieved articles identified patient-, provider-, and system-level barriers to the effective management of adults with T1DM in Alberta, nor did any evaluate whether/how they impact care for this population in Alberta.

The literature search did not reveal any published information on the demand for, access to, and utilization of IT for adults with T1DM in Alberta, or any published reports on the appropriate provision of IT for this indication in Alberta.

Healthcare providers from Alberta were contacted by email and telephone and asked for a description of the current practice and information on the treatment options available for adults with T1DM in the province. They were also asked questions regarding the demand for and usage of IT services for adults with T1DM, issues related to access and barriers to using this procedure, training of healthcare providers, and the current number of trained/certified healthcare providers and support staff who provide IT services for adults.

The following commentary summarizes the information gathered from the healthcare providers and via personal communication with Alberta Health Services (AHS), as well from the AHS website (www.albertahealthservices.ca) and the CITP website (www.islet.ca).

Current options and standard method of managing adults with T1DM

According to experts in Alberta, most adult Albertans with T1DM are treated with IIT delivered either by MDI or by IPT (most are MDI users, with approximately 13% of them using IPT).[124] Pancreas or islet transplantation is considered when optimal IIT fails to achieve good glycemic control while avoiding/preventing complications or their progression. ITA is considered for adults with preserved renal function (non-uremic), particularly for those with persistent metabolic instability characterized by severe glycemic lability and/or severe hypoglycemia unawareness. PTA is rarely considered for some of these patients. SPK is considered for adults who also have end stage renal failure. IT may also be considered for these patients, but only after the patient had a successful kidney transplant.

IT services for adults with T1DM in Alberta

IT services for adults with T1DM are provided as part of the CITP in Edmonton, within the AHS global budget. The CITP was initiated in 2001, and serves 'non-research' patients undergoing ITA from across Canada. AHS recognizes the potential benefits of IT for adults with T1DM who have severe hypoglycemia or uncontrolled diabetes, despite their compliance with an appropriate or optimized IIT regimen and is currently providing special public funding for patients who meet CITP eligibility criteria.

The Clinical Islet Transplant Program in Edmonton

The CITP in Edmonton is an AHS/University of Alberta program. It is located at the University of Alberta Hospital where there is a pancreas transplant program and considerable experience in post-transplant care and immunosuppressant therapy. The CITP uses the clinical infrastructure provided by AHS and provides IT services within a standard care stream, as well as an evolving research protocol.

Patients access the CITP through referral from their physicians/endocrinologists or can self-refer to the program. Patients may be eligible for IT if they meet the following criteria:

1. They are adults (over 18 years) who have had T1DM for at least 5 years.
2. They present with hypoglycemic episodes (frequent or severe episodes of hypoglycemia) with minimal or no warning symptoms (hypoglycemia unawareness), despite optimization of medical therapy (including IIT delivered by MDI or IPT).
3. They suffer from brittle T1DM or extreme variability in their blood glucose levels despite optimization of medical therapy (including IIT delivered by MDI or IPT).
4. They exhibit progressive complications of diabetes such as vision, kidney, nerve, or blood vessel problems.
5. They are a resident of Canada.

The presence of severe kidney dysfunction (creatinine above 200 μmol/L or other parameters) or renal failure, having a body weight greater than 90 kg (or Body Mass Index above 30 kg/m^2), and requiring insulin use greater than 0.9 units/kg/day can disqualify a patient from receiving IT. However, patients who have previously received a kidney transplant may be eligible to take part in a research study of IT.

Other contraindications for IT include: severe cardiac disease, active alcohol or substance abuse, currently smoking, presence of an active infection (including hepatitis C, hepatitis B, HIV, or tuberculosis), any history of cancer (except skin cancer), a positive pregnancy test, an intent for future pregnancy, or failure to follow effective contraception.

Following receipt of an individual's referral/application, the patient, if deemed eligible, undergoes a comprehensive pre-transplant assessment. The timeline between applying and active listing is approximately 3 months. The program treats patients from across Canada, who need to come to Edmonton to be assessed and can return home while they are waiting to be called for a transplant. The waiting times for transplant vary from a few weeks to a year or more and are dependant on weight, blood type, and organ availability.

Organ procurement teams across Canada make arrangements for the removal, storage, and transportation of all acceptable donated pancreases to the CITP isolation laboratory. The isolation process takes 4 to 6 hours. Islets can be kept safely in culture for a few days until it is time for the transplant. The islet cells are then infused via the patient's portal vein using local anesthetic in a non-surgical procedure. The average length of stay in hospital after transplant is 2 days. Before the transplant, and again shortly after transplant, the patient is given induction medication to suppress his/her immune system. In the longer term the patient is required to take maintenance immunosuppression for as long as the islets are working.

After the transplant, the patient needs to stay in Edmonton for approximately 1 month, as a number of tests and follow-up visits are needed as part of the ongoing clinical monitoring. A number of tests need to be repeated each year after transplant and additional testing and appointments may be required. A few need to be done in Edmonton, but it can be arranged for most tests to be conducted closer to the patient's home.

Patients are under the care of a multidisciplinary team that includes interventional radiology specialists and staff, recipient/transplant coordinators (nurses), islet isolation laboratory staff (including technical staff, islet specialists, a quality assessment coordinator, and a senior specialist), a transplant dietitian, a patient and family support coordinator/transplant social worker, a metabolic coordinator, research staff, and clerical staff (clerk and secretary). The research team involves three transplant surgeons and two physicians (endocrinologists). The program has access to other allied healthcare providers and staff as needed.

For accreditation and quality control, CIPT has to comply with Health Canada's Safety of Human Cells, Tissues and Organs for Transplantation Regulations, which is administered by the Biological and Genetic Therapies Directorate, Health Products and Food Branch. This regulatory framework states that the use of allogeneic islet cells for transplantation should follow the regulations in terms of processing, storage, record keeping, distribution, error, accident, and adverse reaction investigation reporting.

Training in clinical IT is provided in-house.

Demand for IT as a treatment for adults with T1DM in Alberta

Although the demand for IT to manage adults with T1DM in Alberta is currently unknown, it is believed that not all potential candidates for IT are seen and considered in current waiting list numbers. According to Alberta clinicians, 10% of people with T1DM would meet the criteria used to define those who would benefit from clinical IT services.

The current waiting list for the CITP in Edmonton is not long. The majority of patients on the current waiting list are adult Albertans, and one third of the patients are from out of province.

Utilization of IT and WPT for managing adults with T1DM in Alberta

According to aggregate data provided by the AHS, between 2005 and 2010 the CITP in Edmonton performed an average of 24 IT procedures per year for an average of 20 adults with T1DM (see Table S.4).

Table S.4: Number of islet isolations and patients transplanted by fiscal year

	Fiscal year				
Islet isolations	**05/06**	**06/07**	**07/08**	**08/09**	**09/10**
Islets transplanted [1]	24	25	12	24	34
Research [2]	35	28	31	20	32
Discarded [3]	32	17	19	15	7
Total islet isolations	91	70	62	59	73
Patients Transplanted [1,4]	20	22	10	22	25

[1] In 2007-2008 the program was temporarily on hold for new transplants due to issues with enzyme

[2] Isolations are always performed with the intent to transplant. Isolations go to research if unable to transplant and research consent exists

[3] Insufficient islet yield for eligible recipients, and no research consent was obtained

[4] Patients may receive multiple islet transplants; therefore, the number of patients transplanted is less than the number of transplants performed. A patient transplanted in multiple fiscal years is counted in each fiscal year in which they were transplanted.

See Appendix S.B for demographic information (obtained from various sources) about patients who received IT at the CITP in Edmonton.

IT services were provided to both in-province (Alberta) and out-of-province residents (see Tables S.5, S.6, and S.7). According to data from Table S.6, of all islet transplant procedures performed between 2005 and 2010, 40% were provided for out-of-province patients. Table S.7 shows the number of patients who received transplants per fiscal year, and their home province/territory.

Table S.5: Number of in-province and out-of-province patients transplanted*

Patients transplanted	**Fiscal year**				
	05/06	**06/07**	**07/08**	**08/09**	**09/10**
In-province patients	10	10	6	12	20
Out-of-province patients	10	12	4	10	5
Total number of patients who received transplants	**20**	**22**	**10**	**22**	**25**

* Totals are the number of patients who received islet transplantation within the specified fiscal year (>1 transplant within the fiscal year is only counted as one patient).

Table S.6: Number of IT procedures by in- or out-of-province patient residence

IT rocedures	Fiscal year				
	05/06	06/07	07/08	08/09	09/10
IT procedures performed for in-province patients	12	12	7	14	26
IT procedures performed for out-of-province patients	12	13	5	10	8
Total IT procedures performed	**24**	**25**	**12**	**24**	**34**

Table S.7: Patients transplanted by province/territory of permanent residence

	Fiscal year				
Province/territory of permanent residence	**05/06**	**06/07**	**07/08**	**08/09**	**09/10**
Alberta	10	10	6	12	20
British Columbia	3	5	3	3	2
Saskatchewan	4	1		1	2
Newfoundland		1			
Ontario	2	3		3	1
Quebec	1	2	1	2	
Yukon Territory				1	
Total	**20**	**22**	**10**	**22**	**25**

Table S.8 describes the utilization of islet and whole pancreas transplantation for managing (in-province and out-of-province) adults with T1DM in Alberta between 2005 and 2010.

Table S.8: Utilization of IT and WPT to treat adults with T1DM (2005–2010)

Procedure	05/06		06/07		07/08		08/09		09/10	
	Patients	Txs	Patients	Txs	Patients	Txs	Patients	Txs	Patients	Txs
Islet transplants (IT)	16	1	19	1	8	1	20	1	16	1
	4	2	3	2	2	2	2	2	9	2
Whole pancreas transplants	0	1	1	1	0	1	2	1	0	1
Kidney/pancreas transplants	7	1	5	1	7	1	6	1	4	1

IT – islet transplantation; Txs – transplants

The volume of patients who received multiple islet transplants since the inception of the CITP, as at the end of the fiscal year 2009–2010, is presented in Table S.9.

Table S.9: Number of islet transplants per patient

Number of transplants	1	2	3	4
Frequency (number of patients)	14	79	24	5

According to data presented in Table S.9, most patients received two IT procedures. In general, a second transplant would be performed with the aim of achieving insulin independence if that was not achieved with the initial transplant. Patients may also require repeat transplants as "supplementary islet infusions" or top-ups. These are generally given to patients who have done well with previous transplants but who have some graft dysfunction. Patients with graft failure (defined as a loss of C-peptide), are generally not given subsequent transplants, especially if there is no avoidable explanation for the graft loss.

Operational impact

No reimbursement code exists for the CITP surgical team. This team is responsible for in-patient care, including the intraportal delivery of safe islets, intensive post-procedural monitoring for potential complications, and complex management of all aspects of immunosuppressive induction and maintenance therapies. Generally the selection of patients for IT also requires complex assessment. Endocrinology has a medical fee code for initial islet transplant assessment for in-province patients only.

Barriers to using IT as a treatment for adults with T1DM in Alberta

Alberta is in a unique position worldwide to continue leading the clinical IT field. The CITP in Edmonton established a large clinical network with considerable expertise in all aspects of the IT procedure. It continues to have the largest single centre experience in the world and it is deemed as an established research and development program focusing on islet isolation and transplantation, including established systems for monitoring and ongoing data collection at the site. Its model of care is well developed and is based on well matured clinical pathways that provide the IT service, including processes for appropriate referral, pre-transplant assessment, post-transplant monitoring, intensive care, and short- and long-term follow-up. The co-location of the islet isolation laboratory with the transplant service within CITP removes the time delays in transplant post-isolation and transport costs, and enables closer collaboration between islet scientists and IT clinicians. The CITP has the capacity to ensure access to IT services for patients from across Canada.

The main barrier to using IT in Alberta is availability of donor pancreases. The CITP depends on donor pancreases from out of province. The supply of human islets is limited, with most donated pancreases coming from young and middle-aged people who have had fatal auto accidents. The CITP is currently investigating the possibility of living donor islet transplantation, but no active program has as yet been set up in Edmonton.

There is a lack of awareness that IT is an option for a select group of adults with T1DM. Physicians/endocrinologists may be uncertain or unaware about the referral criteria for IT. Although potential candidates can self-refer to the program, many have been reluctant to apply, often because they are not aware that IT is an option for them.

Patients (particularly those outside of Edmonton and those from out of province) also face emotional and financial barriers. IT recipients spend a substantial period of time in Edmonton after

transplantation; this may require separation from family and friends and absence from work. Absence of usual support networks can be difficult, because the peri-transplant period is challenging both emotionally and physically. Loss of income as a result of absence from work or restricted duties because of adverse effects from the procedure itself and from immunosuppressive medication can prove to be a significant strain.

The cost for the assessment, the IT procedure, and the immunosuppressive medication (induction medication prescribed for immediately before and shortly after the transplant, plus long-term maintenance immunosuppression medication required for as long as the islets are working) is covered for patients who meet CITP eligibility criteria. However, for those who do not live in Edmonton, the cost of transportation to Edmonton for assessment, transplant, and follow-up visits (and in some cases the cost for accommodation when they come for maintenance appointments) remains their responsibility.

In relation to training, the challenge is to maintain a balance between competency and the number of transplants performed per year. With the current level of activity in Alberta, it takes 1 year to train a professional in the IT procedure. This is specific to the islet isolation procedure performed in the isolation laboratory and the training required for islet specialists. Those performing other roles within the program require less training.

Limitations

The present review has several limitations. The literature review was limited to published reports of articles and documents that were written in English. Proprietary reports were excluded. Only full-text articles were included.

Qualitative research literature, which reports patients' and providers' perspectives on the use of IT, was not included.

The present review only summarizes the recommendations from reports of relevant clinical practice guidelines and consensus statements and does not appraise their scientific foundations.

Clear answers could not be provided for some questions due to the absence of relevant data for Alberta.

Summary

The social and system demographics analysis report summarizes the available evidence from the scientific literature in Canada and worldwide and from Canadian databases to address questions about the burden of illness of T1DM, the population dynamics of affected individuals, current patterns of care, and issues related to the provision of IT. The following commentary highlights the key findings.

Overview of T1DM

T1DM is a chronic metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both. It encompasses cases that are primarily the result of pancreatic beta cell destruction.

T1DM is mostly an autoimmune disorder that is likely caused by a complex interaction of both genetic and environmental factors. Its onset is often sudden, and clinical presentation can vary from non-emergency symptoms to severe dehydration, shock, DKA, or diabetic coma.

If uncontrolled or poorly controlled, T1DM can cause disabling and life-threatening acute and chronic complications related to the disease itself, to its treatment, or to both.

T1DM morbidity and treatment affect quality of life and place a heavy burden—both monetary and nonmonetary—on the affected individual, the family, the healthcare system, and society.

Epidemiology and population dynamics of affected individuals

Although T1DM usually accounts for only a minority (approximately 10%) of the total burden of diabetes in a population, it is the most predominant form of the disease in younger age groups in most developed countries. It can develop at any age but usually appears in childhood or adolescence. Males and females tend to be equally vulnerable.

Potential risk factors include having a parent with T1DM, early exposure to viruses and toxins, reduced exposure to ultraviolet light, lower vitamin D levels, and early exposure to some nutritional factors.

The incidence and prevalence of T1DM vary according to age, gender, and ethnicity, and large variations are observed among and within countries.

Worldwide, the incidence of T1DM has been increasing steadily during recent decades. T1DM incidence is increasing at a noticeable rate in children (approximately 70,000 children develop T1DM annually, at a rate of approximately 3% per year), and there is evidence indicating a shift toward a younger age of onset. The cause of this rise is unknown, but epidemiological studies suggest the involvement of some environmental factors.

Increases in the incidence of T1DM in North America are similar to those observed in other parts of the world.

- More than one million individuals (children and adults) have T1DM in the United States, and more than 30,000 new cases are diagnosed every year. T1DM prevalence in 2007 was relatively constant across age groups, at 0.3 percent of the US population.
- Over 300,000 Canadians (children and adults) live with T1DM. In 2007, the estimated number of cases of T1DM among Canadian youth (aged 0 to 14) was 8400. In 2010, the incidence rate for this age group was estimated at 21.7 per 100,000 cases per year.

- Childhood T1DM is of particular importance in the Canadian province of Newfoundland and Labrador, where the incidence has been found to be the highest in North America and one of the highest in the world.
- According to data from Alberta Health, the total number of T1DM cases (males and females) increased in the 18- to 65-year-old age group, from 15,260 in 2006–2007 to 15,939 in 2008–2009.

Patterns of care

Intensive management, including IIT, dietary restrictions, and physical activity, is the accepted standard of care for adults with T1DM to achieve and maintain near-normal blood glucose levels in order to reduce the risk of complications. Evidence-based guidance recommends an individualized IIT regimen delivered either by MDI or by IPT. IPT is usually considered after MDI has been tried and has failed to optimize glycemic control safely. In Alberta, both MDI and IPT are available and most adults with T1DM use MDI.

Despite recent advances in IIT, and regardless the delivery method, IIT is still associated with an increased risk of developing recurrent and frequent severe hypoglycemic episodes and hypoglycemia unawareness, which can lead to disabling and potentially life-threatening outcomes. Fear of hypoglycemia and the risk of developing disabling and life-threatening hypoglycemia remain major barriers in the appropriate management of T1DM.

Approximately 10% of individuals with T1DM are especially prone to developing disabling and life-threatening hypoglycemia due to blood glucose instability. Despite optimal IIT, satisfactory and safe control of blood glucose levels cannot be achieved in many of these patients.

Beta cell replacement therapy by WPT or IT may be an alternative to IIT for highly selected adults with unstable and uncontrolled T1DM. Successful WPT or IT offers the advantages of attaining normal or near-normal blood glucose control with prevention of hypoglycemia and the potential for insulin independence. Some general recommendations have been made regarding the role of WPT and IT in the context of current clinical experience. Either PTA or ITA can be considered for non-uremic adults who have severe hypoglycemia or uncontrolled diabetes despite compliance with an appropriate IIT regimen. WPT or IT performed in combination with kidney transplantation (simultaneously or after) is considered for uremic patients (with T1DM and ESRD).

Clinical IT for adults with T1DM

The potential advantage of clinical IT over IIT is that the transplanted islets would maintain normal blood sugar levels under all conditions and would not produce excess insulin resulting in hypoglycemia. IT is attractive as a less invasive and safer alternative to WPT (which requires major surgery).

Although clinical IT can restore euglycemia, this restoration is not long term. The combination of a functioning graft and exogenous insulin therapy can help patients experiencing hypoglycemic unawareness to prevent hypoglycemic episodes while normalizing HbA1c and reducing glucose variability. However, IT requires islets from multiple donors and necessitates life-long immunosuppression, so any advantages and benefits must be weighed against the associated challenges and adverse effects. Patients selected as appropriate candidates need to be informed that they will likely not remain insulin independent in the long term and must accept the risks of immunosuppression.

Clinical IT is technically demanding and requires significant individual and institutional dedication and resources to perform the procedure on a regular basis. To be successful, clinical IT requires management of patients within a care framework suitably equipped and operated to take account of the technological particularities and the complexity of this procedure (which comprises a number of different components, each presenting different challenges) and its associated risks. The evaluation and selection of appropriate candidates need to be performed by a multidisciplinary team. Key factors in providing high-quality IT services are: identifying adults with T1DM who would benefit from IT by first balancing the risk-to-benefit ratio for each potential candidate, ensuring appropriate composition of the multidisciplinary team, long-term monitoring of and provision of support to the IT recipients.

The risks associated with the procedure itself and the immunosuppressant agents, the shortage of human donor islets, and long-term posttransplant care and follow-up of recipients suggest that selecting the most appropriate patients is essential.

The best candidates appear to be adults between 18 and 65 years of age who present with severe hypoglycemic episodes, hypoglycemia unawareness or glycemic lability that is causing a major disruption of their life, have reliable psychosocial support and adequate financial resources, and are up to the challenge of undertaking life-long immunosuppressive therapy and frequent contact with the diabetes care team. The greatest chances for success have those who are slim, have good diabetes control and self-management skills, and whose goal is to avoid hypoglycemia viewing insulin independence as a bonus.

The majority of the specialized training and facilities required for IT are involved with the islet processing procedures (islet isolation and preparation). The islet processing requires a purpose-built, accredited facility and highly skilled and experienced staff.

Clinical IT in Alberta

Approximately 10% of all people with T1DM in Alberta would meet the criteria used to define those who would benefit from clinical IT services.

Clinical IT services are provided only as part of the CITP in Edmonton within the AHS global budget. The CITP serves 'non-research' adults with unstable T1DM undergoing ITA from across Canada and has secured special provincial funding for providing islet ITA to manage unstable T1DM in adults refractory to optimized IIT who meet the program's eligibility criteria. Between 2005 and 2010, CITP performed an average of 24 IT procedures per year for an average number of 20 individual patients. Most patients received two IT procedures. Of all IT procedures performed over this period, 40% were provided for out-of-province patients.

Alberta is in a unique position worldwide to continue leading the clinical IT field. The CITP continues to have the largest single centre experience in the world. Its model of care and research is well developed based on considerable expertise and the maturity of the IT clinical pathways.

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Appendices

Appendix S.A: Data Sources and Synthesis Methods for the Social and System Demographics Analysis

Data Sources

The medical literature was searched to identify relevant articles and documents published between 2005 and 2010 using key health and sociological information resources including PubMed/MEDLINE, the Cochrane Library, and Centre for Reviews and Dissemination (CRD) databases (See Table S.A.1 for more details).

The literature search was focused on articles and documents providing information on the profile (definition, etiology, pathogenesis), epidemiology (incidence and prevalence) and psychosocial impact of T1DM in adults (≥ 18 years, both genders). It was also aimed at retrieving documents on the patterns of care and type of services provided for adults with T1DM (of any duration or stage and severity), and on the demand for and usage of IT in Alberta, in Canada, and in other countries with developed market economies. Also considered were articles reporting on QoL and on social, ethical, and legal issues or considerations when using these treatment options in the management of adults with T1DM.

Only articles reporting on research/analyses/discussions conducted in countries with developed market economies were considered, since the health status and disease burden of individuals, cultural and legal norms, and access to health care in countries with another status were likely to be too different from those of Canada to be clinically relevant. Countries deemed to have developed market economies, as defined by the United Nations, include Australia, Canada, Japan, New Zealand, the United States, and European countries (except for countries with market economies in transition) (http://unpan1.un.org/intradoc/groups/public/documents/un/unpan008092.pdf).

Also, a search was conducted for published local data and information from sources including Health Canada, Statistics Canada, the Canadian Diabetes Association, the Alliance for Canadian Health Outcomes Research in Diabetes, the Surveillance Branch of Alberta Health, and Alberta Health Services.

Healthcare providers from Alberta with interest and expertise in the management of T1DM in adults were contacted and asked questions regarding local context and practice.

Literature Searches

The literature searches were conducted by the IHE Research Librarian who retrieved articles published between 2005 and 2010. The search strategy was developed and carried out prior to the study selection process. The searches were limited to human studies published in English. The date restriction was applied to ensure that the evidence collected was current and clinically relevant.

In addition to the search strategy outlined in Table S.A.1, reference lists of retrieved articles were reviewed for potentially relevant articles and Internet searches were conducted to retrieve grey literature. Grey literature searches were conducted to identify literature from non-indexed sources, health technology assessment reports, guidelines, government documents, coverage policy documents, books and theses (from the National Guidelines Clearinghouse, NEOS, Alberta Health, Health Canada, and Google).

Medical Subject Headings (MeSH) terms relevant to this topic are: "Islets of Langerhans transplantation" and Diabetes mellitus; Diabetes mellitus, Type 1".

Table S.A.1: Search strategy

Database	Edition or date searched	Search Terms ††
Core Databases		
Cochrane Library Licensed Resource (Wiley Interface)	November 12, 2010	islet* AND (transplant* OR allotransplant*) **in Title, Abstract or Keywords**, from 2005 to 2010 **CDSR = 0 reviews** **Clinical Trials 14 results (1 new)**
MEDLINE (includes in-process citations) (Ovid interface)	February 1, 2011	Social and System Demographic Search (includes, epidemiology, burden, management and treatment related issues) 1. Diabetes Mellitus, Type 1/ 2. (diabet* adj5 (type 1 or type one or insulin dependen*)).tw. 3. 1 or 2 4. limit 3 to yr="2005 - 2011" 5. limit 4 to english language 6. limit 5 to animals 7. limit 6 to humans 8. 5 not (6 not 7) 9. limit 8 to "all child (0 to 18 years)" 10. limit 9 to "all adult (19 plus years)" 11. 8 not (9 not 10) 12. (diabet* or islet* or transplant* or insulin* or glyc?emic or hypogly* or hypergly*).ti. 13. exp Canada/ 14. (Canad* or BC or British Columbi* or Ontario or Alberta* or Saskatchewan or Manitoba* or Quebec* or Newfoundland or Yukon or NWT or Nunavut or Prince Edward Island or Nova Scotia* or New Brunswick or Toronto or Ottawa or Montreal or Halifax or Edmonton or Calgary or Vancouver).tw,in. 15. 13 or 14 16. review.pt. or meta-analy*.mp,pt. or ((systematic* adj2 review*) or Medline or pubmed or psychinfo or psycinfo).tw. or (hta or technology appraisal or technology assessment).ti. 17. technology assessment, biomedical/ 18. 16 or 17 19. 15 or 18 20. Mortality/ or morbidity/ or mortality.ti. 21. incidence/ or prevalence/ or inciden*.ti. or prevalen*.ti. 22. demography/ or census/ or population dynamics/ or exp population surveillance/ 23. age of onset/ or age distribution/ or age factors/ or age.ti. 24. exp sex distribution/ or sex factors/ or sex.ti. or gender.ti. 25. "emigration and immigration"/ or Minority Groups/ or culture/ or cultural characteristics/ 26. exp population groups/ 27. (aboriginal* or first nation* or native* or ethnic* or cultur* or minorit*).ti.

		28. epidemiologic factors/ 29. Epidemiologic Methods/ 30. "confounding factors (epidemiology)"/ 31. causality/ 32. risk factors/ or risk factor*.ti. 33. *educational status/ or education*.ti. 34. income/ or (income or salar* or earning*).ti. 35. Diabetes Mellitus, Type 1/ep 36. Diabetes Mellitus, Type 1/eh 37. or/20-36 38. 11 and 19 and 37 (Epidemiology results) 39. ("20636963" or "19466209" or "18937992" or "18729155" or "17259471" or "17130535" or "17130533" or "18729178" or "16764047" or "16316598" or "16164619" or "16037280").ui. 40. disease progression/ and 11 and 19 41. burden*.ti. and 11 42. comorbidity/ and 11 and 19 43. Hypoglycemia/co and 11 and 19 44. exp social environment/ and 11 45. "Quality of Life"/ and 11 and 19 46. Quality-Adjusted Life Years/ and 11 and 19 47. ("quality of life" or well-being or wellbeing or qol or hrqol or rql or quality adjusted life year* or QALY or self-rated health).ti. and 11 and 19 48. (Sociodemographic* or socio-demographic* or social demographic* or "social and demographic").tw. and 11 49. (socioeconomic or socio-economic or (social and economic)).ti. and 11 50. exp "Activities of Daily Living"/ and 11 51. Diabetes Mellitus, Type 1/px and 11 and 19 52. hypoglycemia/px and 11 53. (psychological or psychosocial or emotional).ti. and 11 and 19 54. cognition/ and 11 55. cognition disorders/ and 11 56. psychomotor performance/ and 11 57. Mental Health/ and 11 and 19 58. depression/ and 11 and 19 59. (depressive disorder/ or depressive disorder, major/) and 11 and 19 60. anxiety disorder/ and 11 and 19 61. stress, psychological/ and 11 and 19 62. fear/ and 11 63. (*accidents, traffic/ or *automobile,driving/ or (driv* or accident*).ti.) and 11 64. exp socioeconomic factors/ and 11 and 19 65. Diabetes Mellitus, Type 1/ec and 11 and 19 66. (socioeconomic or socio-economic or (social and economic)).ti. and 11 67. ((individual or personal or out of pocket) adj4 (expense* or cost* or economic)).tw. and 11 68. (work/ or employment/ or unemployment/ or exp income/ or occupations/) and 11 69. (employment or earning* or workplace or productivity).tw. and 11 70. work.ti. and 11 71. (exp exercise/ or exp motor activity/ or movement/ or physical exertion/ or physical fitness/) and 11 and 19 72. travel/ and 11

		73. or/39-72 74. 12 and 73 (Burden results) 75. hypoglycemia/pc and 11 and 19 76. (manag* and (hypoglyc* or type 1 or type one or insulin dependent or transplant*)).ti. and 11 and 19 77. standard of care.ti. and 11 78. practice guideline/ and 11 79. guideline*.ti. and 11 80. best practice*.ti. and 11 81. or/75-80 82. 12 and 81 (Management results) 83. ((child* or youth* or young or adolescent* or pediatric*) not adult*).ti. 84. "Islets of Langerhans Transplantation"/ 85. (islet* adj4 (allotransplant* or transplant*)).tw. 86. (multiple daily adj3 injections).tw. 87. ((continuous or subcutaneous or intensive) adj2 insulin).tw. 88. Insulin Infusion Systems/ 89. (insulin pump* or insulin infusion* or csii).tw. 90. pancreas transplantation/ 91. hypoglycemia/th 92. ((or/84-91) and 11 and 12) not 83 93. "Islets of Langerhans Transplantation"/px, td, ut, ct, st, sn 94. pancreas transplantation/px, ut 95. (adherence or compliance or acceptability or dropout* or drop out* or noncompliance or acceptable or satisfaction or attrition or preference* or incentive*).tw. 96. exp *"Patient Acceptance of Health Care"/ 97. "Quality of Life"/ 98. Quality-Adjusted Life Years/ 99. (quality of life or well-being or wellbeing or qol or hrqol or hrql or quality adjusted life year* or QALY or self-rated health).ti. 100. patient reported outcomes.tw. 101. attitude to health/ 102. Health knowledge, attitudes, practice/ 103. (perception* or perceived or knowledge or belief* or attitude* or perspective* or views).ti. 104. attitude of health personnel/ 105. (barrier* or disparit* or inequalit*).ti. 106. health services accessibility/ 107. access.ti. 108. regulat*.ti. 109. (quality not quality of life).ti. 110. "quality of health care"/ or guideline adherence/ or program evaluation/ or quality assurance, health care/ 111. (cultural or ethnic or psychological or linguistic or economic or socioeconomic or psychological or social or policy or financial or lifestyle or emotional or psychological).ti. 112. "health services needs and demand"/ 113. waiting lists/ 114. (demand or wait*).ti. 115. ut.fs. 116. utili?ation.ti. 117. "use of".ti. 118. exp social environment/ 119. exp population characteristics/

		120. (sociodemographic or (social adj2 demographic) or socio-demographic).tw. 121. minority groups/ 122. exp continental population groups/ 123. exp culture/ 124. cultural competency/ 125. age factors/ 126. sex factors/ 127. exp psychology/ 128. (or/93-127) and 92 129. "Islets of Langerhans Transplantation"/ae, mo 130. pancreas transplantation/ae, mo 131. insulin infusion systems/ae, mo 132. (adverse adj3 (reaction or event* or effect*)).tw. 133. (or/129-132) and 92 and 19 134. 128 or 133 (Treatment-related results) 135. 38 or 74 or 82 or 134 (combined results) Ethics search 1. "Islets of Langerhans Transplantation"/ 2. (islet* adj4 (transplant* or allotransplant*)).tw. 3. pancreas transplantation/ 4. (pancreas and transplant*).ti. 5. or/1-4 6. "tissue and organ harvesting"/ or donor selection/ or transplantation/ or organ transplantation/ or tissue transplantation/ or transplantation, homologous/ or "tissue and organ procurement"/ or directed tissue donation/ or transplants/ or tissue donors/ or kidney tranplantation/ 7. limit 5 to english language 8. limit 7 to yr="2005 - 2011" 9. (semen or sperm or oocyte or egg or cord or face or facial or embryo or insemination or cornea or uterus or lung or stem cell or heart or cardiac or animal or xenotransplant* or pig or porcine).ti. 10. ((child* or p?ediatric* or adolescen* or youth* or infant*) not adult*).ti. 11. 8 not (9 or 10) 12. limit 6 to english language 13. limit 12 to yr="2005 - 2011" 14. 13 not (9 or 10) 15. exp Canada/ 16. (Canad* or BC or British Columbi* or Ontario or Alberta* or Saskatchewan or Manitoba* or Quebec* or Newfoundland or Yukon or NWT or Nunavut or Prince Edward Island or Nova Scotia* or New Brunswick or Toronto or Ottawa or Montreal or Halifax or Edmonton or Calgary or Vancouver).tw,in. 17. 15 or 16 18. review.pt. or meta-analy*.mp,pt. or ((systematic* adj2 review*) or Medline or pubmed or psychinfo or psycinfo).tw. or (hta or technology appraisal or technology assessment).ti. 19. technology assessment, biomedical/ 20. 18 or 19 21. 17 or 20 22. "Islets of Langerhans Transplantation"/es, lj 23. pancreas transplantation/es, lj 24. "tissue and organ harvesting"/es, lj or donor selection/es,

		lj or transplantation/es, lj or organ transplantation/es, lj or tissue transplantation/es, lj or transplantation, homologous/es, lj or "tissue and organ procurement"/es, lj or directed tissue donation/es, lj or transplants/es, lj or tissue donors/es, lj or kidney transplantation/es, lj 25. exp ethics/ 26. exp Human Rights/ 27. Altruism/ 28. Social Values/ 29. value of life/ 30. exp resource allocation/ 31. exp disclosure/ 32. exp Jurisprudence/ 33. legislation as topic/ or legislation, medical/ 34. (ethic* or moral* or bioethic* or rights or consent or law or legal or legislation or jurispruden*).ti. 35. or/25-34 36. 11 and (22 or 23 or 35) 37. 14 and 21 and (24 or 35) 38. 36 or 37
CRD Databases (DARE, HTA & NHS EED) www.crd.york.ac.uk/crdweb/	November 13, 2010	Islet* AND (transplant* OR allotransplant*) RESTRICT YRS 2005 to 2010 **12 results**
Philosopher's Index (for ethical information only)	January 18, 2011	(TI=transplant* or DE=transplant* or DE=organ donation or DE=organ procurement) NOT TI=(semen or sperm or oocyte or egg or cord or face or facial or uterus or embryo or inseminat* or xenotransplant* or animal* or pig or stem cell or liver or bone marrow or limb or womb or alien* or China or Korea* or Romania* or Iran* or Spain) **169 results**

Library Catalogues		
NEOS (Central Alberta Library Consortium) www.library.ualberta.ca/catalogue	April 14, 2011	Islet AND transplant
AMICUS (National Library of Canada) www.collectionscanada.ca/amicus/index-e.html	April 14, 2011	ANY KEYWORD: Islet AND transplant
Guidelines		
AMA Clinical Practice Guidelines www.topalbertadoctors.org/TOP/CPG/	April 12, 2011	Browsed list **0 results**
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	April 12, 2011	Islet, transplantation **0 results**
National Guideline Clearinghouse www.ngc.gov	April 12, 2011	Islet AND transplantation **0 relevant results**
New Zealand Guidelines Group	April 12, 2011	Islet

www.nzgg.org.nz		**0 results**
Scottish Intercollegiate Guidelines Network www.sign.ac.uk	April 12, 2011	Browsed list and searched latest diabetes guideline **0 results**
Guidelines International Network (International Guidelines Library) www.g-i-n.net/	April 12, 2011	Islet **3 results (AHRQ and NICE)**
Guidelines Advisory Committee www.gacguidelines.ca/index.cfm	April 12, 2011	Browsed list and searched recent diabetes **0 relevant results**
BC Guidelines and Protocol Advisory Committee www.health.gov.bc.ca/gpac	April 12, 2011	Browsed alphabetical list and searched diabetes guideline **0 relevant results**
NICE guidance http://guidance.nice.org.uk/	April 12, 2011	Islet **2 relevant results**
Clinical Trials		
ClinicalTrials.gov (US) http://clinicaltrials.gov/	April 12, 2011	Islet AND transplant **100 results**
CenterWatch Clinical Trials Listing Service www.centerwatch. com/	April 12, 2011	Islet **7 results**
CCT Current controlled trials www.controlled-trials.com (did not search clinical trials.gov)	April 14, 2011	Islet **0 relevant results**
IFPMA Clinical Trials Portal http://clinicaltrials.ifpma.org/clinicaltrials/no_cache/en/myportal/index.htm	April 14, 2011	Transplantation Islets of Langerhans **0 new results**
Coverage/Regulatory/Licensing Agencies		
Alberta Health and Wellness www.health.gov.ab.ca	April 14, 2011	Islet **0 relevant results**
Health Canada www.hc-sc.gc.ca	April 14, 2011	Islet AND transplant **5 potentially relevant results**
US Medicare Coverage Database www.cms.hhs.gov/mcd/search.asp?	April 14, 2011	Search all states and islet (a National Coverage Decision)
Data Sources and Topic-relevant Websites		
Statistics Canada www.statcan.gc. ca	May 5, 2011	Islet, type 1 diabetes
Canadian Diabetes Association www.diabetes.ca	May 5, 2011	Islet

Alliance for Canadian Health Outcomes Research in Diabetes www.achord.ca/	May 5, 2011	Islet, type 1 diabetes
Alberta Health and Wellness (Interactive Health Data Application) www.health.alberta.ca/health-info/IHDA.html	May 5, 2011	Crude diabetes rate
Clinical Information Sources		
Aggressive Research Intelligence Facility (ARIF) www.arif.bham.ac.uk/completed.shtml	April 14, 2011	Islet **0 relevant results**
ACP Journal Club http://acpjc.acponline. org	April 14, 2011	Islet, islets **0 relevant results**
ATTRACT www.attract.wales.nhs.uk	April 14, 2011	Islet **0 relevant results**
Bandolier www.medicine.ox.ac.k/bandolier/	April 14, 2011	Islet **0 results**
BestBETS www.bestbets. org	April 14, 2011	Browse by topic: Endocrine > diabetes
Clinical Evidence** www.clinicalevidence.com	April 14, 2011	Islet **0 relevant results**
TRIPdatabase www.tripdatabase.com	April 14, 2011	Reviewed results for systematic reviews and guidelines
Health Economics Information		
Centre for Health Economics and Policy Analysis www.chepa.org	April 14, 2011	Islet **0 results**
Centre for Health Economics Research and Evaluation www.chere.uts.edu.au/index.html	April 14, 2011	Browsed economic evaluations and policy evaluations **0 results**
Manitoba Centre for Health Policy http://umanitoba.ca/medicine/units/mchp/	April 14, 2011	Browsed deliverables and active research pages **0 results**
Other HTA Resources		
AETMIS www.aetmis.gouv.qc.ca/site/home.phtml	April 12, 2011	Islet **0 results**
CADTH www.cadth.ca/index.php/en/hta/reports-publications/search	April 12, 2011	Islet **0 results**

BC Centre for Health Services and Policy Research (CHSPR) www.chspr.ubc.ca/publications	April 12, 2011	Islet **0 results**
Institute for Clinical and Evaluative Sciences (ICES), Ontario www.ices.on.ca/	April 12, 2011	Islet **0 results**
Health Technology Assessment Unit at McGill University www.mcgill.ca/tau/	April 12, 2011	Browsed list **0 results**
Medical Advisory Secretariat www.health.gov.on.ca/english/providers/program/mas/mas_mn.html	April 12, 2011	Browsed list **1 result** (2003)
EuroScan www.euroscan.org.uk/technologies/public/do_public_search	April 12, 2011	Islet **1 relevant result**
ASERNIP-S www.surgeons.org/asernip-s/	April 14, 2011	Islet **0 relevant results**
MSAC www.msac.gov.au	April 14, 2011	Islet **0 relevant results**
NZHTA http://nzhta.chmeds.ac.nz/ publications.htm	April 14, 2011	Islet **0 relevant results**
National Horizon Scanning Centre www.haps.bham.ac.uk/publichealth/horizon/outputs/technology.shtml	April 14, 2011	Islet **0 relevant results**
CCE www.southernhealth.org.au/page/Health_Professionals/CCE/Evidence_ reviews/Current/	April 14, 2011	Islet **0 relevant results** (searched current and archived)
California Health Benefits Review Program (CHBRP) www.chbrp.org/	April 14, 2011	Browsed complete analyses page **0 results**
California Technology Assessment Forum (CTAF) www.ctaf.org/section/assessment/	April 14, 2011	Islet **0 results**
AHRQ www.ahrq.gov	April 12, 2011	Islet **1 result**
NHS Health Technology Assessment Programme www.ncchta.org	April 12, 2011	Islet **1 result**

VA Technology Assessment Program www.va.gov/VATAP/Phase2pubspage.asp	April 12, 2011	Islet **0 results**
Health Evidence Network (HEN) www.euro.who.int/en/what-we-do/data-and-evidence/health-evidence-network-hen/publications/by-keyword	April 12, 2011	Islet **0 results**
Australia and New Zealand Horizon Scanning Network www.horizonscanning.gov.au	April 12, 2011	Islet **4 results (2 relevant)**
HSTAT www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat	April 12, 2011	Islet **1 relevant result**
AETNA www.aetna.com/cpb/cpb_menu.html	April 12, 2011	Islet **1 result**
Blue Cross and Blue Shield www.bcbs.com/blueresources/tec/tec-assessments.html	April 12, 2011	Islet **1 result** (same as AHRQ)
Washington State Health Care Authority www.hta.hca.wa.gov/assessments.html	April 12, 2011	Browsed list **0 results**
Metabrowsers/Search Engines		
Google www.google.com	April 28, 2011	Islet transplantation guideline Islet transplantation systematic-review technology-assessment

Note: ††, *, and $ are truncation characters that retrieve all possible suffix variations of the root word; e.g., surg* retrieves surgery, surgical, surgeon, etc. Semi-colons separate searches that were entered separately.

Study selection

A set of inclusion and exclusion criteria was developed *a priori* and used to determine eligibility of studies for the social and system demographics analysis. One reviewer evaluated the title and abstract of each retrieved citation to select potentially relevant references. When an article met the screening criteria or when there was not enough information to definitely exclude it, the full text was retrieved.

The study selection process was focused on secondary research studies including systematic reviews, health technology assessments, evidence-based clinical practice guidelines, policy papers, overviews, clinical reviews, and/or discussion papers on the topic of interest that were conducted or developed in Alberta, in Canada or in other countries with developed market economies. Primary research studies and/or papers reporting on secondary analyses of research data (such as health surveys and claims data) were included only if they provided information about T1DM in adults and its management in Alberta and in Canada.

Clinical practice guidelines (CPGs), consensus statements and/or position statements were included if they provided definitive recommendations for the management of adults (≥ 18 years, both genders) with T1DM (of any duration or at any stage) and the use of pancreas or islet

transplantation in T1DM. Those that referred to diabetes mellitus were included only if they provided recommendations specific to the management of T1DM in adults.

Only publicly available guidance developed by national bodies in Canada and other countries with developed market economies was considered.

Literature search results

Electronic literature searches conducted for the SSDA yielded 1718 citations. After screening of titles and abstracts, full text articles were retrieved for 192 potentially relevant articles. Following a systematic review of the retrieved full-text articles, 94 references were selected to summarize information for this section of the report.

Alberta Administrative Health Databases

Local data on T1DM prevalence and on the utilization of IT and whole pancreas transplantation (WPT) for treating adults with T1DM in Alberta were derived from consulting the Alberta Health and Alberta Health Services administrative health databases. See the "Economic Analysis" section in this report for more information.

Data analysis and synthesis

A population health approach was used to describe the data on T1DM in adults and the current status of IT for this indication. The overview of the social and system demographics situation around T1DM in adults, as well as the overview of IT as a treatment for this condition and patterns of utilization and practice, were considered within international, national and provincial contexts.

Appendix S.B: Demographic information for IT recipients treated at CITP in Edmonton

Demographic characteristics	Estimates
Transplants/yr, mean (SD)	21.1 (7.8)[1]
Recipients, out-of-province (%)	31% (43/138)
Organs, out-of-province (%)	37.8% (65/172)
Total organs accepted/yr, mean (SE)	78.3 ± 4.4 (n=548)[2]
Organs resulting in tx/yr, mean (SE)	26.6 ± 2.1 (n=186)[2]
Wait time for tx, mo., mean (SD) NOTE: values verified	tx#1: 9.7±11.5 subsequent tx: 3.7±4.3
Pre-tx age, year (mean SD)	46.5 (10.1)
Male (%)	45% (62/138)
HbA1C, mean (SD): pre-tx 1 yr post-tx#1 3 yr post-tx#1 5 yr post-tx#1	8.2 (1.3) 6.2 (0.8) 6.6 (1.2) 6.9 (1.6)
Insulin use, mean (SD) (partial function: mean insulin use post-tx#1 and pre and post all subsequent transplants); all patients	Pre-tx#1 u/day: 42.7 (14.5) Pre-tx#1 u/kg: 0.60 (0.17) Partial function u/day: 15.9 (7.0) Partial function u/kg: 0.24 (0.16)

mo – month(s); SE – standard error; SD – standard deviation; tx – transplant; u – unit

Sources

[1]Data from the CITP patient tracking system and databases for all 138 patients (300 transplants) for the entire program between January 01, 1999 and December 31, 2011; 136 patients received islet transplantation alone and two received islet after kidney/pancreas transplantation

[2]Data from the CITP patient tracking system and databases for all transplants performed between January 01, 2004 and December 31, 2010

Comorbidity at time of transplant	% of recipients
Proliferative retinopathy[4]	36
Renal failure[6]	0
Microalbuminurea or macroalbuminurea	25
Autonomic neuropathy[1]	15
Peripheral neuropathy[3]	35
Coronary artery disease[5]	40
Amputation	1
Legally blind	2

Immunosuppression complications	# of recipients
Intolerance[1]	1
Anemia[1]	3
Leucopenia/neutropenia[1]	15
Skin cancer[1]	4
CMV disease[1]	1
Epstein Barr virus conversion	0
PTLD	0

Severe opportunistic infections	2
Secondary complications	**# of recipients**
ESRD[1]	4
Coronary artery disease events[5]	11/1000 pt yrs
Procedural complications	**# / % of recipients**
Surgical procedure[1]	3
Bleeds[2,7]	current=5; total=13.6
Portal vein thrombosis[2]	4
MI	0.7 (1/138 patients)
Deaths	**# / % of recipients**
Procedural	0
Post-transplant	4% (6/138 patients: 1 post withdrawal of IS and listed for pancreas transplant, 3 accidental, 2 complications of diabetes)
Other adverse effects	**# / % of recipients**
Incidental malignant neoplasms[1]	1
Hepatic steatosis[1]	45

CMV – cytomegalovirus; ESRD – end stage renal disease; IS – immunosuppression; MI - myocardial infarction; PTLD – post-transplantation lymphoproliferative disorder

Sources

[1]CITP patient tracking system and databases

[2]Insulin-heparin infusions peritransplant substantially improve single-donor clinical islet transplant success. A Koh, P Senior, A Salam, T Kin, S Imes, P Dinyari, A Malcolm, C Toso, B Nilsson, O Korsgren, AMJ Shapiro. Transplantation. 89(4):465-71. 2010

[3]Diabetic Peripheral Neuropathy is Stabilized After Clinical Islet Transplantation—7 Year Follow-Up Study. W Al-Baker, A Koh, EA Ryan, AMJ Shapiro, P Senior. J Clin Endocrinol Metab 93 (supp 1):OR26-2. 2008

[4]Positive Effects of Clinical Islet Transplantation on Diabetic Retinopathy Over 5 Years. A Koh, C Rudnisky, M Tennent, AMJ Shapiro, P Senior. Diabetes Suppl 1. 2011

[5]Coronary Artery Disease Remains Stable After Islet Transplantation. A Koh, E Ryan, R Welsh, A Shuaib, AMJ Shapiro, P Senior. Diabetes Suppl 1 2008.

[6]Changes in Renal Function after Clinical Islet Transplantation: Four-Year Observational Study. P Senior, M Zeman, BW Paty, EA Ryan AMJ Shapiro. Am J Transplantation 7:91-98. 2007

[7]Prevention of Bleeding after islet Transplantation - Lessons Learned from a Multivariate Analysis of 128 Cases at a Single Institution. P Villiger, EA Ryan, R Owen, K O'Kelly, J Oberholzer, F Al Saif, T Kin, H Wang, I Larsen, S Blitz, V Menon, P Senior, D BIgam, B Paty, NM Kneteman, JRT Lakey, AMJ Shapiro. Am J Transplant 12:2992-2998. 2005.

SECTION TWO: SAFETY AND EFFECTS OF ISLET TRANSPLANTATION

Bing Guo, MD, MSc; Paula Corabian, BA, MPH;Christa Harstall, BSc MLS, MHSA

Introduction

Purpose of assessment

To determine, for the treatment of patients with T1DM in Alberta, the potential role of islet transplantation compared to whole pancreas transplantation or intensive insulin therapy.

Objective

To perform a systematic review and critical appraisal of currently best available research evidence on the safety and efficacy or effectiveness of islet transplantation compared to whole pancreas transplantation or intensive insulin therapy in the treatment of patients with T1DM.

Research questions

The Technology (T) section of the report attempted to address the following questions:

- Is islet transplantation safe compared to whole pancreas transplantation or intensive insulin therapy, in terms of complications and side effects, in the treatment of patients with T1DM?
- Is islet transplantation effective compared to whole pancreas transplantation or intensive insulin therapy, in terms of short-, intermediate-, and long-term outcomes, in the treatment of patients with T1DM?
- For what sub-populations of patients is treatment with islet transplantation most appropriate?

The scope of the Technology section of the report was defined as follows:

Population:

1) non-uremic adult patients with T1DM with severe hypoglycemia/hypoglycemia unawareness/high variability of glucose levels, or
2) uremic adult patients with end-stage renal disease

Intervention:

1) islet transplantation alone
2) islet transplantation after kidney transplantation
3) simultaneous islet and kidney transplantation

Comparators:

1) intensive insulin therapy (either by multiple daily injection, or insulin pump therapy), or
2) whole pancreas transplantation (pancreas transplantation alone, simultaneous pancreas and kidney transplantation, or pancreas after kidney transplantation)

Outcomes:

1) Safety outcomes include procedure-related and immunosuppression-related adverse events.

2) Efficacy/effectiveness outcomes include patient survival, graft function and glycemic control, prevention of hypoglycemia, health-related quality of life, or secondary complications of diabetes.

Description of Technology

Overview

Islet transplantation is a minimally invasive procedure that involves pancreas procurement and preservation, islet cell processing (islet isolation, purification, or culture), islet infusion, and the life-long use of an immunosuppressive regimen after transplantation.[1,2] A detailed description of the islet transplantation procedure was provided in an early IHE report.[3]

Pancreas procurement and preservation

Donor pancreata are procured by careful excision of the gland before the liver and by maintenance of a low core pancreas temperature by adequate surface cooling of the pancreas. The procured pancreata are then preserved in solutions such as two-layer oxygenated perfluorocarbons or University of Wisconsin (UW) solution.[1,4]

Islet isolation and purification

The process of islet isolation from the pancreas involves dissociation of islets from the exocrine pancreas by enzymatic digestion combined with mechanical agitation, followed by purification on density gradients.[1,4]

Islet culture

Islet culture prior to transplantation allows sufficient time for extensive viability and functionality testing of islets, screening human islet preparations for additional pathogens, patient preparation for immunosuppressive treatment, and transportation of islets to remote centres.[1]

Islet infusion

Islet cell products obtained from the islet isolation process are infused into the hepatic portal system of the recipient by transhepatic cannulation of the portal vein using minimally invasive interventional radiology techniques (ultrasound and fluoroscopic guidance).[5]

Immunosuppressive protocols

The immunosuppressive treatment following islet transplantation is generally based on the use of an induction treatment with antibodies, including antilymphocyte serum (ALS) or antithymocyte globulins (ATG), anti-CD25 (IL-2 receptor), and anti-CD152 (Campath-1 H) antibodies, which are combined with different maintenance immunosuppressive medications.[5]

Types of islet transplantation procedures

Islet transplantation can be performed under three clinical scenarios:

- islet transplantation alone (ITA), for patients with preserved renal function (non-uremic)
- simultaneous islet and kidney transplantation (SIK)
- islet after kidney transplantation (IAK), for patients who have already developed end stage renal disease (uremic)[6]

ITA for non-uremic patients

Original Edmonton protocol

In 2000, investigators from Edmonton reported a novel islet transplantation protocol that resulted in insulin independence in seven consecutive patients.[7] The original Edmonton protocol is characterized by the following features:

- selection of patients with life-threatening hypoglycemia episodes, hypoglycemia unawareness, and brittle diabetes, but without end-stage renal disease
- infusion of an adequate amount of viable islets, usually obtained from two to four pancreas donors;
- preparation of islet cells in xenoprotein-free medium, limitation of prolonged cold ischemia, and transplantation of freshly harvested islets without culture, and
- use of a less diabetogenic, glucocorticoid-free immunosuppression regimen consisting of daclizumab, tacrolimus, and sirolimus

Transplantation of a large mass of high-quality islets and the use of a novel, steroid-free immunosuppression regimen to reduce β-cell toxicity and diabetogenicity are considered the two most important factors contributing to the success of the first reported Edmonton series.[8,9] The safety and efficacy of the Edmonton protocol has since been examined by an Immune Tolerance Network-sponsored international multicentre trial[10] and in a number of single-centre studies.

Clinical issues with the original Edmonton protocol

Widespread adoption of the Edmonton protocol over the last 10 years has revealed several important clinical issues associated with feasibility, safety, and efficacy.

The original Edmonton protocol applied very stringent patient selection criteria. Only a small portion of patients with T1DM are suitable candidates for the Edmonton protocol.

The requirement of adequate islets prepared from two to four donors limits the widespread use of the Edmonton protocol. Restoration of insulin independence needs to be achieved with a single donor to reduce the risks and costs of the procedure and to increase the availability of islet transplantation.[11]

For some clinical centres, transplantation of fresh islets immediately after islet isolation is not possible due to the lack of capacity to prepare islets from donors.[12]

The use of sirolimus is considered a key component of the novel, steroid-free immunosuppression regimen in the Edmonton protocol.[13] However, a high incidence of hematologic (leukopenia, anemia, or thrombocytopenia), metabolic (dyslipidemia), gastrointestinal (mouth ulcer, diarrhea, vomiting), and dermatologic (skin rash, edema) side effects of sirolimus, as well as its potential nephrotoxicity, have necessitated a switch from sirolimus to other immunosuppressive drugs in some patients.[13,14]

Finally, the Edmonton protocol has encountered challenges in reproducibility of results and durability of clinical benefits. Insulin independence rates at one year after islet transplantation varied significantly across clinical centres participating in the international multicentre trial.[10] Longer-term follow-up of patients who received transplants using the Edmonton protocol has revealed an

inexorable deterioration in islet graft over time, with 90% of recipients returning to insulin therapy by 5-years post-transplantation.[15] While the causes for the progressive loss of functional islet mass still remain unknown, a number of possibilities have been proposed, including subclinical allograft rejection, recurrent autoimmunity, site-related dysfunction, marginal mass exhaustion, and toxicity of immunosuppressive drugs.[16,17]

In addition, some recipients develop donor-HLA-specific alloantibodies (allo-sensitization), which is significantly exacerbated by the frequent requirement for multiple islet donors to achieve insulin independence under the Edmonton protocol.[18] The allo-sensitization may impede subsequent access to more conventional forms of transplantation (such as kidney or pancreas transplantation) or to better islet transplantation protocols developed in the future.[19]

Ongoing modification of the Edmonton protocol

In addressing the above-mentioned clinical issues, new methods have been developed and tested by the Edmonton clinical islet transplant centre and other centres over the last 10 years to improve the safety and efficacy profile of the original Edmonton protocol. Highlights of these modifications include:

- use of islet culture to ensure the quality of islet products and to allow additional time for patient preparation, pre-transplant interventions, and the opportunity to ship processed islets to remote transplantation sites[20] Islet culture before transplantation is now a routine practice at the Edmonton clinical islet transplant centre (Dr. Senior, personal communication, September 2011)
- use of immunosuppressive medications other than sirolimus to avoid its side effects;[18] while islet recipients at the Edmonton centre no longer use sirolimus, basiliximab, alemtuzumab (Campath®), thymoglobulin®, and etanercept are used for induction, and tacrolimus (Prograf®) and mycophenolate mofetil (CellCept®) are used for maintenance (www.islet.ca; accessed October 13, 2011)
- use of islets prepared from a single donor to achieve insulin independence[11]
- use of an infusion bag rather than a syringe for islet delivery, to further improve the sterility and safety of the procedure[21]
- use of physical and mechanical ablation of the catheter tract, using combinations of coils and thrombostatic agents, to reduce the risk of bleeding following percutaneous transhepatic access to the portal vein[2]
- intravenous heparin/insulin infusion after islet transplantation, to reduce immediate blood-mediated inflammatory reaction and prevent its deleterious effects on islet engraftment[22,23]
- use of additional medications such as etanercept (a TNFα receptor antagonist) and exenatide (a glucagon-like peptide-1 analogue) to improve islet graft survival[24,25]

Indications for ITA

The Edmonton clinical islet transplant program used the following criteria to determine the eligibility of patients for islet transplantation:[2,26]

- aged between 18 and 65 years

- have had diabetes for more than 5 years
- have undetectable stimulated C-peptide
- have severe hypoglycemia
- have hypoglycemia unawareness
- have glucose liability (brittle diabetes, high variability in glucose levels)

Contraindications for ITA

Patients with the following characteristics are not considered for islet transplantation:[2,26](www.islet.ca)

- age: children, and the elderly (> 65 years of age)
- obesity and insulin resistance: patients with high body weight (> 90 kg), obesity (BMI > 28, or BMI > 30 in some centres), or with high insulin requirements (> 1 unit/kg/day). Insulin independence may be more readily achieved in normal weight patients and in insulin-sensitive individuals having a low pre-transplant insulin requirement. It is difficult to provide an overweight individual with an adequate islet mass without the procedure requiring multiple islet infusions. Procedure-related complications may increase with sequential procedures.
- a blood HbA1c level greater than 12%
- severe kidney dysfunction (creatinine above 200 μmol/L or other parameters)
- infection and neoplasia
- psychiatric disease, cognitive impairment, and non-compliance
- smoking, alcohol use, and drug use
- taking systemic steroids in supra-physiologic doses
- young women who wish to become pregnant

Islet and kidney transplantation for uremic patients

Nephropathy is one of the most common and most serious complications in patients with T1DM.[27] Glomerular hyperfiltration is the first feature of renal impairment that can be observed shortly after diabetes onset, accompanied by a loss of renal functional reserve. Microalbuminuria and morphological changes of the kidney occur at a later stage.[27]

Historically, 20% to 40% of patients with diabetes develop diabetic nephropathy over a period of 25 years from the onset of the disease, and 5% to 15% progress to end stage renal disease (ESRD).[28] Most patients with diabetes will die of cardiovascular events prior to developing chronic kidney disease or progressing to ESRD.[28] For uremic patients with T1DM, poor survival with the treatment of hemodialysis can be improved by kidney transplantation.

For uremic patients, islet transplantation can be performed after kidney transplantation (islet after kidney transplantation, IAK) or at the same time (simultaneous islet and kidney transplantation, SIK).[6,26] IAK has potential advantages over SIK:

1) The risk/benefit considerations are more favourable because the recipient is already obligated to life-long immunosuppression.
2) The chronically immunosuppressed host may provide a more receptive milieu for islet engraftment and long-term survival.[17]

Indications

Indications for IAK or SIK have not been well established (Dr. Senior, personal communication, September 2011). The following criteria were used in some clinical centres to determine the eligibility for IAK or SIK[26]

- undetectable C-peptide
- body weight < 80 kg
- BMI < 28 kg/m^2

IAK can be performed for patients who have previously received simultaneous pancreas and kidney transplantation with a secondary loss of the pancreatic graft but functional kidney draft.

Immunosuppressive regimens for islet-kidney transplantation

While ITA allows flexibility in the selection of immunosuppressive medications, the immunosuppression for patients who already had a kidney graft is often dictated by the standard of care for the kidney graft (steroid, cyclosporine, ATG).[29] However, it is still possible for patients to convert to the immunosuppressive drugs used in the Edmonton protocol or other regimens.[17]

To use the Edmonton protocol, a progressive steroid weaning in the six months following the kidney transplantation should be considered if no acute rejection episode has occurred.[26] However, when other protocols are used, low dose steroids are sometimes maintained in high-risk patients to avoid acute kidney rejection.[26]

Potential benefit of islet transplantation over alternative treatment options

Islet transplantation versus intensive insulin therapy

Intensive insulin therapy is administered by multiple daily injections or by continuous infusion through an insulin pump. In combination with dietary therapy and physical exercise, intensive insulin therapy remains the treatment of choice for the majority of patients with T1DM.[5]

Intensive insulin therapy can delay the onset or slow the progression of long-term diabetic complications;[30] however, it is associated with increased risk of severe hypoglycemic events compared to conventional insulin therapy and with suboptimal glycemic control. In about 3% to 4% of patients with unstable diabetes, glycemic instability leads to repeated hypoglycemic coma.[31] Despite technical advancements, such as fast-acting and long-acting insulin analogs, nearly instantaneous self-monitoring of capillary blood glucose, fine needles, pens, and insulin pumps, about 50% of patients do not reach the target of an HbA1c level below 7.5% without repeated episodes of severe hypoglycemia.[31]

Given the limitation of exogenous insulin management, there has been a sustained interest in strategies for beta cell replacement (by islet or whole pancreas transplantation) to achieve more physiologic and less cumbersome glucose control. In particular, islet transplantation has continued to be a conceptually appealing approach.

Islet transplantation versus whole pancreas transplantation

The current benchmark for islet transplantation is whole pancreas transplantation, which results in a 3-year insulin independence rate of 80%.[32] Whole pancreas transplantation is performed either as simultaneous pancreas and kidney transplantation (SPK), pancreas after kidney transplantation (PAK), or pancreas transplantation alone (PTA), according to the renal function status of the recipient.[33–35]

While PTA is restricted to patients with severe diabetic metabolic complications, usually with hypoglycemic unawareness,[36] SPK is considered the treatment of choice for T1DM patients with non-reversible renal failure.[33,36,37] The main advantage of SPK is the increased success rate of the pancreas graft, because concurrent acute rejection in both pancreas and kidney can be detected by an increase in serum creatinine concentrations.[35] PAK has become more common with increased use of living donors for kidney transplantation.[38,39]

The first whole pancreas transplant was performed in 1966. By the end of 2004, more than 23,000 pancreas transplants had been reported to the International Pancreas Registry.[40] In the United States, 78%, 16%, and 7% of recipients have undergone SPK, PAK, and PTA, respectively.[40]

Whole pancreas transplantation has clearly demonstrated, sustained long-term outcomes and prevention or stabilization of secondary complications of diabetes.[39] Pancreas transplantation, however, is a major surgical procedure, and is associated with significant perioperative complications such as thrombosis, pancreatitis, and peritonitis.[41,42] Islet transplantation, a minimally invasive procedure, offers an attractive alternative to whole pancreas transplantation.

Regulatory status

Health Canada

In June 2007, Health Canada released a new regulatory framework titled *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*. It is administrated by the Biological and Genetic Therapies Directorate, Health Products and Food Branch.[43] Use of allogeneic islet cells for transplantation must follow these regulations in terms of processing, storage, record keeping, distribution, importation, error, accident, and adverse reaction investigation reporting.[44,45]

United States Food and Drug Administration (FDA)

In the United States, allogeneic pancreatic islets meet FDA criteria for regulation as both a drug product and a biologic product; therefore, islets cannot be used clinically without an investigational new drug application or an approved biologics license application (BLA).[46] Allogeneic islets are considered a somatic cell therapy and require an approved BLA before they can be marketed for treatment of patients with diabetes. Islet transplantation has not been approved for marketing by the US FDA because of the current lack of information showing the safety, purity, potency, and effectiveness of the final product. Currently, the use of allogeneic islets for the treatment of T1DM is investigational and is only used in clinical trials under investigational new drug application.[46]

Islet isolation must follow current Good Manufacturing Practice guidelines and biological product standards. The source material (deceased donor pancreases), the process (islet isolation), and the final product (islet preparation) must meet pre-established quality criteria.[47]

The Clinical Islet Transplantation Consortium is currently conducting phase III licensure trials on islet transplantation alone and islet after kidney transplantation in T1DM.[48,49] Sponsored by the United States National Institute of Allergy and Infectious Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases, these trials were designed as registration trials to apply for a biological license by the US FDA (Dr. Shapiro, personal communication, May 2011). This will allow islet transplantation to be recognized as standard medical care for brittle T1DM patients and is mandatory for reimbursement by medical insurances.

Diffusion of technology

Alberta

The clinical islet transplantation program at the University of Alberta, Edmonton, is the only clinical centre in Alberta to provide islet transplantation for patients with T1DM (see section S for more details).

Canada

The University of Alberta, Edmonton, and the University of British Columbia, Vancouver, are the only two clinical centres in Canada to provide clinical islet transplantation programs for patients with T1DM (see section S for more details).

International

Since 1999, the Collaborative Islet Transplant Registry (CITR) collects and monitors comprehensive data on allogeneic islet transplantation in North America, Europe, and Australia. Twenty-eight of 32 US/Canadian medical institutions, active in islet transplantation since 1999, and three European and two Australian Juvenile Diabetes Research Foundation-sponsored centres, participate in the registry.[50]

Worldwide, 47 centres perform islet transplantation (18 of those perform islet auto-transplant, as well). Eleven of those (seven in Europe and four in North America) perform more than 20 transplantation procedures per year. More than half of the islet transplantation procedures were performed by these 11 centres.[51]

Of the 1200 islet allo-transplantations performed worldwide, 700 were performed after the introduction of the Edmonton protocol.[51] The total number of islet transplantation procedures performed in the centres of Gissen, Germany, and Edmonton, Canada, has recently reached 100 at each centre.[52]

Because of the high cost of establishing an islet preparation laboratory, some clinical islet transplantation centres develop collaborative networks with islet isolation labs in the United States (for example, Huston–Miami) and Europe (for example, the GRAGIL network).[6]

Methodology

Literature search

A comprehensive literature search was conducted to identify the most recent systematic reviews/HTAs and primary studies that examined the safety and efficacy/effectiveness of islet transplantation for the treatment of patients with T1DM. A detailed description of the literature

search strategy, including data sources, dates searched, and search terms used, is provided in Appendix T.A.

Study selection

One reviewer (BG) screened titles and abstracts from the literature search and retrieved full-text publications of relevant articles. Two reviewers (BG and PC) determined eligibility of key studies (that is, systematic reviews/HTAs and primary studies) according to the predefined inclusion and exclusion criteria (see Appendix T.A). Excluded studies are listed in Appendix T.B.

Methodological quality assessment

Two reviewers (BG and PC) assessed independently the methodological quality of the included primary studies, using the Downs and Black checklist[53] to appraise the quality of the comparative studies and the IHE case series quality assessment checklist to appraise the quality of the case studies (see Appendix T.C). The reviewers discussed the questions prior to assessing the studies. The two reviewers compared quality assessment results and resolved discrepancies by discussion.

Data extraction and synthesis

Information about the safety and treatment effects of islet transplantation in patients with T1DM was extracted from the included studies according to pre-developed data extraction forms (see Appendix T.A). Data were described and integrated utilizing a narrative approach.

Description of the Included Studies

Characteristics of the included studies

The literature search identified 1352 citations using the search strategy described in Appendix T.A. On closer examination of the full text articles that appeared to be potentially relevant, two systematic reviews,[3,54] six non-randomized comparative studies with eight publications,[27,55–61] and 13 case series studies with 20 publications[10,12,15,18,20,22,24,62–74] met the inclusion criteria and were selected for analyses and synthesis. Excluded systematic reviews and primary studies and the reasons for their exclusion are listed in Appendix T.B.

Of the two systematic reviews, one review[3] focused on the safety and efficacy of islet transplantation alone (ITA) in the treatment of T1DM patients without end-stage renal failure, and the other review[54] focused on patient-reported outcomes. The information from these two reviews is considered insufficient to address the broader questions of the present report. Thus, evidence about safety and treatment effects of islet transplantation in both uremic and non-uremic patients comes mainly from the six comparative studies (with eight publications) and 13 case series studies (with 20 publications), which are referred to as key studies hereinafter. Independent methodological quality assessment and detailed data extraction were conducted for these key studies (Appendices T.C to T.E). Another 10 studies reported safety outcomes from the clinical centres where their main results were already reported in the included key studies; these studies are referred to as safety-only studies hereinafter. Data from these safety-only studies are supplementary to the key studies. The main findings from the safety-only studies are briefly summarized in Appendix T.F and in the text, but no quality assessment was conducted for these studies.

Characteristics of the comparative studies

As shown in Table T.1, for non-uremic patients with T1DM, two studies[55,56] compared islet transplantation alone (ITA) with intensive insulin therapy (IIT). No study was found that compared ITA with pancreas transplantation alone in this group of patients.

For uremic patients with T1DM, one study[57] compared simultaneous islet and kidney transplantation (SIK) with simultaneous pancreas and kidney transplantation (SPK), which is the treatment of choice for patients with end stage renal disease. However, no study was found that specifically compared islet after kidney transplantation (IAK) with SPK. One study with three publications[27,58,59] compared IAK or SIK with SPK or intensive insulin therapy.

The other two studies[60,61] included a mix of non-uremic and uremic patients and compared ITA or IAK with IIT,[60] SPK, or pancreas after kidney transplantation (PAK).[61]

Outcome measures varied across these comparative studies, including short-term graft function and glycemic control outcomes, intermediate- or long-term outcomes of diabetic complications, and patient survival with a follow-up ranging from 1 year to more than 5 years.

Table T.1: Characteristics of the included comparative studies

Study	Patient (N)	Intervention/ comparator	Main outcome measures				Length of follow-up
			Glycemic control	SH	HrQoL	Diabetic complications	
Warnock et al. 2008[55]	Non-uremic (42)	ITA/IIT	√	×	×	√	Up to 5 years
Venturini et al. 2006[56]	Non-uremic (20)	ITA/ IIT	√	×	×	√	1 year
Gerber et al. 2008[57]	Uremic (38)	SIK/SPK	√	√	×	√	Up to 5 years
Fiorina et al. 2005[58]	Uremic (42)	IAK/IIT	√	×	×	√	3 years
Fiorina et al. 2005[27]	Uremic (234)	IAK or SIK/SPK or IIT	√	×	×	√	Up to 6 years
Fiorina et al. 2003[59]	Uremic (241)	IAK or SIK/SPK or IIT	√	×	×	√	Up to 5 years
Vantyghem et al. 2009[60]	Non-uremic + uremic (30)	ITA or IAK/IIT	√	√	×	√	Up to 3 years
Frank et al. 2004[61]	Non-uremic + uremic (43)	ITA or IAK/SPK or PAK	√	×	×	×	Up to 2.5 years

Abbreviations: IAK – islet after kidney transplantation; IIT – intensive insulin therapy; ITA – islet transplantation alone; PAK – pancreas after kidney transplantation; SH – severe hypoglycemia; SIK – simultaneous islet and kidney transplantation; SPK – simultaneous pancreas and kidney transplantation

Characteristics of the case series studies

Table T.2 summarized characteristics of the included case series studies conducted at different clinical islet transplantation centres. Case series from the same clinical centre with different outcome measures are considered the same study with multiple publications. Some studies were conducted at the same clinical centre but patients groups were completely different. For example, the GRAGIL trial 1 included 10 uremic patients who received IAK,[70] and the GRAGIL trial 2 included 10 non-uremic patients who received ITA.[12] A recent study[20] reported QoL outcomes of the two patient groups (GRAGIL trial 1 and 2). Such studies are considered as two separate studies with three publications.

There are one international multicentre trial[10] that involved nine clinical centres and three European multicentre trials with four publications.[12,20,69,70] Other studies are single-centre studies with the patient numbers ranging from 10 to 99. Half of the case series studies included non-uremic patients who received ITA, while three studies with four publications[67–70] focused on uremic patients who received IAK and the other three[20,64,65] included both uremic and non-uremic patients. Most studies reported graft function/glycemic control outcomes, a few reported secondary complications of diabetes, and four studies[20,62,64,72] focused on health-related QoL outcomes.

Table T.2: Characteristics of the included case series studies

Centre	Study	Patients (N)	Intervention	Main outcome measures	Length of follow-up
International	Shapiro et al. 2006[10]	Non-uremic (36)	ITA	Glycemic control	2 years
Edmonton	Ryan et al. 2005[15]	Non-uremic (65)	ITA	Glycemic control	Up to 5 years
	Toso et al. 2007[62]	Non-uremic (99)	ITA	HrQoL	Up to 3 years
	Koh et al. 2010[22]	Non-uremic (97)	ITA	Glycemic control	3 years
Miami	Froud et al. 2005[63]	Non-uremic (16)	ITA	Glycemic control	Up to 3 years
	Tharavanij et al. 2008[64]	Uremic + non-uremic (40)	ITA + IAK	HrQoL	Up to 6 years
	Leitao et al. 2008[65]	Uremic + non-uremic (31)	ITA + IAK	Restoration of hypo-awareness	4 years
Milan	Maffi et al. 2007[66]	Non-uremic (19)	ITA	Renal function	2 years
	Fiorina et al. 2003[67]	Uremic (36)	IAK	Renal function	Up to 7 years
	Fiorina et al. 2003[68]	Uremic (34)	IAK	Cardiovascular	Up to 3 years

	Bertuzzi et al. 2002[69]	Uremic (15)	IAK	Glycemic control	1 year
GRAGIL	Benhamou et al. 2009[20]	Uremic + non-uremic (20)	ITA + IAK	HrQoL	1 year
	Badet et al. 2007[12]	Non-uremic (10)	ITA	Glycemic control	Up to 3 years
	Benhamou et al. 2001[70]	Uremic (10)	IAK	Glycemic control	1 year
Houston	Lee et al. 2005[71]	Non-uremic (12)	ITA	Retinopathy	1 year
	Barshes et al. 2005[72]	Non-uremic (10)	ITA	HrQoL	1 year
Atlanta	Turgeon et al. 2010[18]	Non-uremic (12)	ITA	Glycemic control	Up to 3 years
Chicago	Gangemi et al. 2008[24]	Non-uremic (10)	ITA	Glycemic control	1 year
Belgium	Keymeulen et al. 2006[73]	Non-uremic (24)	ITA	Glycemic control	1 year
France	Vantyghem et al. 2009[74]	Non-uremic (14)	ITA	Glycemic control	Up to 3 years

Abbreviations: IAK – islet after kidney transplantation; ITA – islet transplantation alone; HrQoL – health-related quality of life

Methodological quality of the included studies

Quality of the comparative studies

Methodological quality of the six comparative studies (with eight publications) was assessed using the modified Downs and Black checklist[53] with a total possible score of 27 (Appendix T.C).

As shown in Table T.C.1, none of the studies met 20 or more criteria (75% of total score). Four studies[57,58,60,61] that met 14 to 16 criteria were considered of moderate quality, and the other two studies,[55,56] which met less than half of the criteria, were considered of poor quality.

Of the four domains (reporting, external validity, internal validity, and power), rating in the reporting domain was better than in the other three domains. Except for one study,[61] almost all studies did not meet any criterion in the external validity domain, and none of the studies demonstrated sufficient power to detect a clinically important effect. Only one study[58] met more than half of the 12 items in the internal validity domain.

Overall, quality assessment revealed considerable methodological limitations associated with the included comparative studies. Caution should be taken when interpreting results from these studies.

Quality of the case series studies

Methodological quality of the 13 case series studies (with 20 publications) was assessed using the IHE checklist and results are presented in Table T.C.2 (see Appendix T.C).

As shown in Table T.C.2, seven publications[10,12,24,69,70,73,74] that met 15 or more criteria were considered of good quality; two publications[62,75] that met less than 10 criteria were considered of poor quality; the other 11 publications were considered of moderate quality.

Five of the 18 criteria, including prospective data collection, multicentre trial, consecutive patients, before- and after-outcome measurement, and number lost to follow-up, are considered most important in the context of islet transplantation clinical research. All studies measured main outcomes before and after the intervention and reported on patients lost to follow-up, but only four studies[18,24,73,74] clearly reported that consecutive patients were included. Some studies did not clearly state whether they were prospective or retrospective, making it difficult to determine their study design. While most studies were single-centre studies, one was an international multicentre trial[10] and three were European multicentre studies with four publications.[12,20,69,70]

Safety Profile of Islet Transplantation

Evidence from comparative studies—comparative safety

Non-uremic patients

For this group of patients, no study was found that compared ITA with PTA, precluding the comparison of safety profiles between these two procedures in terms of procedure- or immunosuppression-related adverse events.

Of the two studies[55,56] that compared ITA with intensive insulin therapy, none reported any procedure-related adverse events (see Table T.D.2) One study[55] reported that immunosuppression withdrawal due to side effects occurred in 12% of the patients; however, no comparisons can be made as immunosuppression-related adverse events are not relevant to intensive insulin therapy.

Uremic patients

As shown in Table T.D.2, one study[57] that included 13 SIK recipients and 25 SPK recipients showed a significantly higher frequency of procedure-related adverse events following SPK than SIK. While only two minor intraperitoneal bleeds without the need for surgery occurred in the SIK group, 40% of the SPK recipients required surgery for their complications, including two major bleeding events. No information was available in terms of immunosuppression-related adverse events in either group.

The other study with three publications[27,58,59] did not report any procedure- or immunosuppression-related adverse events.

Mix of uremic and non-uremic patients

Two studies[60,61] included both uremic and non-uremic patients. One study[60] found a four-fold higher total adverse event rate in the islet transplantation (ITA or IAK) group than in the intensive insulin therapy group (see Table T.D.2). Impaired renal function was found in up to 23% of the patients in the islet transplantation group, but no comparison can be made to intensive insulin therapy.

The other study[61] that compared islet transplantation with pancreas transplantation showed that while whole pancreas transplantation was associated with a higher frequency of procedure-related adverse events (intraperitoneal bleeding and the requirement for post-transplant surgery), islet transplantation recipients had more immunosuppression-related complications such as mouth ulcer (in all nine ITA recipients), mild renal function decline, and skin cancer (see Table T.D.2). CMV infection was found in three pancreas transplantation recipients, but not in ITA recipients.

Evidence from the case series studies

Safety data extracted from the included case series studies are summarized in Table T.E.1 and Table T.E.2 (see Appendix T.E).

Non-uremic patients

As shown in Table T.E.1, none of the studies reported any perioperative deaths that could be directly related to the islet transplantation procedure.

In terms of **procedure-related adverse events**, acute intraperitoneal bleeding occurred in 9% of the 77 procedures in the international multicenter trial[10] and 23% of the Edmonton series of 65 patients.[15]

Portal vein thrombosis (mostly partial) occurred in 5% to 10% of patients in some studies, but in four studies no such event was reported to have occurred.[24,63,73,74]

Transient elevation of liver enzymes was common, occurring in 100% of patients in some studies. Hepatic steatosis (liver fatty tissues presenting on imaging) following the ITA procedure was observed in 31% of the 36 patients in the international trial[10] and in 8% (at the Miami centre)[63] to 22% (at the Edmonton centre) [15] of the patients who underwent imaging tests.

In terms of **immunosuppression-related adverse events**, statistically (but not all clinically) significant decline of renal function in patients was observed in some studies following immunosuppressive therapy.[10,15,24,63,66,73,74] The immunosuppressive drugs used in the original Edmonton protocol (high-dose sirolimus and low-dose tacrolimus) had to be switched to an alternative immunosuppressive regimen (for example, MMF) in some patients because of the drugs' side effects.

As shown in Table T.E.1, other types of complications are common. In the international multicentre trial[10] the most commonly reported non-serious adverse events included mouth ulcers (92%), anemia (81%), leucopenia (75%), diarrhea (64%), headache (56%), neutropenia (53%), nausea (50%), vomiting (42%), acne (39%), and fatigue (39%). This study noted that, while the frequency of mouth ulceration, anemia, and leucopenia was high, the frequency of immunosuppression-related complications was similar to that typically seen in solid organ transplantation. This study did not report any post-transplantation lymphoproliferative disease, cancer, opportunistic infections, or disease related to cytomegalovirus or Epstein-Barr virus. However, cancer and CMV infections were reported in other single-centre studies.[15,63]

Uremic patients

Of the three studies that included uremic patients only, one study with two publications[67,68] did not report any procedure- or immunosuppression-related adverse events. Another study[69] reported two bleedings but no immunosuppression-related complications. In the GRAGIL trial 1,[70] intraperitoneal bleeding and elevated liver enzymes occurred in some patients, and two patients developed anti-GAD (anti-glutamic acid decarboxylase) and IA-2 (insulinoma antigen-2) antibodies and lost graft function.

Evidence from safety-only studies

Data extracted from the 10 safety-only studies are summarized in Table T.F.1 (see Appendix T.F). The total number of patients included in these studies ranged from 11 to 67. Seven of the 10 studies

reported adverse events in non-uremic patients after ITA, while the other three studies[76–78] also reported adverse events in uremic patients who had received IAK or SIK.

Procedure-related AEs

Of the four studies[76,77,79,80] that reported procedure-related adverse events, no deaths were reported following ITA. Intraperitoneal bleeding occurred in 12% of the Miami series of 26 patients[77] and 25% of the Edmonton series of 67 patients;[79] both studies were published in 2005. Portal vein thrombosis occurred in patients in 3.8% of all ITA procedures in the Edmonton series[79], while none occurred in another two studies.[77,80] Elevated AST or ALT was reported in 100% of the ITA recipients in two studies.[77,80]

Immunosuppression-related AEs

While one study[77] provided a comprehensive list of immunosuppression-related adverse events, other studies reported a specific adverse event, such as decline of renal function, presence of ovarian cysts, CMV infection, or Graves hyperthyroidism following islet transplantation.

Decline in renal function was reported in the Edmonton series of 41 patients[81] and in the Miami series of 35 patients.[82] Both studies reported an increased number of patients with microalbuminuria after islet transplantation. Estimated GFR declined in the Edmonton series but not in the Miami series.

Ovarian cysts were observed in about 60% of female ITA recipients in two studies,[77,83] and one study[77] reported that 43% of female patients presented with clinically significant ovarian cysts between one and 21 months after islet transplantation.

CMV infection was reported in 13% of 23 ITA recipients (Vancouver)[84] and in 60% of 48 IAK or SIK recipients (in this study, a post-transplant CMV reactivation was defined as a positive qualitative CMV–DNA–PCR) (Giessen).[78]

One study[85] reported the occurrence of Graves hyperthyroidism in four of the 13 patients (31%) after they stopped the immunosuppressive regimen.

Summary

Evidence on the safety of islet transplantation is very limited from the included comparative studies because of the lack of direct comparisons between ITA and PTA in non-uremic patients, and between IAK and SPK (the recommended treatment for patients with end stage renal failure). Available evidence suggests that, compared to intensive insulin therapy, islet transplantation is associated with a higher risk of procedure-related complications. Compared to pancreas transplantation, islet transplantation resulted in fewer and less severe procedure-related complications but in a higher frequency of immunosuppression-related complications.

Evidence from case series studies suggested that islet transplantation procedure-related complications were manageable and improved over time. Complications such as elevation of liver enzymes were transient and of no clinical significance. On the other hand, immunosuppression-related adverse events were common and affected hematologic, metabolic, neurologic, ophthalmologic, gastrointestinal, dermatologic, renal, and gynecologic systems, which sometimes led to a change or discontinuation of the immunosuppressive treatment.

Treatment Effects of Islet Transplantation

Evidence from comparative studies

For non-uremic patients

Description of the included studies

Two studies[55,56] reported treatment effects of ITA compared to intensive insulin therapy in non-uremic patients with T1DM (see Table T.3). Details extracted from the two studies are presented in Table T.D.4 (see Appendix T.D).

The study[55] conducted in Vancouver, Canada was a single-centre, prospective, crossover study. This study included 42 patients (the control group) who received intensive insulin therapy; 31 of them (the transplantation group) then received islet transplantation procedures. The two groups were comparable in terms of age, weight, BMI, and duration of diabetes. However, the HbA1c level was lower in the transplantation group immediate prior to islet transplantation than that in the control group at entry into intensive insulin therapy.

Of the 31 patients who received a total of 70 (range 1 to 4) islet transplantation procedures, 20 patients also received exenatide, a glucagon-like peptide-1 (GLP-1) analogue.

The other study,[56] conducted in Milan, Italy, included 20 patients; 10 patients received ITA and 10 received intensive insulin therapy (no details were provided). The two groups were comparable in terms of age, gender distribution, BMI, and duration of diabetes; however, baseline insulin requirement and HbA1c levels were higher in the patients treated with insulin therapy than in the patients who received islet transplantation.

Glycemic control

The Vancouver study[55] reported that 16 of 25 patients who completed the ITA procedure remained insulin independent; four of them maintained insulin independence at 3 to 5 years post-transplant. During an up-to- 5-year follow-up, ITA recipients had lower HbA1c levels than did the patients treated with intensive insulin therapy. Thirty-eight percent of the 31 ITA recipients experienced partial loss of islet graft function and resumed insulin therapy with reduced daily insulin requirements (33% to 75% of their pre-transplant doses).

The Milan study[56] showed that, at 1-year follow-up, a statistically significant increase in C-peptide secretion, a reduction of mean HbA1c levels from 7.95% to 7.50% (the difference of 0.45% is not considered clinically significant), and a reduction of the mean insulin requirement from 31.1 to 20.3 units/day (a 35% reduction of the pre-transplant doses) were observed in the ITA group, but no changes in these parameters were observed in the intensive insulin therapy group. Insulin independence rate was not reported.

Table T.3: Treatment effect of ITA in non-uremic patients with T1DM

	Warnock et al. 2008[55*]	Venturini et al. 2006[56**]
No. of patients	N = 42 (ITA 31 vs. IIT 42)	N = 20 (ITA 10 vs. IIT 10)
No. of islet infusions	Total 70 (range 1–4)	Total 18 (range 1–3)
Immunosuppression	ATG, SIR, or MMF and TAC	Edmonton protocol: DAC, SIR, TAC
Co-intervention	Exenatide in 20 ITA recipients	NA
Length of follow-up	Up to 5 years	1 year
Glycemic control		
HbA1C (%)	Median value for ITA lower than IIT during all time periods Pooling all numbers during follow-up: ITA: 6.6 vs. IIT 7.4 (P<0.01)	ITA: 7.95±0.29 pre- vs. 7.50±0.46 at 1 year (P=0.06) IIT: 8.28±0.36 pre- vs. 8.15±0.22 at 1 year (NS)
Insulin requirement (U/day)	38% of ITA recipients returned to insulin therapy. Patients with partial graft function took 33% to 75% of pre-transplant doses.	ITA: 31.1±4.2 pre- vs. 20.3±5.5 at 1 year (P=0.06) IIT: 49.0±3.51 pre- vs. 48.0±4.05 at 1 year post: (NS)
Hypoglycemia	N/A	N/A
HrQoL	N/A	N/A
Diabetic complications		
Cardiovascular disease	N/A	No significant change in blood pressure, cholesterol, triglyceride, or glycemia in either group
Retinopathy	Progression occurred in ITA 0/51 eyes vs. IIT 10/82 eyes (P<0.01)	Blood flow velocity of central retinal artery and central retinal vein: increased in ITA (ss) but not in IIT group (NS)
Nephropathy	Decline of GFR (mL/min/month): ITA 0.12±0.7 vs. IIT 0.45±0.7 (P=0.1).	NA
Neuropathy	No significant deterioration from baseline to 1 year in either group.	NA

*Data are expressed as mean ± SD; **Data are expressed as mean ± SE

Abbreviations: ATG – antithymocyte globulin; DAC – daclizumab; GFR – glomerular filtration rate; HrQoL – health-related quality of life; IIT – intensive insulin therapy; ITA – islet transplantation alone; MMF – mycophenolate mofetil; N/A – not available; No – number; NS – not significant; SIR – sirolimus; ss – statistically significant; TAC – tacrolimus; U – unit; vs. – versus

Prevention of hypoglycemia

None of the two studies reported the frequency or severity of hypoglycemia episodes prior to or after ITA.

HrQoL

Although improved health-related quality of life is considered an important benefit of islet transplantation over intensive insulin therapy, neither of the two studies reported any HrQoL outcomes.

Diabetic complications

Both studies examined the effects of islet transplantation in preventing or reversing diabetic complications in the heart, kidneys, eyes, and nerves (see Table T.3).

One study[56] looked at several cardiovascular risk factors and found no significant changes in blood pressure, cholesterol, triglyceride, or glycemia in both groups during one-year follow-up. No information was available regarding cardiovascular outcomes such as cardiovascular events or cardiac death, probably due to the short follow-up period.

In terms of retinopathy, one study[55] showed a significant reduction in the progression of retinopathy in the ITA group compared to the IIT group during an up-to- 5 years follow-up. The other study[56] showed a significant increase in the blood flow velocity of the central retinal artery and vein in the ITA group but not in the IIT group.

With regard to renal function, one study[55] showed that the glomerular filtration rate (GFR) declined in both groups; the difference between the two groups was not statistically significant. While not observed in the ITA group, the slope of GFR decline in the IIT group differed from 0 and was faster than expected for the general population.

The Vancouver study[55] observed no significant difference between the two groups in neuropathy measured by nerve conduction velocity during the first 12 months post-transplant.

Summary

Evidence from two non-randomized comparative studies[55,56] suggested that, while insulin independence was not sustained in most non-uremic patients who received one to four islet transplantation procedures, ITA was associated with increased C-peptide secretion, reduction of HbA1c levels, and reduced daily insulin requirement. However, neither of the two studies reported on prevention of severe hypoglycemia and health-related quality of life outcomes, which are the two major problems associated with intensive insulin therapy.

Although measurements were different, both studies were consistent in showing improved retinopathy during short- to intermediate-term follow-up. Evidence from one study did not reveal any statistically significant differences in the progression of nephropathy and neuropathy between ITA and IIT groups.

No evidence was available about the short-, intermediate-, or long-term effects of ITA on preventing or reversing cardiovascular complications of diabetes.

For uremic patients

Description of the included studies

Two studies[27,57–59] focused on uremic patients who had received kidney transplantation (see Table T.D.1).

One retrospective study[57] compared simultaneous islet and kidney (SIK) transplantation with simultaneous whole pancreas and kidney (SPK) transplantation in T1DM patients with end stage renal disease. In this study, patient selection for SIK (13 patients) or SPK (25 patients) was determined by careful evaluation of potential advantages and disadvantages, with special consideration given to patient age and comorbidities. Patients at higher risk of intraoperative complications were preferentially assigned to the less invasive procedure of islet transplantation, whereas younger, healthier patients were offered both treatment options. The two groups were similar in terms of baseline BMI and HbA1c levels. However, compared to the SPK recipients, the SIK recipients were older and had had diabetes for a longer duration (see Table T.D.1, Appendix T.D).

The other study with three publications[27,58,59] compared treatment effects of islet transplantation (either IAK or SIK) with SPK or kidney transplantation only on various outcome measures. Because patients in the kidney transplantation-only group were also treated with IIT, for the purposes of the present report, this group served as one of the comparators—intensive insulin therapy. These publications reported on difference outcomes, thus, data were extracted from all three articles (see Table T.D.5, Appendix T.D).

As shown in Table T.D.5, a great deal of patient overlap occurred in the three publications. [27,58,59] One publication[59] separately reported the outcomes of successful as well as unsuccessful islet transplantation, but in the other two publications[27,58] the kidney transplantation-only (IIT) group included not only those who had only received kidney transplantation but also those who had had failed islet or pancreas transplantation; the results of such groups were compared with the results of patients who had had successful islet transplantation. Caution is needed when interpreting the results from these three publications. The following section focused on the study that compared SIK with SPK.[57]

SIK versus SPK

As shown in Table T.D.5, the study[57] that compared SIK with SPK showed much higher insulin independence rates at one year in the SPK group (96%) than in the SIK group (31%). Stimulated C-peptide levels were significantly higher in the SPK group than in the SIK group. Insulin requirements were reduced to 50% of pre-transplant doses in the SIK group. HbA1c levels were reduced from pre-transplant levels in both group (from 8.1±1.5 and 8.7±1.9 to 6.2±0.8 and 6.0±0.6, respectively) at 1 year post-transplant and remained stable over 3 years. The HbA1c values between the two groups did not differ at baseline and during follow-up. Ten of the 13 SIK recipients experienced severe hypoglycemic episodes prior to islet transplantation, but no such episodes occurred in any patient post-transplant.

This study also found a tendency toward better renal function (as measured by GFR) of the transplanted kidney in the SPK group, which may be attributed to the significantly lower donor and recipient ages in this group. In addition, despite a much higher insulin independence rate and a younger age in the SPK group, the post-transplant cardiovascular risk profile (blood pressure, lipid profile, and HbA1c level) was not significantly different between the two groups.

This study demonstrated that SPK transplantation resulted in a much higher rate of insulin independence, at the cost of more surgical complications, than did SIK transplantation. Glycemic control (HbA1c) was comparable in both groups. According to the authors, endogenous insulin production by transplanted islets combined with optimal insulin therapy seems to be sufficient for maintenance of near-normal glucose levels and prevention of severe hypoglycemia, which should be the primary goals of islet transplantation. Given the organ shortage, the primary goal should not be to achieve the same rate of insulin independence as in whole pancreas transplantation, but to achieve a significant improvement in glucose control through a much less invasive procedure.

For mixed uremic and non-uremic patients

Description of the included studies

Two studies[60,61] included both uremic or non-uremic patients. One study[60] compared islet transplantation (ITA or IAK) with intensive insulin therapy using implantable insulin pumps and the other study[61] compared islet transplantation (ITA or IAK) with whole pancreas transplantation (SPK or PAK). Results were not separately reported for ITA.

Islet transplantation versus insulin pump therapy

The study by Vantyghem et al.[60] compared clinical outcomes of 13 consecutive islet transplantation recipients (6 IAK and 7 ITA) using the Edmonton protocol with 17 consecutive patients who received insulin pump therapy during a 3-year follow-up. The two groups did not differ significantly in terms of mean age, gender distribution, weight, diabetes duration, insulin requirement, renal function, HbA1c levels, or frequency of diabetic complications (see Table T.D.1, Appendix T.D).

Insulin independence was achieved in 77% of the 13 islet transplantation recipients. While HbA1c decreased significantly from the baseline level in both groups, insulin requirements and the frequency of severe hypoglycemia episodes decreased significantly from baseline only in the islet transplantation group. No information was available regarding health-related quality of life and diabetic complication outcomes.

Islet transplantation versus pancreas transplantation

A retrospective study[61] analyzed a consecutive series of whole pancreas transplantations and islet transplantations performed at a single centre. The study compared results from 13 islet transplantation recipients (nine ITA and four IAK) with 30 pancreas transplantation recipients (25 SPK and five PAK). No comparison was available for ITA with PTA in non-uremic patients. The two groups were similar in terms of age, gender, BMI, and duration of diabetes, but the percentage of patients with a history of dialysis was much higher in the pancreas transplantation group than in the islet transplantation group (73.3% vs. 0).

Compared to the donors for pancreas transplantation, donors for islet transplantation were significantly older and heavier, with the majority of donors (93%) having steatosis of pancreas. All pancreata used for islet transplantation were rejected for use in pancreas transplantation, indicating better donor quality for pancreas transplantation than for islet transplantation.

No statistically significant difference was observed between the two groups in terms of patient survival and graft survival. Pancreas transplantation was statistically superior to islet transplantation (as evidenced by C-peptide levels, HbA1c levels, and insulin requirements) and in the duration of insulin independence achieved if partially functioning islet grafts were included.

According to the authors, because donor pancreata that are unsuitable for pancreas transplantation can often be used successfully for islet transplantation, islet transplantation should continue to be evaluated as a complementary alternative rather than as a replacement for the better-established pancreas transplantation.

Evidence from case series studies

Glycemic control

As shown in Table T.E.3 and Table T.E.4, insulin independence rates reported in the included case series studies varied from 20% to 69% at 1 year post-transplant, 13% to 31% at 2 years post-transplant, and 7.5% at 5 years post-transplant.

In all studies, HbA1c levels were reduced following islet transplantation, even in patients with partial graft function. In patients who achieved insulin independence, the HbA1c levels could return to normal ranges. In insulin-dependent patients, HbA1c levels were also significantly reduced with a lower dose of insulin therapy. In the international multicentre study,[10] during a 24-month follow-up, mean HbA1c levels were under 6.0% in patients who achieved insulin independence and under 7.0%

for patients with partial graft function. The Edmonton study[15] demonstrated well controlled HbA1c in those patients who remained off insulin and even in those who resumed insulin but who were C-peptide positive (indicating partial graft function), than in those who had lost all graft function. These results suggest that persistent islet function, even without insulin independence, could provide the benefits of improved glycemic control.

Hypoglycemia

As demonstrated by the information in Table T.E.3, in the case series studies that reported results on hypoglycemia, patients who achieved insulin independence were completely free from hypoglycemia episodes. Hypoglycemia episode occurred in some patients who were still on insulin therapy, but with reduced severity because of their decreased insulin requirement.

HrQoL

Four case series studies (conducted in Edmonton,[62] Miami,[64], Houston,[72] and in the GRAGIL trials 1 and 2[20]) compared HrQoL measurements after islet transplantation with baseline values. The HrQoL measurement tools used in these studies are summarized in Table T.4.

Table T.4: HrQoL measurement tools used in the key studies

Tool	Domain	Scoring
Generic tools		
Short Form (36) Health Survey (SF-36)	Eight domains: • vitality • physical functioning • bodily pain • general health perceptions • physical role functioning • emotional role functioning • social role functioning • mental health	0–100
Health Status Questionnaire (HSQ) Adapted from SF-36 with the same questions and scoring algorithm except as relating to body pain. Validated with good consistency and reliability.	Eight domains: • health perception • physical functioning • role limitation-physical health • role-limitation emotional problems • social functioning • mental health • bodily pain • energy or fatigue	0–100 (from worst to best)
Health Utility Index Mark2 (HUI2)	Six domains: • sensation (vision, hearing, speech) • mobility • emotion (anxiety) • cognition • self-care • pain/discomfort	Score range: -0.03 (worst possible health state) to 1.0 (perfect health)

Disease-specific tools		
Diabetes Quality of Life (DQoL) Previously validated in T1DM patients.	Three domains: • satisfaction of treatment • impact of therapy • worry about diabetes or social and vocational aspects	0–100 (from worst to best)
Hypoglycemia Fear Survey (HFS) Validated and has demonstrated good test–retest stability.	27 items: The first half of the questionnaire asks respondents to use Likert-type scales to rate how hypoglycemia or concerns about hypoglycemia cause anxiety. The second half of the questionnaire asks how respondents have altered their behaviour in attempts to prevent or treat hypoglycemia.	0–100 (from no worry or behavioural modification to significant worry or behavioural modification) A higher HFS score indicates greater fear of hypoglycemia.
Fatigue questionnaire	54 items, six domains: • physical well-being • social well-being • relationships • emotional health • functional status • additional or miscellaneous aspects	

Sources: [62,64,72]

Generic

The Edmonton study[62] of 99 ITA recipients found that the HrQoL assessed with the HUI2 score remained stable overall. A decreased pain score after ITA is likely to relate to pain induced by the islet infusion itself or by side effects (for example, by sirolimus-induced mouth ulcers). Patients experienced fewer emotion problems, which was probably related to management of hypoglycemic events.

The Miami study[64] used a generic tool—the HSQ 2.0—and found significant improvements in health perception (at 1 and 6 years), physical functioning (at 3, 4, and 6 years), social functioning (at 4 and 5 years), and bodily pain (at 6 years; only five patients were available for follow-up at 6 years). A transient decrease was noted in role-limitation physical health, role-limitation emotional problems, and mental health problems at various time points, which was not sustained after adjustment for confounding factors. No significant change in energy was observed at any time.

This study showed that IAK recipients had the lowest scores in many HSQ 2.0 scales in comparison with recipients of ITA and islet with bone marrow transplantation, which might be explained by a more severe nature of the underlying disease. Patients on exenatide rated higher on the mental health and health perception scales of HSQ 2.0. Those with higher HbA1c levels had a trend toward worse scores on most HrQoL scales. Age and specific diabetic complications did not influence any HrQoL scales.

Two studies[20,72] used SF-36 to measure health-related quality of life. While the GRAGIL trial[20] found a significant improvement in the dimensions of physical functioning, role-physical, bodily pain, general health, and social functioning—yielding significant improvement in the physical component score and health transition at 6 and 12 months—the other study[72] showed a trend (not statistically significant) toward improvement in all component scores after ITA.

Disease-specific

Various tools, including DQoL (two studies), HFS (two studies), and the Fatigue Questionnaire (one study), were used to measure the changes in disease-specific aspects of quality of life.

Of the two studies that used DQoL[20,64], the GRAGIL trial[20] found a significantly improved global DQoL score (for dimensions of satisfaction and the impact of diabetes) at 6 and 12 months after ITA.

The Miami study[64] found that impact scores were higher than pre-transplant measures at all post-transplant time points. The worry scale showed a significant improvement except in the first three months after transplantation. A significant increase in the satisfaction score was observed at most time points except at 3, 30 to 42, and 72 months. No significant difference was observed in the three domains of DQoL among ITA, IAK, and islet with bone marrow transplantation, indicating no impact of protocols on DQoL.

This Miami study[64] explored factors that may have influenced HrQoL, including diabetes duration, transplantation protocols, number of islet infusions, insulin dosages, adverse events, and use of exenatide.

Two studies used HFS to measure quality of life after islet transplantation. The Houston study[72] found a significant decrease in hypoglycemia-related anxiety symptoms and hypoglycemia-induced behaviour modification after ITA. The Edmonton study[62] found a significant decrease in fear of hypoglycemia at 6, 12, and 24 months post-transplant, but an increase in the level of fear at 36 months post-transplant.

The only study[72] that used the Fatigue Questionnaire found no significant changes in fatigue-related symptoms.

The reason for minimal impact of islet transplantation on generic HrQoL might be explained by the use of generic HrQoL measurement tools, which provide more information about functional health status.[64] Disease-specific HrQoL tools such as DQoL are known to be more sensitive in detecting the negative effects of diabetic complications or changes after intervention.[64] Insulin requirements, number of islet infusions, and glucose stability had an impact on HrQoL after islet transplantation; however, a systematic evaluation of factors affecting HrQoL is still lacking.[64] Furthermore, evaluating ITA recipients whose baseline HrQoL is more clearly impaired would further clarify the impact of ITA on HrQoL.[72]

Diabetic complications

Most case series studies did not report any long-term diabetic complications. The Edmonton study[15] of 65 patients reported deterioration in eye disease in four patients following ITA. Another study[71] reported retinopathy and neuropathy in eight ITA recipients during 1-year follow-up. No progression in retinopathy was found when compared with pre-transplant measures in all eight patients, while one patient showed an improvement. No significant correlation between changes in HbA1c values and retinopathic changes. Improvement or stabilization of diabetic neuropathy was observed in 50% of the eight patients.

A study[68] that included uremic patients found the cardiovascular death rate was higher in recipients of unsuccessful islet after kidney transplants (4 of 13 patients, or 30%) than in recipients of successful islet after kidney transplant (1 of 21 patients, or 4.7%). This study also reported

significantly higher patient survival at 10 years in the recipients of successful rather than unsuccessful islet after kidney transplantations.

Findings from Systematic Reviews

Main findings extracted from the two systematic reviews[3,54] are summarized in Table T.G.1 (see Appendix T.G) and described briefly in the following section.

The review by Speight et al. and colleagues[54] included 12 case series studies; six of them were included in the present report and the other six studies did not meet our inclusion criteria (either they focused on pancreas transplantation, autologous islet transplantation, or xenotransplantation, or their patient number was fewer than 10). The methodological quality of the included studies was informally assessed and discussed, but no quality assessment checklist was used.

This review focused on patient-reported quality of life outcomes and included both uremic and non-uremic patients. Results of different interventions (ITA or IAK) were not reported separately.

Results from the included studies were mixed but demonstrated some benefits, such as improvement in fear of hypoglycemia and some aspects of Diabetes QoL and general health status, which remained apparent up to 36 months after islet transplantation. Negative impacts of islet transplantation included short-term pain associated with the procedure, immunosuppressant side effects, and depressed mood associated with loss of graft function.

This review did not identify any studies that assessed patient satisfaction with the islet transplantation procedure or any qualitative research on the impact of islet transplantation or pancreas transplantation on HrQoL.

The review identified several limitations with the included studies. None of the studies used transplantation-specific QoL measures, which may be more sensitive to detecting any benefits and disadvantages of islet or pancreas transplantation. As pointed out by the authors, such measures have not been administered in islet or pancreas transplantation research, so neither their content validity nor their psychometric properties have been established for these patient groups. The existing patient-reported outcome measures are unlikely to be sufficient to capture the full impact of islet or pancreas transplantation on HrQoL. In addition, understanding patient perceptions and their level of satisfaction with transplantation may highlight the specific advantages and disadvantages of islet transplantation or pancreas transplantation as compared to other treatment options.

The IHE 2008 review[3] focused only on non-uremic patients who had received ITA (using the Edmonton protocol or other protocols), thus the scope was narrower than that of the present report.

This review included 14 primary studies (12 case series studies and two comparative studies) and performed a formal quality assessment using a checklist for case series studies. The review covered a broad range of outcome measures, including:

- safety outcomes—procedure- and immunosuppression-related complications
- efficacy/effectiveness outcomes—insulin independence/glycemic control, HrQoL, and secondary complications of diabetes

In terms of procedure-related complications, intraperitoneal bleeding and portal vein thrombosis were reported in up to 23% of patients and in up to 17% of patients, respectively. The risks of these complications were reduced as clinical experience with the procedure increased and with the use of

prophylaxis measures. Elevated liver enzyme levels were observed in the majority of patients, but resolved spontaneously within one month after transplantation. Decline in renal function following the use of sirolimus and tacrolimus was observed in up to 50% of the patients; this sometimes led to discontinuation or change of the original immunosuppressive regimen.

Transplantation of an adequate mass of islet cells (usually from two to three pancreas donors) could restore insulin independence in the short-term (one year or less) with adequate glycemic control in 30% to 69% of the patients; however, islet function appeared to deteriorate over time. In the international multicentre trial, only 14% of the patients remained insulin independent at two years. The Edmonton 5-year follow-up study reported that less than 10% of patients remained insulin free at 5 years, while 82% of patients maintained some graft function as measured by C-peptide secretion. Partial islet function with reduced insulin requirement provides protection from severe hypoglycemia and improved glycemic control.

Two studies demonstrated a reduction in fear of hypoglycemia, but improvements in overall HrQoL measures were inconsistent. In addition, two small studies showed an improvement in diabetic retinopathy and neuropathy 1 year after ITA. The review did not identify any study that compared ITA with IIT in patients with severe hypoglycemia or hypoglycemia unawareness. No study directly compared ITA with PTA in non-uremic patients.

These results suggest that ITA may be effective in a small group of highly select patients for whom the benefits of stable glycemic control and freedom from hypoglycemia outweigh the potential risks of islet transplantation. However, these studies, due to their weak design, are subject to biases and hence preclude any firm conclusion about these outcomes.

Evidence from CITR

Since 1999 the Collaborative Islet Transplant Registry (CITR) continues to collect and monitor comprehensive data on allogeneic islet transplantation in North America, Europe, and Australia.[86] Information from the most recently published annual report[50] is summarized below.

As of April 2009, 28 North American CITR centres had performed a total of 783 islet transplantations on 408 recipients; detailed information was available for 637 islet infusions on 329 adult recipients. Three European and two Australian CITR centres had performed islet transplantation on 183 recipients; detailed information was available for 83 recipients. The 2009 CITR annual report presented results from 412 recipients who had received 828 islet transplantation procedures derived from 905 pancreas donors.

All islet transplant recipients were between 18 and 65 years of age, had had T1DM for longer than 5 years, and had poor diabetes control, including episodes of severe hypoglycemia and hypoglycemia unawareness, wide swings in blood glucose levels, or consistently high HbA1c levels (> 8%).

The number of US/Canadian (North American) islet transplantation centres has declined from a peak of 23 in 2005, down to 15 in 2008. CITR-participating centres decreased from 20 in 2005 to 14 in 2008. Correspondingly, the number of North American islet transplantation recipients decreased from 65 in 2005 to 32 in 2008.

As shown in Table T.5, of the 412 recipients, the majority (86%) received ITA; 14% received a kidney transplant before the islet transplant. The total number of islet infusions ranged from one to four, with half of the patients receiving two infusions. Over the last 5 years, immunosuppressive

regimen has undergone substantial shifts away from anti-interleukin 2 induction and sirolimus/tacrolimus maintenance.

Table T.5: Summary of the 2009 CITR data[50]

	Outcomes
No. of recipients	412 adults
Recipient characteristics: mean (range)	Age: 44 (19 to 67) % female: 63% Duration of DM: 28 (2 to 54) Weight: 66 (35 to 98) kg BMI: 24 (16 to 32)
Type of procedure	ITA: 347 (86%) recipients; IAK: 65 (14%) recipients
No. of infusions	1 infusion: 107 (26%) 2 infusions: 202 (49%) 3 infusions: 95 (23%) 4 infusions: 8 (2%)
Adverse events (Both ITA and IAK recipients)	
No. of serious AEs	N = 592 • life threatening: 29% • requiring inpatient hospitalization: 52% • related to islet transplantation procedure: 25% • related to immunosuppressive treatment: 29% • resolved with no residual effects: 82%
Death	9 deaths: • viral meningitis: 1 • stroke: 2 • drug toxicity: 1 • acute respiratory distress syndrome: 1 • pneumonia: 1 • diabetic ketoacidosis: 1 • atherosclerotic coronary artery disease: 1 • unknown cause: 1
Neoplasms	21 recipients: • procedure-related – 0 • may have been related to immunosuppression medications – 9 • basal cell carcinoma – 2 • squamous cell carcinoma – 3 • breast cancer (1) • ovarian cysts (1) • papillary thyroid cancer (2)
Most common AEs	Within the first year after transplantation: • elevated liver function tests: 13.1% • neutropenia: 9.1% • procedural hemorrhage: 6.4% • abdominal pain: 3.3%

	• diarrhea: 2.7% • lymphopenia: 2.4% • pneumonia: 2.4% • hypoglycemia: 2.2% • portal vein thrombosis: 2.0% • anemia: 2% • leucopenia: 2%
Treatment effects (ITA recipients only, N=347)	
SH & HbA1c	**Recipients with no SH and HbA1c < 6.5%:** Pre-transplant: 2% 1 year afterlast infusion: 51% to 63% 4 years afterlast infusion: 20% to 45% **Four events:** Pre-transplant: 81% 1 year after last infusion: 5% 4 years after last infusion: <10%
Graft function	**C-peptide > 0.5ng/ml (censored at re-infusion):** 1 year: 66% 3 years: 45% 4 years: 32% **Re-transplant:** By 1 year: 65%
Insulin independence	**Post last infusion:** 6 months: 55% 1 year: 46% 3 years: 27% 4 years: 16%

Abbreviations: HbA1c – glycosylated hemoglobin; IAK – islet after kidney transplantation; ITA – islet transplantation alone; No. – number; SH – severe hypoglycemia

CITR data are rigorously monitored to comply with 21 Code of Federal Regulations requirements, thus providing the most accurate description of adverse events experienced by islet recipients.[86] The incidence of serious adverse events related to infusion procedures or to the effects of immunosuppressive regimens is now characterized as less than one event per person year in the first year post-transplant, with a marked decline after that period. As shown in Table T.5, more than 80% of adverse events were resolved without sequelae, indicating the overall relative safety of the procedure and of immunosuppressive therapy.

In terms of treatment effects, the most recent update of CITR data confirmed the chief benefits of islet transplantation previously described, including stabilization of glucose metabolism, restoration of hypoglycemia awareness, and reduction of HbA1c to less than 6.5% for at least 50% of the recipients at 1 year post-transplant.

Ongoing Research

The United States National Institute of Health-funded Clinical Islet Transplantation Consortium is recruiting patients, including those with kidney transplants, for eight clinical trials aimed at

improving the safety and long-term success of islet transplantation in T1DM patients.[87]. These clinical trials will focus on:

- improving the number of islets that survive transplantation
- reducing complications of the islet transplantation procedure
- achieving good blood glucose control without hypoglycemia
- following the status of islets after transplantation and determining causes of donor islet failure
- evaluating new ways to safely prevent immune system rejection of donor tissues

Discussion

Summary of the main findings

Compared to the IHE 2008 report,[3] the present report includes data about both non-uremic patients and uremic patients with a previous kidney transplant. Accordingly, interventions also included islet after kidney transplantation and simultaneous islet and kidney transplantation. Comparisons were made between (1) islet transplantation and intensive insulin therapy, or (2) islet transplantation (alone or simultaneous with kidney transplantation or after kidney transplantation) and whole pancreas transplantation (alone or simultaneous with kidney transplantation or after kidney transplantation).

Among the six comparative studies, no direct comparison was available between ITA and PTA in the treatment of non-uremic patients. Furthermore, no direct comparison was available between IAK and SPK (the ADA-recommended treatment option) for the treatment of uremic patients with T1DM.

Available evidence from the six comparative studies indicates that ITA was associated with more procedure-related adverse events than was intensive insulin therapy. Compared to whole pancreas transplantation, islet transplantation was associated with fewer procedure-related adverse events but more immunosuppression-related adverse events, which sometimes led to a change or discontinuation of the original immunosuppressive drugs (for example, sirolimus) in IT recipients.

Whole pancreas transplantation resulted in significantly higher insulin independence rates than did islet transplantation; however, similar glycemic control can be achieved in islet transplantation recipients with reduced exogenous insulin doses. Long-term patient survival after successful islet transplantation was similar to that after pancreas transplantation.

While quality of life outcome was not reported in any of the comparative studies, four case series studies measured health-related quality of life (HrQoL) following ITA. Despite the tendency toward graft dysfunction over time, a significant improvement in some aspects of Diabetes QoL (DQoL) has been shown following ITA for up to three years. Better Hypoglycemia Fear Survey scores after islet transplantation were observed in two studies,[62,72] but this effect was not sustained at three years. However, islet transplantation had no or minimal effects on generic health-related QoL evaluated by HSQ2.0, HUI2, and SF-36.

Most case series studies did not report any long-term diabetic complications. The Edmonton study[15] of 65 patients reported deterioration of eye condition in four patients following ITA. Another study[71] reported retinopathy and neuropathy in eight ITA recipients during 1-year follow-up. No

progression in retinopathy was found when compared with pre-transplant measures in all eight patients, while an improvement was indicated in one patient. No significant correlation was reported between changes in HbA1c values and retinopathic changes. Compared to pre-transplant measures, improvement or stabilization of diabetic neuropathy was reported in 50% of the eight patients.

Very few studies reported on diabetic complications, possibly due to the short follow-up periods in most of the studies. One comparative study did not find any difference in cardiovascular risk factors between SIK and SPK recipients. Case series studies demonstrated a lower cardiovascular death rate and higher patient survival in successful IAK recipients than in unsuccessful IAK recipients at 10 years.

Patient selection

The aim of appropriately selecting candidates for clinical islet transplantation is to maximize benefit while minimizing risk. The objectives, indications, and criteria for successful islet transplantation have not yet been clearly defined.[20] Islet transplantation is still a relatively novel treatment for T1DM; it continues to evolve, and the long-term effects remain unknown. There may be tensions between short-term benefits and long-term risks.[2]

Most case series studies used the ITA patient selection criteria developed by the Edmonton group. Only a small portion of T1DM patients meet the strict inclusion criteria for islet transplantation. In the international multicentre trial,[10] of approximately 2000 prospective patients screened for eligibility, only 149 (7%) met the initial stringent screening criteria and were referred to the sites. Another recent study[24] reported that, of 88 patients screened, 60 were eliminated based on the exclusion criteria, 15 withdrew because of safety concerns, and three were excluded because of medical conditions; only 10 patients were eventually included in that study.

Patients with brittle diabetes and end stage kidney disease may represent the best candidates for IT, as this group of patients benefits from kidney transplantation and will require life-long immunosuppression.[32]

Treatment goals

The expectations for and success criteria of islet transplantation remain undefined and controversial. From the recent literature, the definition for success of islet transplantation has undergone a shift from a 'cure' (that is, insulin independence; a 100% of success rate) toward 'persistent islet graft function with optimal and stable metabolic control avoiding severe hypoglycemic episodes.' Some authors suggest that insulin independence should be neither the main goal of islet transplantation, nor the main criterion of success.[12,61] At present, a realistic goal for islet transplantation could be the conversion from a 'brittle' diabetes state into a more easily manageable disease state, because the combination of a functioning graft and reduced exogenous insulin therapy can help patients who have been experiencing hypoglycemia unawareness prevent hypoglycemic episodes, achieve normalized HbA1c levels, and reduced glucose variability.[20,32]

Long-term outcomes

Despite protocol modifications in donor selection, islet preparation, or recipient management strategies, insulin independence with adequate metabolic control has rarely been prolonged beyond 2 years. The most frequently proposed explanations include chronic allogeneic rejection, recurrence of autoimmunity, and beta-cell toxicity from administered immunosuppressive medications.[32] Alloimmunity could be a major factor. A significant number of patients will become panel reactive

antibody (PRA) positive following transplantation and around half of those with high PRA may lose graft function. Autoimmunity is another potential factor whereby patients who develop autoantibodies may exhibit a decrease in graft function.[2]

Program context

Patients with insulin resistance or who are overweight are not eligible for the islet transplantation procedure because their chances of achieving insulin independence with an adequate islet mass are less than the chances of those who have a normal BMI and are not insulin resistant. Islets are lost in the isolation process and after administration, and only patients with small insulin requirements are eligible for the islet transplantation programs. Furthermore, the toxicity and expense of immunosuppression makes islet transplantation an option only for a patient seriously at risk while on the current optimized therapy.

The site-to-site variation in clinical outcomes may be explained by the difference in the baseline experience with human islet processing and transplantation or with the use of sirolimus-based immunosuppressive therapy, which ranged from none to substantial at various centers. Achievement of insulin independence with adequate glycemic control at 1 year was significantly affected by the experience of the experts at each site.[10]

Appropriate allocation of donor pancreata should be considered within a program context. Currently SPK and IAK do not substantially compete for organs, as donor pancreata not qualified for whole pancreas transplantation are used for islet transplantation. These two procedures should be considered as complimentary rather than competitive treatment options for T1DM patients with end stage renal failure.[10,39]

Future research

Large scale comparative studies are required to address a number of unanswered questions. However, at present, clinical trials in islet transplantation face stringent federal regulations that define islets as a biological drug and islet transplantation as an experimental procedure.[24] Limited resources make sufficiently powered, large-scale trials unrealistic. Furthermore, a randomized design for direct comparison of different procedures is not ethically justifiable due to the overt differences among the surgical procedures.[57]

Gaps in research evidence identified in this report point to some areas for future research, including:

- studies that compare the safety and treatment effects of ITA and PTA in non-uremic patients
- studies that compare the safety and treatment effects of IAK and SPK (current treatment of choice) in uremic patients
- studies that compare the impact of islet transplantation and intensive insulin therapy on HrQoL measures.
- development of more sensitive methods to predict and detect graft loss and to elucidate its mechanisms for preserving islet mass over time
- development of more sensitive HrQoL tools specific to the priorities and preferences of islet transplantation recipients

- establishment of safety profiles for new immunosuppression drugs that have received approval from Health Canada and are still on the market
- larger studies using single donors for islet transplantation and standardized immunosuppressive regimen
- studies with longer follow-up (> 5 years) to examine the impact of islet transplantation on secondary complications of diabetes

Conclusions

The present report has examined the safety and efficacy/effectiveness of ITA in non-uremic patients as well as of IAK or SIK in uremic patients. Evidence mainly comes from six comparative studies (with eight publications) and 13 case series studies (with 20 publications) that included 10 or more patients and followed them for at least 1 year.

Comparative studies have demonstrated that islet transplantation is associated with a higher risk of procedure-related adverse events than is intensive insulin therapy, but with significantly fewer procedure-related complications than are associated with whole pancreas transplantation.

The insulin independence rates achieved following islet transplantation was shown to be significantly lower than that achieved following pancreas transplantation; however, with the use of reduced insulin doses, islet transplantation can still maintain similar levels of glycemic control to the levels achieved with pancreas transplantation, and can prevent severe hypoglycemia in a small group of highly select patients.

While no HrQoL outcomes were reported in any of the six comparative studies, four case series studies showed improvements of the disease-specific QoL but not the generic QoL scores. More sensitive tools, such as transplant-specific measures, should be used to capture the full impact of islet transplantation on HrQoL and on patients' preferences and perceptions of islet transplantation.

Although limited data indicated a positive impact of islet transplantation on some diabetic complications such as retinopathy, findings from the included studies are inconclusive at this time. Larger, controlled trials with better design are required to further clarify the true impact of islet transplantation on long-term clinical outcomes.

No information is currently available on the comparison of islet transplantation alone with intensive insulin therapy in patients with severe hypoglycemia or hypoglycemia unawareness. No study directly compared islet transplantation alone with pancreas transplantation alone in non-uremic patients. No study was found that directly compared islet after kidney transplantation with spontaneous pancreas and kidney transplantation (the treatment of choice). Therefore, no firm conclusion could be drawn about the superiority of one intervention over another.

The definition of success for islet transplantation remains controversial. Insulin independence may not be an appropriate main outcome for islet transplantation. Rather, islet transplantation should aim at reducing the doses of required insulin therapy and reducing the frequency of severe hypoglycemia, which in turn result in improvements in patients' quality of life, and in improving glycemic control to prevent long-term diabetic complications.

Islet transplantation is a complex procedure that has undergone a continuous evolution over the past decade. For a small group of patients who have failed standard treatment and management, islet transplantation offers an alternative treatment option for severe hypoglycemia, hypoglycemia

unawareness, and brittle diabetes. Its safety and efficacy/effectiveness in these highly select patients has been extensively investigated. At present, the role of islet transplantation in the long-term treatment of T1DM remains to be further determined because of the potential risk of immunosuppression-related side effects, the absence of sustained long-term treatment effects, allo-sensitization that may impede subsequent transplants, and insufficient supply of donor pancreata.

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Appendices

Appendix T.A: Methodology

Literature search

The IHE research librarian conducted a literature search that retrieved articles published between 2000 and November 2010. A grey literature search was conducted in April 2011. Searches were limited to human studies. Reference lists of relevant articles were also browsed to find more studies.

Medical Subject Headings (MeSH) terms relevant to this topic are: "Islets of Langerhans Transplantation"; Diabetes mellitus; Diabetes mellitus, Type 1

Table T.A.1: Search strategy

Database	Edition or date searched	Search Terms ††
Core Databases		
Cochrane Library Licensed Resource (Wiley Interface)	November 12, 2010	islet* AND (transplant* OR allotransplant*) **in Title, Abstract or Keywords** , from 2000 to 2010 **CDSR = 0 reviews** **Clinical Trials – 14 results (1 new)**
MEDLINE (includes in-process citations) (Ovid interface)	December 3, 2010	1. "Islets of Langerhans Transplantation"/ 2. (islet* adj4 (transplant* or allotransplant*)).tw. 3. diabetes mellitus/ or diabetes mellitus, type 1/ 4. diabet*.tw. 5. (1 or 2) and (3 or 4) 6. limit 5 to animals 7. limit 6 to humans 8. 5 not (6 not 7) 9. (rat or rats or pig or pigs or porcine or mouse or mice or murine or xeno*).ti. 10. 8 not 9 11. limit 10 to yr="2000 - 2011" 12. meta-analys*.pt,mp. 13. ((systematic* adj2 review*) or Medline or pubmed or psychinfo or psycinfo or search*).tw. 14. exp epidemiologic studies/ 15. exp clinical trial/ 16. comparative study/ 17. (trial or cohort or follow-up or longitudinal or outcomes or random* or groups).tw. 18. mortality/ 19. death.tw. 20. survival.tw. 21. course*.tw. 22. registr*.tw. 23. or/12-22 24. 11 and 23 25. 11 and review.pt. and (transplant* or allotransplant*).ti. 26. 24 or 25 **745 results**

CRD Databases (DARE, HTA, & NHS EED) www.crd.york.ac.uk/crdweb/	November 13, 2010	Islet* AND (transplant* OR allotransplant*) RESTRICT YR 2000 2010: **12 results**
EMBASE Licensed Resource (OVID Interface)	December 3, 2010 (to 2010, Week 45)	1. pancreas islet transplantation/ 2. (islet* adj4 (allotransplant* or transplant*)).tw. 3. diabet*.mp. 4. (1 or 2) and 3 5. limit 4 to yr="2000 - 2011" 6. (exp vertebrate/ or animal/ or exp experimental animal/ or nonhuman/ or animal.hw.) not (exp human/ or human experiment/) 7. (rat or rats or pig or pigs or porcine or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cats or bovine or sheep or murine or primate*).mp. not (exp human/ or human experiment/) 8. (rat or rats or pig or pigs or porcine or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cats or bovine or sheep or murine or primate* or xeno*).ti. 9. 5 not (6 or 7 or 8) 10. human experiment/ 11. exp clinical study/ 12. comparative study/ 13. exp controlled study/ 14. experimental study/ 15. quasi experimental study/ 16. observational study/ 17. case finding/ or cohort analysis/ or control group/ or cross-sectional study/ or crossover procedure/ or double blind procedure/ or exp evidence based practice/ or nonequivalent control group/ or open ended questionnaire/ or qualitative research/ or quantitative study/ or single blind procedure/ or triple blind procedure/ 18. ((systematic* adj2 review*) or meta-analys* or Medline or pubmed or psychinfo or psycinfo or search*).tw. 19. (trial or cohort or follow-up or longitudinal or registr*).tw. 20. follow up/ 21. or/10-20 22. 9 and 21 23. limit 9 to "review" 24. 23 and (transplant* or allotransplant*).ti. 25. 22 or 24 **1013 results**
Web of Science SCI-EXPANDED, SSCI Licensed Resource (ISI Interface)	November 15, 2010	#1 TS=(((islet* SAME (transplant* OR allotransplant*)) AND diabet*) NOT (rat OR rats OR rodent OR mice OR mouse OR murine OR dog* OR monkey OR pig OR pigs OR porcine OR xeno*)) #2 TS = ((systematic* SAME review*) or meta analys* or Medline or pubmed or psychinfo or psycinfo or search* or trial or cohort or observational study or case series or prospectiv* or retrospectiv* or random*

		or longitudinal or outcomes or group* or survival or registr* or death or mortality) #1 AND #2 *Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2000-2010* **379 results**
CINAHL Licensed Resource (EBSCO Interface)	December 3, 2010	S1 ((MH "Islets of Langerhans") and (transplant* OR allotransplant*)) or (islet* cell* transplant* or islet* transplant* or islet* allotransplant* and islet* cell* allotransplant*) S2 diabet* S3 (MH "Study Design+") S4 (MH "Systematic Review") S5 (MH "Meta Analysis") S6 (S1 AND S2 AND (S3 OR S4 OR S5)) (33 results)
Proquest Dissertations and Theses, full text	December 3, 2010	(islet W/4 transplant*) AND (diabet*) AND TITLE(islet OR transplant* OR diabet*) AND NOT (rat OR rats OR primate OR primates OR rodent OR mice OR mouse OR murine OR dog* OR monkey OR pig OR pigs OR porcine OR xeno*) (18 results)
Library Catalogues		
NEOS (Central Alberta Library Consortium) www.library.ualberta.ca/catalogue	April 14, 2011	Islet AND transplant
AMICUS (National Library of Canada) www.collectionscanada.ca/amicus/index-e.html	April 14, 2011	ANY KEYWORD: Islet AND transplant
Guidelines		
AMA Clinical Practice Guidelines www.topalbertadoctors.org/TOP/CPG/	April 12, 2011	Browsed list **0 results**
CMA Infobase http://mdm.ca/cpgsnew/cpgs/index.asp	April 12, 2011	Islet, transplantation **0 results**
National Guideline Clearinghouse www.ngc.gov	April 12, 2011	Islet AND transplantation **0 relevant results**
New Zealand Guidelines Group www.nzgg.org.nz	**April 12, 2011**	**Islet** **0 results**
Scottish Intercollegiate Guidelines Network www.sign.ac.uk	April 12, 2011	Browsed list and searched latest diabetes guideline **0 results**
Guidelines International Network (International Guidelines Library) www.g-i-n.net/	April 12, 2011	Islet **3 results** (AHRQ and NICE)
Guidelines Advisory Committee www.gacguidelines.ca/index.cfm	April 12, 2011	Browsed list and searched recent diabetes **0 relevant results**
BC Guidelines and Protocol Advisory Committee	April 12, 2011	Browsed alphabetical list and searched diabetes guideline

www.health.gov.bc.ca/gpac		**0 relevant results**
NICE guidance http://guidance.nice.org.uk/	April 12, 2011	Islet **2 relevant results**
Clinical Trials		
ClinicalTrials.gov (US) http://clinicaltrials.gov/	April 12, 2011	Islet AND transplant **100 results**
CenterWatch Clinical Trials Listing Service www.centerwatch.com/	April 12, 2011	Islet **7 results**
CCT Current controlled trials www.controlled-trials.com (did not search clinical trials.gov)	April 14, 2011	Islet **0 relevant results**
IFPMA Clinical Trials Portal http://clinicaltrials.ifpma.org/clinicaltrials/no_cache/en/myportal/index.htm	April 14, 2011	Transplantation Islets of Langerhans **0 new results**
Coverage/Regulatory/Licensing Agencies		
Alberta Health and Wellness www.health.gov.ab.ca	April 14, 2011	Islet **0 relevant results**
Health Canada www.hc-sc.gc.ca	April 14, 2011	Islet AND transplant **5 potentially relevant results**
US Medicare Coverage Database www.cms.hhs.gov/mcd/search.asp?	April 14, 2011	Search all states and islet (a National Coverage Decision)
Aggressive Research Intelligence Facility (ARIF) www.arif.bham.ac.uk/completed.shtml	April 14, 2011	Islet **0 relevant results**
ACP Journal Club http://acpjc.acponline.org	April 14, 2011	Islet, islets **0 relevant results**
ATTRACT www.attract.wales.nhs.uk	April 14, 2011	Islet **0 relevant results**
Bandolier www.medicine.ox.ac.uk/bandolier/	April 14, 2011	Islet **0 results**
BestBETS www.bestbets.org	April 14, 2011	Browse by topic: Endocrine > diabetes
Clinical Evidence** www.clinicalevidence.com	April 14, 2011	Islet **0 relevant results**
TRIPdatabase www.tripdatabase.com	April 14, 2011	Reviewed results for systematic reviews and guidelines
Centre for Health Economics and Policy Analysis www.chepa.org/	April 14, 2011	Islet **0 results**
Centre for Health Economics Research and Evaluation www.chere.uts.edu.au/index. html	April 14, 2011	Browsed economic evaluations and policy evaluations **0 results**
Manitoba Centre for Health Policy http://umanitoba.ca/medicine/units/mchp/	April 14, 2011	Browsed deliverables and active research pages **0 results**

Other HTA Resources		
AETMIS www.aetmis.gouv.qc.ca/site/home.phtml	April 12, 2011	Islet **0 results**
CADTH www.cadth.ca/index.php/en/ hta/reports-publications/search	April 12, 2011	Islet **0 results**
BC Centre for Health Services and Policy Research (CHSPR) www.chspr.ubc.ca/publications	April 12, 2011	Islet **0 results**
Institute for Clinical and Evaluative Sciences (ICES), Ontario www.ices.on.ca/	April 12, 2011	Islet **0 results**
Health Technology Assessment Unit at McGill www.mcgill.ca/tau/	April 12, 2011	Browsed list **0 results**
Medical Advisory Secretariat www.health.gov.on.ca/english/providers/program/mas/mas_mn.html	April 12, 2011	Browsed list **1 result** (2003)
EuroScan www.euroscan.org.uk/technologies/public/do_public_search	April 12, 2011	Islet **1 relevant result**
ASERNIP-S www.surgeons.org/asernip-s/	April 14, 2011	Islet **0 relevant results**
MSAC www.msac.gov.au/	April 14, 2011	Islet **0 relevant results**
NZHTA http://nzhta.chmeds.ac.nz/publications.htm	April 14, 2011	Islet **0 relevant results**
National Horizon Scanning Centre www.haps.bham.ac.uk/publichealth/horizon/outputs/technology.shtml	April 14, 2011	Islet **0 relevant results**
CCE www.southernhealth.org.au/page/Health_Professionals/CCE/Evidence_reviews/ Current/	April 14, 2011	Islet (searched current and archived) **0 relevant results**
California Health Benefits Review Program (CHBRP) www.chbrp.org/	April 14, 2011	Browsed complete analyses page **0 results**
California Technology Assessment Forum (CTAF) www.ctaf.org/section/assessment/	April 14, 2011	Islet **0 results**
AHRQ www.ahrq.gov	April 12, 2011	Islet **0 results**
NHS Health Technology Assessment Programme www.ncchta.org	April 12, 2011	Islet **1 result**
VA Technology Assessment Program www.va.gov/VATAP/Phase2pubspage.asp	April 12, 2011	Islet **0 results**
Health Evidence Network (HEN) www.euro.who.int/en/what-we-do/data-and-evidence/health-evidence-network-hen/publications/by-keyword	April 12, 2011	Islet **0 results**
Australia and New Zealand Horizon Scanning Network www.horizonscanning.gov.au	April 12, 2011	Islet **4 results (2 relevant)**
HSTAT www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat	April 12, 2011	Islet **1 relevant result**

AETNA www.aetna.com/cpb/cpb_menu.html	April 12, 2011	Islet **1 result**
Blue Cross and Blue Shield www.bcbs.com/blueresources/tec/tec-assessments.html	April 12, 2011	Islet **1 result** (same as AHRQ)
Washington State Health Care Authority www.hta.hca.wa.gov/assessments.html	April 12, 2011	Browsed list **0 results**
Metabrowsers/Search Engines		
Google www.google.com	April 28, 2011	Islet transplantation guideline (browsed first 50 results) Islet transplantation systematic-review technology-assessment (browsed first 50 results)

Note: ††, *, and $ are truncation characters that retrieve all possible suffix variations of the root word; e.g., surg* retrieves surgery, surgical, surgeon, etc. Semi-colons separate searches that were entered separately.

Study selection

Selection of key studies

One reviewer (BG) screened titles and abstracts. Full-text publications of relevant articles were retrieved. Two reviewers (BG and PC) determined eligibility of studies according to the following predefined inclusion/exclusion criteria.

Inclusion criteria

Studies were included if they met all of the following criteria:

Study design: systematic reviews/health technology assessments (HTAs) published in the last 5 years (2006 to 2011); randomized or nonrandomized controlled trials, cohort studies, case control studies, or case series studies published during the last 10 years (2000 to 2010)

Note: An article was deemed to be a systematic review if it met all of the following criteria as defined by Cook et al., 1997:[88]

- had a focused clinical question
- had an explicit search strategy
- used explicit, reproducible, and uniformly applied criteria for article selection
- provided a critical appraisal of the included studies
- provided qualitative or quantitative data synthesis

Population: adult patients (≥ 18 years old) with type 1 diabetes, with or without kidney failure

Interventions:

For patients without kidney failure: islet allo-transplantation alone

For patients with kidney failure:

1) islet allo-transplantation after kidney transplantation
2) simultaneous islet and kidney allo-transplantation

Comparators:

For patients without kidney failure:

1) intensive insulin therapy, either by MDI or IPT
2) whole organ pancreas transplantation alone

For patients with kidney failure:

1) simultaneous whole organ pancreas and kidney transplantation
2) whole organ pancreas transplantation after kidney transplantation (PAK)
3) intensive insulin therapy

Outcomes of interest: at least one of the following:

- safety: any adverse events associated with the procedure or immunosuppressive medications
- efficacy/effectiveness: graft function/glycemic control (insulin independence, reduction in insulin requirement, prevention of severe hypoglycemia, C-peptide secretion, HbA1c levels), health-related quality of life, secondary complications (retinopathy, nephropathy, neuropathy, cardiovascular disease, and so on), or patient survival; the follow-up period for efficacy/effectiveness outcome should be at least one year after first transplantation

Publication: full text articles, written in English, published between 2000 and 2010

Exclusion criteria

Studies were excluded if they met any of the following criteria:

Study design: case reports, conference abstracts, letters, news, editorial comments; primary studies that included < 10 patients in case series studies or < 10 patients in each arm of the comparative studies; animal studies

Population: pediatric patients (< 18 years); patients with type 2 diabetes, chronic pancreatitis, or pancreas tumors

Interventions: studies that assessed islet auto-transplantation, xenotransplantation (or xenogeneic transplantation), genetically altered islets, islets prepared from stem cells, fetal pancreatic islet transplantation, liver-islet transplantation, lung-islet transplantation, pancreas transplantation, or liver transplantation as the primary interventions of interest

Outcome measures: studies that focused on technical aspects of islet cell isolation, purification, storage, or delivery without any clinical outcomes; studies that focused on correlations between various factors (for example, blood biomarkers) and clinical outcomes, in which the length of follow-up was less than one year

Selection of other studies

Review articles: for information regarding the etiology of the condition that the technology is meant to address; current options and standard treatments; advantage/disadvantages of islet transplantation and other treatment alternatives.

Regulatory documents from federal regulation agencies: for regulatory status of islet transplantation

Clinical practice guidelines/position statements: for clinical indication/contraindications for islet transplantation

Quality assessment

For comparative studies

Two reviewers (BG, PC) independently assessed the methodological quality of the six non-randomized comparative studies (with eight publications) using the Downs and Black's checklist.[53] Quality assessment results were compared and any disagreements were solved by discussion. Prior to assessing the studies, the two reviewers discussed the checklist with respect to the interpretation of the questions and modified the dictionary. See Appendix T.C. for the checklist with the modified dictionary and critical appraisal results for all included comparative studies.

For case series studies

Two reviewers (BG and PC) independently assessed the methodological quality of the 13 case series studies (with 20 publications) using a 20-item IHE case series quality assessment checklist. Quality assessment results were compared and any disagreements were solved by discussion. Prior to assessing the studies, the two reviewers discussed the checklist with respect to the interpretation of the questions and slightly modified the dictionary. See Appendix T.C. for the checklist with the modified dictionary and the critical appraisal results for all included case series studies.

Data extraction

From systematic reviews/HTAs

- search strategy
- study selection
- study characteristics
- quality assessment
- Results
- Conclusions

From key primary studies

Study

- author
- year of publication
- country where the study was conducted

- study design

Patient

- age
- gender distribution
- weight/BMI
- duration of diabetes
- baseline HbA1c level
- presence of end stage kidney disease
- previous kidney transplantation
- other co-morbidities

Intervention

- islet transplantation protocol
    - types
    - islet culture/other treatment
    - number of islet transplantations
    - total islet equivalents infused
- immunosuppressive drugs
    - name of immunosuppressive drugs
- concurrent treatment(s): for example, other medications used to improve islet graft function or to prevent the side effects of immunosuppressive drugs

Comparator

- intensive insulin therapy:
    - MDI: insulin/insulin analogues, frequency of daily injections
    - IPT: insulin/insulin analogues, pumps, blood glucose monitors
- pancreas transplantation
    - types

Results

Safety outcomes

- procedure-related adverse events
- immunosuppression-related adverse events

Treatment effects

- graft function/glycemic control
    - insulin independence
    - reduction in insulin requirement
    - C-peptide secretion
    - HbA1c levels
    - prevention of severe hypoglycemia
- health-related quality of life
    - generic
    - disease-specific
- secondary complications of diabetes
    - cardiovascular disease
    - retinopathy
    - nephropathy
    - neuropathy (and the resulted amputation)
- patient survival

Appendix T.B: Excluded studies

Table T.B.1: Excluded studies and reasons for exclusion

Excluded studies	Reason for exclusion
Albisser et al. Home blood glucose prediction: Clinical feasibility and validation in islet cell transplantation candidates. *Diabetologia* 2010;48(7):1273-79	No outcomes of interest
Andrea et al. Impact of a sirolimus/tacrolimus-based immunosuppressive regimen on kidney function after islet transplantation. *Transplantation Proceedings* 2005;37(2):1327-27	FU <1 year
Andres et al. Impairment of renal function after islet transplant alone or islet-after-kidney transplantation using a sirolimus/tacrolimus-based immunosuppressive regimen. *Transplant International* 2005;18(11):1226-30	Cases <10
Baidal et al. Early metabolic markers of islet allograft dysfunction. *Transplantation* 2009;87(5):689-97	Correlation study of a key study[63]
Bellin et al. Prolonged insulin independence after islet allotransplants in recipients with type 1 diabetes. [Erratum appears in American Journal of Transplantation 2010 May;10(5):1337. Papas, K [corrected to Papas, KK]]. *American Journal of Transplantation* 2008;8(11):2463-70	Cases <10
Bhargava et al. Prevalence of hepatic steatosis after islet transplantation and its relation to graft function. *Diabetes* 2004;53(5):1311-17	Old report of Edmonton series (reported in Ryan et al.[15])
Bucher et al. Islet of Langerhans transplantation for the treatment of type 1 diabetes. *Swiss Surgery* 2003;9(5):242-46	Not original primary study, more a review
Cure et al. Alterations of the female reproductive system in recipients of islet grafts. *Transplantation* 2004;78(11):1576-81	Earlier report of Hafiz et al.[77]
Cure et al. Improved metabolic control and quality of life in seven patients with type 1 diabetes following islet after kidney transplantation. *Transplantation* 2008;85(6):801-12	Cases <10
Del CU, Fiorina P, Amadio S et al. Evaluation of polyneuropathy markers in type 1 diabetic kidney transplant patients and effects of islet transplantation: neurophysiological and skin biopsy longitudinal analysis. *Diabetes Care.* 2007;30(12):3063-3069.	Cases in control group <10
Deng et al. Islet alone versus islet after kidney transplantation: metabolic outcomes and islet graft survival. *Transplantation* 2009;88(6):820-25	Cases in each arm <10; follow-up <1 year
Faradji et al. Long-term insulin independence and improvement in insulin secretion after supplemental islet infusion under exenatide and etanercept. *Transplantation* 2008;86(2):1658-65	Cases <10
Faradji et al. Long-term metabolic and hormonal effects of exenatide on islet transplant recipients with allograft dysfunction. *Cell Transplantation* 2009;18(10):1247-59	Focused on exenatide
Froud et al. Islet transplantation with alemtuzumab induction and calcineurin-free maintenance immunosuppression results in improved short- and long-term outcomes. *Transplantation* 2008;86(12):1695-1701	Earlier report and subgroup analysis of Leitao et al.[82]
Fung et al. The effect of medical therapy and islet cell transplantation on diabetic nephropathy: an interim report. *Transplantation* 2007;84(1):17-22	An earlier report of Warnock et al. 2008[55]
Geiger et al. Evaluation of metabolic control using a continuous subcutaneous glucose monitoring system in patients with type 1 diabetes	Focused on glucose monitoring system

mellitus who achieved insulin independence after islet cell transplantation. *Cell Transplantation* 2005;14(2-3):77-84	
Gillard et al. Comparison of sirolimus alone with sirolimus plus tacrolimus in type 1 diabetic recipients of cultured islet cell grafts. *Transplantation* 2008;85(2):256-63	Follow-up <1 year (6 months)
Goss et al. Achievement of insulin independence in three consecutive type-1 diabetic patients via pancreatic islet transplantation using islets isolated at a remote islet isolation center. *Transplantation* 2002;74(12):1761-66	Cases <10
Hering et al. Transplantation of cultured islets from two-layer preserved pancreases in type 1 diabetes with anti-CD3 antibody. *American Journal of Transplantation* 2004;4(3):390-401	Cases <10
Hering et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. [Erratum appears in JAMA. 2005 Apr 6;293(13):1594]. *JAMA* 2005;293(7):830-35	Cases <10
Hirshberg et al. Benefits and risks of solitary islet transplantation for type 1 diabetes using steroid-sparing immunosuppression: the National Institutes of Health experience. *Diabetes Care* 2003;26(12):3388-95	Cases <10
Huurman et al. Cellular islet autoimmunity associates with clinical outcome of islet cell transplantation. *PLoS ONE* [Electronic Resource] 2008;3(6):e2435	Correlation study; same cohort of an earlier report[73] of more comprehensive outcomes
Kenmochi et al. Successful islet transplantation from the pancreata of non-heart-beating donors. *Transplantation Proceedings* 2008;40(8):2568-70	Cases <10
Kessler et al. Reduction of blood glucose variability in type 1 diabetic patients treated by pancreatic islet transplantation: interest of continuous glucose monitoring. *Diabetes Care* 2002;25(112):2256-62	Follow-up <1 year
Koh. Supplemental Islet infusions restore insulin independence after graft dysfunction in islet transplant recipients. *Transplantation* 2010;89(3):361-65	Focused on supplemental islet infusion (not the original cases)
Lakey et al. Long-term graft function after allogeneic islet transplantation. *Cell Transplantation* 2007;16(4):441-46	Cases <10
Langer et al. Successful islet after kidney transplantations in a distance over 1000 kilometres: preliminary results of the Budapest-Geneva collaboration. *Transplantation Proceedings* 2004;36(10):3113-15	Cases <10
Lehmann et al. Successful simultaneous islet-kidney transplantation using a steroid-free immunosuppression: two-year follow-up. *American Journal of Transplantation* 2004;4(7):1117-23	Cases <10
Leitao et al. Lipotoxicity and decreased islet graft survival. *Diabetes Care* 2010;33(3):658-60	Correlation study of a key study[63]
Leitao et al. Nonalbumin proteinuria in islet transplant recipients. *Cell Transplant.* 2010;19(1):119-125.	Kidney function was only available in 27/36 patients.
Luzi et al. Metabolic effects of restoring partial beta-cell function after islet allotransplantation in type 1 diabetic patients. *Diabetes* 2001;50(2):277-82	Follow-up <1year
Maffi et al. Minimal focal steatosis of liver after islet transplantation in humans: a long-term study. *Cell Transplantation* 2005;24(10):727-33	Earlier report of Venturini et al.[76]
Markmann et al. Insulin independence following isolated islet transplantation and single islet infusions. *Annals of Surgery* 2003;237(6):741-50	Cases <10
Matsumoto et al. Follow-up study of the first successful living donor islet transplantation. *Transplantation* 2006;82(12):1629-33	Case report

Molinari et al. Sirolimus-induced ulceration of the small bowel in islet transplant recipients: report of two cases. *American Journal of Transplantation* 2005;5(11):2799-2804	Cases <10
Noguchi et al. Evaluation of islet transplantation from non-heart beating donors. *American Journal of Transplantation* 2006;6(10):2476-82	Cases <10
O'Connell et al. Clinical islet transplantation in type 1 diabetes mellitus: results of Australia's first trial. *Medical Journal of Australia* 2006;184(5):221-25	Cases <10
Oberholzer et al. Human islet allotransplantation with Basiliximab in type I diabetic patients with end-stage renal failure. *Transplantation Proceedings* 2002;34(3):823-25	Mean follow-up <1 year
Onaca et al. False aneurysm of a hepatic artery branch complicating intrahepatic islet transplantation. *Transplant International* 2009;22(6):663-66	Case report
Owen. Percutaneous transhepatic pancreatic islet cell transplantation in type 1 diabetes mellitus: radiologic aspects. *Radiology* 2003;228(1):165-70	Old report of Edmonton series
Pattou. Sequential intraportal islet allografts in immunosuppressed type I diabetic patients: preliminary results. *Transplantation Proceedings* 2000;32(2):391-92	Case report
Paty. Intrahepatic islet transplantation in type 1 diabetic patients does not restore hypoglycemic hormonal counterregulation or symptom recognition after insulin independence. *Diabetes* 2002;51(12):3428-34	Cases <10
Paty et al. Assessment of glycemic control after islet transplantation using the continuous glucose monitor in insulin-independent versus insulin-requiring type 1 diabetes subjects. *Diabetes Technology & Therapeutics* 2006;8(2):165-73	Follow-up <1 year
Petrelli et al. Improved function of circulating angiogenic cells is evident in type 1 diabetic islet-transplanted patients. *American Journal of Transplantation* 2010;10(12):2690-2700	No outcomes of interest
Poggioli et al. Quality of life after islet transplantation. *American Journal of Transplantation* 2006;6(2):371-78	Earlier report of Tharavanij et al.[64]
Ponte et al. Resolution of severe atopic dermatitis after tacrolimus withdrawal. *Cell Transplantation* 2006;16(1):23-30	Case report
Posselt et al. Islet transplantation in type 1 diabetics using an immunosuppressive protocol based on the anti-LFA-1 antibody efalizumab. *American Journal of Transplantation* 2010;10(8):1870-80	Cases <10
Rafael et al. Changes in liver enzymes after clinical islet transplantation. *Transplantation* 2003;76(9):1280-84	Old report of Edmonton series (reported in Ryan et al.[15])
Rickels et al. β-Cell function following human islet transplantation for type 1 diabetes. *Diabetes* 2005;54(1):100-6	Cases <10
Rickels et al. Glycemic thresholds for activation of counterregulatory hormone and symptom responses in islet transplant recipients. *Journal of Clinical Endocrinology & Metabolism* 2006;92(3):873-79	Follow-up <1 year
Rickels et al. Insulin sensitivity, glucose effectiveness, and free fatty acid dynamics after human islet transplantation for type 1 diabetes. *Journal of Clinical Endocrinology & Metabolism* 2006;91(6):2138-44	Follow-up <1 year

Rickels et al. Effect of glucagon-like peptide-1 on beta- and alpha-cell function in isolated islet and whole pancreas transplant recipients. *Journal of Clinical Endocrinology & Metabolism* 2009;94(1):181-89	No outcomes of interest
Saito et al. Islet transplantation using donors after cardiac death: report of the Japan Islet Transplantation Registry. *Transplantation* 2010;90(7):740-47	Age of patients ranged from 16 to 60; no separate reporting for adult patients (i.e., age ≥ 18)
Salehi. Case report: diabetic myonecrosis of the neck complicated by infection in an islet transplanted patient. *Journal of Diabetes and its Complications* 2009;23(2):140-42	Case report
Senior et al. Magnetic resonance-defined perinephric edema after clinical islet transplantation: a benign finding associated with mild renal impairment. *Transplantation* 2004;78(6):945-48	Safety outcomes reported in Ryan et al. 2005[15]
Senior. Proteinuria developing after clinical islet transplantation resolves with sirolimus withdrawal and increased tacrolimus dosing. *American Journal of Transplantation* 2005;5(9):2318-23	Cases <10
Tan et al. Simultaneous islet and kidney transplantation in seven patients with type 1 diabetes and end-stage renal disease using a glucocorticoid-free immunosuppressive regimen with alemtuzumab induction. *Diabetes* 2008;57(10):2666-71	Cases <10
Thompson et al. Reduced progression of diabetic retinopathy after islet cell transplantation compared with intensive medical therapy. *Transplantation* 2008;85(10):1400-5	An earlier report of Warnock et al. 2008[55]
Toso et al. Sequential kidney/islet transplantation: efficacy and safety assessment of a steroid-free immunosuppression protocol. *American Journal of Transplantation* 2006;6(5 Pt 1):1049-58	Cases <10
Tuch et al. Safety and viability of microencapsulated human islets transplanted into diabetic humans. *Diabetes Care* 2002;32(10):1887-89	Cases <10
Warnock et al. Improved human pancreatic islet isolation for a prospective cohort study of islet transplantation vs best medical therapy in type 1 diabetes mellitus. *Archives of Surgery* 2005;140(8):735-44	An earlier report of Warnock et al. 2008[55]
Yakubovich et al. Three cases of cytomegalovirus infection following pancreatic islet transplantation. Transplantation Proceedings 2007;39(5):1599-1603	Cases <10

Appendix T.C: Quality assessment of the key studies

Quality assessment tool for the comparative studies

The methodological quality of the six comparative studies (with eight publications) was assessed using the checklist developed by Downs and Black.[53] The original tool consists of 27 questions in the following sub-sections:

- Reporting
- External Validity,
- Internal Validity (bias and confounding)
- Power

For reasons of relevance, question #19 was removed, reducing the total number of questions to 26. Total scores using the original tool range from 0 to 32. However, we modified the last question about power from a scale of 0 to 5 to a scale of 0 to 1, where 1 was scored if a power calculation or sample size calculation was present while 0 was scored if no power calculation, sample size calculation, or explanation as to whether the number of subjects was appropriate were present. Thus, the total score of our modified version ranged from 0 to 27, with a higher score indicating better methodological quality. The modified check list and dictionary are available upon request. See Table T.C.1 for a summary of the results of quality assessment of the eight publications.

The quality assessment scores of each individual study were not used as inclusion criteria. For descriptive purpose, the quality of the included studies was categorized as good, moderate, or poor.

Good	≥ 20	75% of criteria met
Moderate	≥14 and <20	50% to 75% of criteria met
Poor	<14	50% of criteria met

Table T.C.1: Quality assessment results of the comparative studies

Study Characteristic		Warnock et al.[55]	Venturini et al.[56]	Gerber et al.[57]	Fiorina et al.[58]	Fiorina et al.[27]	Fiorina et al.[59]	Vantyghem et al.[60]	Frank et al.[61]
Reporting	1. Is the hypothesis/aim/objective of the study clearly described?	√	√	√	√	√	√	√	√
	2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	√	×	√	√	√	√	√	√
	3. Are the characteristics of the patients included in the study clearly described?	√	×	√	√	×	×	√	×
	4. Are the interventions of interest clearly described?	×	√	√	×	×	×	×	×
	5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	√	√	√	√	×	×	√	√
	6. Are the main findings of the study clearly described?	√	√	√	√	√	√	√	√
	7. Does the study provide estimates of the random variability in the data for the main outcomes?	√	√	√	√	√	√	√	×
	8. Have all important adverse events that may be a consequence of the intervention been reported?	√	×	√	×	×	×	√	√
	9. Have the characteristics of patients lost to follow-up been described?	×	√	√	√	×	√	√	×
	10. Have actual probability values been reported (0.035 rather than <0.05) for the main outcomes except where the probability value is <0.001?	×	√	√	×	×	×	×	×
External validity	11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	?	?	×	?	√	?	?	√
	12. Were those subjects who were prepared to participate in the study representative of the entire population from which they were recruited?	×	?	×	?	?	?	?	√
	13. Were the staff, places, and facilities where the patients were treated representative of the treatment the majority of patients receive?	×	?	×	×	×	?	?	×

Table T.C.1: Quality assessment results of the comparative studies (cont'd)

Study Characteristic		Warnock et al.[55]	Venturini et al.[56]	Gerber et al.[57]	Fiorina et al.[58]	Fiorina et al.[27]	Fiorina et al.[59]	Vantyghem et al.[60]	Frank et al.[61]
Internal validity – bias	14. Was an attempt made to blind study subjects to the intervention they received?	×	×	×	×	×	×	×	×
	15. Was an attempt made to blind those measuring the main outcomes of the intervention?	×	?	?	√	?	?	?	?
	16. If any of the results of the study were based on "data dredging" was this made clear?	√	√	√	√	√	√	√	√
	17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients?	?	√	×	√	√	√	√	√
	18. Were the statistical tests used to assess the main outcomes appropriate?	√	√	√	√	√	√	√	√
	19. Were the main outcome measures used accurate (valid and reliable)?	×	√	×	√	√	√	×	×
Internal validity – confounding (selection bias)	20. Were the patients in different intervention groups (trials and cohort studies) recruited from the same population?	√	?	√	√	√	?	√	√
	21. Were the patients in different intervention groups (trials and cohort studies) recruited over the same period of time?	√	?	√	?	√	?	×	√
	22. Were study subjects randomized to intervention groups?	×	×	×	×	×	×	×	×
	23. Was the randomized intervention assignment concealed from both patients and healthcare staff until recruitment was complete and irrevocable?	×	×	×	×	×	×	×	×
	24. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	?	?	×	√	×	?	×	×
	25. Were losses of patients to follow-up taken into account?	?	√	√	√	×	√	√	√
Power	26. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is <5%?	×	?	?	?	?	?	?	?
Total score (out of 27)		12	13	16	16	11	10	14	14

Quality assessment of the case series studies

Methodological quality of the 13 case series studies (with 20 publications) was appraised using a 20-item checklist developed by researchers from IHE and HTA agencies in Australia and Spain. The original IHE checklist consisting of 18 items was used in a previous islet transplantation report.[3] Two items not originally included (prospective data collection and blinding of outcome measures) were added to the checklist.

The quality assessment scores of each individual study were not used as inclusion criteria. For descriptive purpose, the quality of the included studies was categorized as good, moderate, and poor.

Good	≥ 15	≥ 75% criteria met
Moderate	10 to 14	50% to 75% of criteria met
Poor	≤ 9	< 50% criteria met

The modified checklist and dictionary are outlined below. See Table T.C.2 for the quality assessment results.

Dictionary for the Quality Assessment Checklist for case series studies

Study objective

1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?

Yes: The hypothesis/aim/objective of the study is clearly stated in the abstract, introduction, or methods section.

No: The hypothesis/aim/objective is not provided in the abstract, introduction, or methods section.

Study design

2. Was the study conducted prospectively?

Yes: Authors clearly state that the design of the study was prospective.

No: Authors clearly state that the design of the study was not retrospective, or authors did not mention anything about this.

3. Were the cases collected in more than one centre?

Yes: Cases were collected in more than one centre (multicentre study).

No: Cases are were not collected from one centre, or it is unclear where patients came from.

4. Were participants recruited consecutively?

Yes: It is clearly stated that participants were recruited consecutively.

No: Participants were recruited based on other criteria, such as access to intervention, determined by the distance or availability of resources. The method used to recruit participants was not clearly stated.

Study population

5. Are the characteristics of the participants included in the study described?

Yes: The most relevant characteristics are presented. The authors should report the total number, age, and gender distribution of the participants. Ethnicity, severity of disease/condition, co-morbidity, or etiology should also be included, if relevant.

No: The most relevant characteristics of the participants are not reported. If only the number of participants was reported or if any of the relevant characteristics are missing the question should be answered no.

Note: Assessor(s) should decide which aspects are important before using the checklist:

Total number of patients, age, gender distribution, duration of diabetes, renal function, severe hypoglycaemia/hypoglycaemia unawareness/high variability of glucose level

6. Are the eligibility (inclusion and exclusion) criteria for entry to the study explicit and appropriate?

Yes: The eligibility criteria are clearly stated and replicable, and match the objective of the study.

No: The eligibility criteria are not clearly stated.

Note: Assessor(s) should decide which aspects are important before using the checklist:

Age, duration of diabetes, with or without severe hypoglycemia/hypoglycemia unawareness/high variability of glucose levels, uremic or nonuremic, with or without previous kidney transplantation.

7. Did participants enter the study at a similar point in the disease?

Yes: There is a clear description about the clinical status, duration of condition (exposure) before the intervention, co-morbidity, severity, or complications of all participants in the study.

No: There is no description as to whether participants entered the study at a similar point in the disease. Participants did not enter the study at similar point in the disease as revealed by a wide range of disease duration before entering the study or by different co-morbidities or complications due to progression of their condition/disease.

Note: Assessor(s) should decide which aspects are important before using the checklist:

For non-uremic patients:

Yes: all of the following criteria should be met:

1) all patients have DM≥ five years (because that's the import turn point that hypoglycemia unawareness, glucagons secretion abnormality, and microalbuminuria may occur)
2) ≥ 80 of patients have severe hypoglycemia or hypoglycemia unawareness
3) ≥ 80% of patients without kidney disease.

No: 1) not all criteria above are met
2) there is no clear description of these characteristics, or
3) information is not available for one of these characteristics

For uremic patients:

Yes: all of the following criteria should be met:

1) all patients have DM≥ five years
2) ≥ 80 of patients have end stage renal disease.

No: 1) not all criteria above are met
2) there is no clear description of these characteristics, or
3) information is not available for one of these characteristics.

Intervention and co-intervention

8. Was the intervention clearly described in the study?

Yes: A detailed description was provided about the characteristics of the intervention (for example, dosage, frequency of administration, duration, permanent or temporary

intervention, and technical parameters/characteristics of a device). It was stated that the intervention was described previously with reference.

No: Intervention was only mentioned by name, without any details, or the information provided was unclear, or important parameters of the intervention were missing from the presentation.

Note: Assessor(s) should decide which aspects are important before using the checklist:

Number of islets/per infusion, frequency of infusion, immunosuppressive therapy.

9. Were additional interventions (co-interventions) clearly reported in the study?

Yes: The name or type of any co-intervention was acknowledged in the study. The question should have been answered 'Yes' if it was obvious (based on study context) that any co-intervention is not necessary.

No: Co-intervention(s) were not reported at all, or name(s) or type(s) of co-intervention(s) were unclear.

Note: Assessor(s) should decide which aspects are important before using the checklist:

Any of the following: diet change, exercise, insulin therapy, other medications, or kidney transplantation.

Outcome measures

10. Are the outcome measures clearly defined in the introduction or methodology section?

Yes: All relevant (primary and secondary) outcomes that match the objective(s) of the study are described in the introduction or method section (for example, these may refer to accomplished, measurable improvements or effects, symptoms relieved, improved function, improved test scores, or quality of life measures).

No: The outcomes are reported for the first time in the results or conclusion section of the study. The relevant outcomes are briefly mentioned without any details in the results, discussion and/or conclusion section(s). The outcomes reported are not relevant to the study objective(s).

Note: Assessor(s) should decide which aspects are important before using the checklist:

Insulin independence or reduction of insulin, C-peptide secretion, HbA1c level, hypoglycemia episodes, secondary complications, quality of life, regain of hypoglycaemia awareness, reduction in variability of blood glucose level, survival/mortality rate.

11. Were the main outcomes assessed blind/independent to intervention status?

Yes: It was mentioned/stated that main outcomes were analyzed by individuals who were not aware of the intervention status.

No: It was not clear/obvious that main outcomes were analyzed by individuals who were aware of the intervention status, or the study did not report on this.

12. Were relevant outcomes appropriately measured by objective and/or subjective methods?

Yes: Appropriate methods used to measure the outcomes were described in the methods section. These measures might be objective (for example, gold standard tests or standardized clinical tests) and/or subjective (for example, self administered questionnaires, standardized forms, or patient symptoms interview forms).

No: No details were provided on the objective and/or subjective methods used to measure study outcomes.

13. Were outcomes measured before and after intervention?

Yes: The relevant outcomes were measured before and after applying the intervention.

No: The outcomes were only measured after applying the intervention.

Statistical analysis

14. Are the statistical tests used to assess the relevant outcomes appropriate?

Yes: The statistical tests are clearly described in the methods section and are used appropriately (for example, parametric test for normally distributed population vs. non-parametric test for non-Gaussian populations).

No: The statistical tests used to assess the relevant outcomes are inappropriate. From the information available, the distribution of the population from which the participants at the study were selected is unclear.

Results and conclusions

15. Was the length of follow-up reported?

Yes: The length of follow-up was clearly reported.

No: The length of follow-up was not reported, or the duration of the study is unclear.

16. Were the number of patients lost to follow-up reported?

Yes: The number or proportion of patients lost to follow-up were reported.

No: The number or proportion of patients lost to follow-up were not reported.

17. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?

Yes: The study reports estimates of the random variability (for example, standard error, standard deviation, confidence intervals) for all relevant primary and secondary outcomes.

No: Estimates of the random variability are not reported for all relevant outcomes. The presentation of the random variability is unclear (for example, measure of dispersion reported without indicating if it is standard deviation or standard error).

18. Are adverse events reported?

Yes: The undesirable or unwanted consequences of the intervention during the study period or within a pre-specified period of time are reported. Absence of any adverse event(s) is acknowledged in the study.

No: There is no statement about the presence or absence of adverse events.

19. Are the conclusions of the study supported by results?

Yes: The main conclusions of the study are supported by the evidence presented in the results section.

No: The conclusions are not supported by the evidence presented in the results section.

Competing interest and source of support

20. Are both competing interest and source of support for the study reported?

Yes: Both competing interest and source of support (financial or other) received for the study are reported, or the absence of any competing interest and source of support are acknowledged.

No: Either no information is available about competing interest and source of support or only one of these elements is reported.

Table T.C.2: Quality assessment results of the case series studies

Study Characteristics		Turgeon et al.[18]	Koh et al.[22]	Benhamou et al.[20]	Vantyghem et al.[74]	Tharavanij et al.[64]
Study objective	1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?	√	√	×	√	√
Study design	2. Was the study conducted prospectively?	√	×	×	√	×
	3. Were the cases collected in more than one centre?	×	×	×	×	×
	4. Were participants recruited consecutively?	√	×	×	√	×
Study population	5. Are the characteristics of the participants included in the study described?	√	×	×	√	×
	6. Are the eligibility criteria for entry to the study explicit and appropriate?	√	×	√	√	×
	7. Did participants enter the study at a similar point in the disease?	×	×	×	×	×
Intervention/ co-intervention	8. Was the intervention clearly described in the study?	√	√	√	√	√
	9. Were additional interventions (co-interventions) clearly reported in the study?	√	√	×	√	√
Outcome measures	10. Are the outcome measures clearly defined in the introduction or methodology section?	√	√	√	√	√
	11. Were the main outcomes assessed blind/independent to intervention status?	×	×	×	×	×
	12. Were relevant outcomes appropriately measured with objective and/or subjective methods?	√	√	√	√	√
	13. Were outcomes measured before and after intervention?	√	√	√	√	√
Statistical analysis	14. Were the statistical tests used to assess the relevant outcomes appropriate?	×	√	√	√	√
Results and conclusion	15. Was the length of follow-up reported?	√	√	√	√	√
	16. Was the number lost to follow up reported?	√	√	√	√	√
	17. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	×	√	√	√	√
	18. Are adverse events reported?	√	√	×	√	√
	19. Are the conclusions of the study supported by results?	√	√	√	√	√
Competing interest and source of support	20. Are both competing interest and source of support for the study reported?	×	√	√	√	√
Total score (20)		14	13	11	17	12

Grey indicates most important criteria

Table T.C.2: Quality assessment results of the case series studies (cont'd)

Study Characteristics		Leitao et al.[65]	Gangemi et al.[24]	Badet et al.[12]	Maffi et al.[66]	Shapiro et al.[10]
Study objective	1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?	√	√	√	√	√
Study design	2. Was the study conducted prospectively?	×	√	√	×	√
	3. Were the cases collected in more than one centre?	×	×	√	×	√
	4. Were participants recruited consecutively?	×	√	×	×	×
Study population	5. Are the characteristics of the participants included in the study described?	√	√	√	√	×
	6. Are the eligibility criteria for entry to the study explicit and appropriate?	×	√	√	√	√
	7. Did participants enter the study at a similar point in the disease?	×	√	√	√	√
Intervention/ co-intervention	8. Was the intervention clearly described in the study?	√	√	√	√	√
	9. Were additional interventions (co-interventions) clearly reported in the study?	×	√	√	√	×
Outcome measures	10. Are the outcome measures clearly defined in the introduction or methodology section?	√	√	√	√	√
	11. Were the main outcomes assessed blind/independent to intervention status?	×	×	×	×	×
	12. Were relevant outcomes appropriately measured with objective and/or subjective methods?	√	×	√	×	×
	13. Were outcomes measured before and after intervention?	√	√	√	√	√
Statistical analysis	14. Were the statistical tests used to assess the relevant outcomes appropriate?	√	√	√	√	√
Results and conclusion	15. Was the length of follow-up reported?	√	√	√	√	√
	16. Was the number lost to follow up reported?	√	√	√	√	√
	17. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	√	√	√	√	√
	18. Are adverse events reported?	×	√	√	√	√
	19. Are the conclusions of the study supported by results?	√	√	√	√	√
Competing interest and source of support	20. Are both competing interest and source of support for the study reported?	×	×	×	×	√
Total score (20)		11	16	17	14	15

Table T.C.2: Quality assessment results of the case series studies (cont'd)

Study Characteristics		Frond et al.[63]	Ryan et al.[15]	Lee et al.[71]	Fiorina et al.[67]	Fiorina et al.[68]
Study objective	1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?	√	√	√	√	√
Study design	2. Was the study conducted prospectively?	√	×	√	×	×
	3. Were the cases collected in more than one centre?	×	×	×	×	×
	4. Were participants recruited consecutively?	×	×	×	×	×
Study population	5. Are the characteristics of the participants included in the study described?	√	√	×	×	√
	6. Are the eligibility criteria for entry to the study explicit and appropriate?	×	×	×	×	×
	7. Did participants enter the study at a similar point in the disease?	√	×	×	√	√
Intervention/ co-intervention	8. Was the intervention clearly described in the study?	√	√	×	√	√
	9. Were additional interventions (co-interventions) clearly reported in the study?	√	√	×	√	√
Outcome measures	10. Are the outcome measures clearly defined in the introduction or methodology section?	√	√	√	√	√
	11. Were the main outcomes assessed blind/independent to intervention status?	×	×	×	×	×
	12. Were relevant outcomes appropriately measured with objective and/or subjective methods?	×	√	√	√	√
	13. Were outcomes measured before and after intervention?	√	√	√	√	√
Statistical analysis	14. Were the statistical tests used to assess the relevant outcomes appropriate?	√	√	√	√	√
Results and conclusion	15. Was the length of follow-up reported?	√	√	√	√	√
	16. Was the number lost to follow up reported?	√	√	√	√	√
	17. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	√	√	×	√	√
	18. Are adverse events reported?	√	√	√	×	×
	19. Are the conclusions of the study supported by results?	√	√	√	√	√
Competing interest and source of support	20. Are both competing interest and source of support for the study reported?	×	×	×	×	×
Total score (20)		14	13	10	12	13

Table T.C.2: Quality assessment results of the case series studies (cont'd)

Study Characteristics		Benhamou et al.[70]	Toso et al.[62]	Keymeulen et al.[73]	Bertuzzi et al.[69]	Barshes et al.[72]
Study objective	1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?	√	√	√	√	√
Study design	2. Was the study conducted prospectively?	×	×	×	√	×
	3. Were the cases collected in more than one centre?	√	×	×	√	×
	4. Were participants recruited consecutively?	×	×	√	×	×
Study population	5. Are the characteristics of the participants included in the study described?	√	×	√	√	×
	6. Are the eligibility criteria for entry to the study explicit and appropriate?	√	×	√	×	×
	7. Did participants enter the study at a similar point in the disease?	√	×	×	√	×
Intervention/ co-intervention	8. Was the intervention clearly described in the study?	√	×	√	√	×
	9. Were additional interventions (co-interventions) clearly reported in the study?	√	×	√	√	×
Outcome measures	10. Are the outcome measures clearly defined in the introduction or methodology section?	√	×	√	√	√
	11. Were the main outcomes assessed blind/independent to intervention status?	√	×	√	×	×
	12. Were relevant outcomes appropriately measured with objective and/or subjective methods?	√	√	√	√	√
	13. Were outcomes measured before and after intervention?	√	√	√	√	√
Statistical analysis	14. Were the statistical tests used to assess the relevant outcomes appropriate?	×	√	√	√	√
Results and conclusion	15. Was the length of follow-up reported?	√	√	√	√	√
	16. Was the number lost to follow up reported?	√	√	√	√	√
	17. Does the study provide estimates of the random variability in the data analysis of relevant outcomes?	×	√	√	√	√
	18. Are adverse events reported?	√	×	√	√	×
	19. Are the conclusions of the study supported by results?	√	√	√	√	√
Competing interest and source of support	20. Are both competing interest and source of support for the study reported?	×	×	√	×	×
Total score (20)		15	8	17	16	9

Appendix T.D: Evidence table—comparative studies

Abbreviations

BP	blood pressure
CG	control group
D	day
DAC	daclizumab
DM	diabetes mellitus
EG	experimental group
EDV s^{-1}	end-diastolic volume per second
G	group
CMV	cytomegalovirus
EBV	Epstein-Barr virus
GFR	glomerular filtration rate
HrQoL	health-related quality of life
IIT	intensive insulin therapy
IAK	islet after kidney transplantation
IPT	insulin pump therapy
ITA	islet transplantation alone
IT-s	successful islet transplantation
IT-u	unsuccessful islet transplantation
Kg	kilogram
N	total number
NA	not available
NR	not relevant
NS	not significant
PAK	pancreas after kidney transplantation
PFR	peak filling rate
Pt(s)	patient(s)
SIK	simultaneous islet and kidney transplantation
SIR	sirolimus
SPK	simultaneous islet and pancreas transplantation
TAC	tacrolimus
Tg	triglyceride
U	unit
UAE	Urinary albumin excretion

Table T.D.1: Characteristics of the included comparative studies

Study	Warnock et al. 2008[55]	Venturini et al. 2006[56]*	Gerber et al. 2008[57]	Fiorina et al. 2005[58]*	Fiorina et al. 2005[27]*	Fiorina et al. 2003[59]	Vantyghem et al. 2009[60]	Frank et al. 2004[61]**
Clinical centre	Vancouver	Milan	Switzerland	Milan	Milan	Milan	France	Philadelphia
Data collection	prospective	Unclear	retrospective	retrospective	prospective	unclear	unclear	retrospective
No. of patients	42	20	38	42	234	241	30	43
EG	31 ITA	10 ITA	13 SIK	17 IAK	24 (18 IAK, 6 SIK)	37 IAK or SIK (24 IT-s, 13 IT-u)	13 (7 ITA, 6 IAK)	13 (9 ITA, 4 IAK)
CG	42 IIT	10 IIT	25 SPK	25 IIT	210 (166 SPK, 44 IIT)	204 (162 SPK, 42 IIT)	17 IIT	30 (25 SPK, 5 PAK)
Age (yrs)								
EG	45.6±8.3	38.0±2.2	52.6±9.5	47.7±1.3	41.1±1.7	IT-s: 42.5±1.4 IT-u: 40.6±3.8	43.1±6.2	42 (28–56)
CG	46±8.5	39.0±3.0	39.9±6.0	49.2±2.0	SPK: 37.9±0.9 IIT: 39.9±2.0	SPK: 38.1±0.5 IIT: 42.1±1.4	40.0±7.7	40 (24–55)
P value	NA	NS	0.0001	NS	NS	NS	NS	NS
Gender (M/F)								
EG	17/14	NA	46%/54%	7/10	NA	NA	7/6	6/7
CG	20/22	NA	52%/48%	16/9	NA	NA	5/12	20/10
P value	NA	comparable	NS	NS	NA	NA	NS	NS
Weight (Kg)								
EG	70.2±10.4	NA	NA	59.7±2.0	59.5±1.9	IT-s: 59.5±1.9 IT-u: 59.3±3.1	65.4±9	NA
CG	73.2±3.4	NA	NA	59.3±3.1	SPK: 58.7±2.7 IIT: 62.0±2.0	SPK: 58.7±2.7 IIT: 62.0±2.0	68.2±15.8	NA
P value	NA	NA	NA	NS	NS	NS	NS	NA

Table T.D.1: Characteristics of the included comparative studies (cont'd)

Study	Warnock et al. 2008[55]	Venturini et al. 2006[56]*	Gerber et al. 2008[57]	Fiorina et al. 2005[58]*	Fiorina et al. 2005[27]*	Fiorina et al. 2003[59]	Vantyghem et al. 2009[60]	Frank et al. 2004[61]**
BMI (kg/m^2)								
EG	25.3±2.9	22.4±0.6	24.7±3.1	22.0±0.8	NA	NA	NA	23.4 (16.6-27.7)
CG	25.7±3.4	24.6±0.9	22.4±2.1	23.4±0.9	NA	NA	NA	23.7 (17.8-28.2)
P value	NA	NS	0.03	NS	NA	NS	NA	NS
Duration of DM (yrs)								
EG	32.9±9.0	24.9±2.3	41.7±9.1	31.9±2.3	24.9±2.1	IT-s: 27.3±2.4 IT-u: 26.7±1.7	25.3±8.7	28 (9–41)
CG	30.2±9.4	25.2±2.8	30.3±7.1	30.4±1.7	SPK: 26.4±0.9 IIT: 22.7±1.4	SPK: 25.2±0.5 IIT: 24.3±1.7	23.3±11.9	27 (11–42)
P value	NA	NS	0.0009	NS	NS	NS	NS	NS
Baseline insulin requirement (U/kg/d)								
EG	NA	31.1±4.2 (U/d)	0.56±0.17	25.2±4.3	NA	NA	46±12 (U/d)	NA
CG	NA	49.0±3.51 (U/d)	NA	32.1±7.0	NA	NA	43±18 (U/d)	NA
P value	NA	NA	NA	<0.05	NA	NA	NS	NA
Baseline HbA1c (%)								
EG	7.0±0.7	7.95±0.29	8.1±1.5	7.7±0.3	8.3±0.3 (lower)	IT-s: 8.3±0.3 IT-u: 7.7±0.6	8.2±1.1	NA
CG	8.1±1.2	8.28±0.36	8.7±1.9	8.6±0.6	SPK: 11.2±1.7 IIT: 11.1±2.3	SPK: 11.2±1.7 IIT: 11.1±2.3	8.4±1.8	NA
P value	NA	NA	NS	NS	NA	NA	NS	NA

Values expressed as mean ±standard deviation unless indicated otherwise; * mean ± standard error; ** mean (range)

Table T.D.2: Procedure–related AEs reported in the comparative studies

AEs	Warnock et al. 2008[55]	Venturini et al. 2006[56]	Gerber et al. 2008[57]	Fiorina et al. 2005[58]	Fiorina et al. 2005[27]	Fiorina et al. 2003[59]	Vantyghem et al. 2009[60]	Frank et al. 2004[61]
Intervention (EG)	31 ITA	10 ITA	13 SIK	17 IAK	24 (18 IAK, 6 SIK)	37 IAK or SIK (24 IT-s, 13 IT-u)	13 (7 ITA, 6 IAK)	13 (9 ITA, 4 IAK)
Comparator (CG)	42 IIT	10 IIT	25 SPK	25 IIT	210 (166 SPK, 44 IIT)	204 (162 SPK, 42 IIT)	17 IIT	30 (25 SPK, 5 PAK)
Death								
EG	0	0	0	0	0	0	0	0
CG	0	0	0	0	0	0	0	1 (unknown cause)
Intraperitoneal bleeding								
EG	NA	NA	2 (15%)[†]	NA	NA	NA	NA	2 pts (15%)
CG	NR	NR	2 (8%)[‡]	NA	NA	NA	NA	13 pts (43%)
PTV								
EG	NA	NA	NA	NA	NA	NA	NA	NA
CG	NA	NR	NA	NA	NA	NR	NR	NA
Elevated liver enzymes								
EG	NA	NA	NA	NA	NA	NA	NA	NA
CG	NA	NR	NA	NA	NA	NR	NR	NA
Hepatic steatosis								
EG	NA	NA	NA	NA	NA	NA	NA	3 pts (3 in ITA, 0 in IAK) (23%)
CG	NA	NR	NA	NA	NA	NR	NR	NA

Table T.D.2: Procedure–related AEs reported in the comparative studies (cont'd)

AEs	Warnock et al. 2008[55]	Venturini et al. 2006[56]	Gerber et al. 2008[57]	Fiorina et al. 2005[58]	Fiorina et al. 2005[27]	Fiorina et al. 2003[59]	Vantyghem et al. 2009[60]	Frank et al. 2004[61]
Laparotomy								
EG	NA	NA	0	NA	NA	NA	NA	0
CG	NA	NA	10 (40%)*	NA	NA	NA	NA	7 (23%)
Infection								
EG	NA	NA	0	NA	NA	NA	9	
CG	NA	NA	2 (20%)	NA	NA	NA	1	
Hospitalization								
EG	NA	NA	NA	NA	NA	NA	NA	4 day (Fig 2.a)
CG	NA	NA	NA	NA	NA	NA	NA	13 days (Fig. 2.a)
Total AEs								
EG	NA	NA	2 (15%)	NA	NA	NA	5.2 AEs/pt/yr (most minor)**	NA
CG	NA	NA	12 (48%)	NA	NA	NA	1.2 AEs/pt/yr (most minor)**	NA
Difference	NA	NA	0.19	NA	NA	NA	4-fold higher in EG than in CG during the 1st, 2nd, and 3rd years	NA

† no surgery required; ‡ surgery required; * P=0.04; ** Common Terminology Criteria for adverse events. Minor: grades 1 and 2, Major: grades 3 and 4. (version 3.0, National Cancer Institute)

Table T.D.3: Immunosuppression-related AEs reported in the comparative studies

AEs	Warnock et al. 2008[55]	Venturini et al. 2006[56]	Gerber et al. 2008[57]	Fiorina et al. 2005[58]	Fiorina et al. 2005[27]	Fiorina et al. 2003[59]	Vantyghem et al. 2009[60]	Frank et al. 2004[61]
Mouth ulcer								
EG	NA	NA	NA	NA	NA	NA	NA	10 pts (9 ITA, 1 IAK) (77%)
CG	NR	NR	NA	NR	NA	NA	NR	NA
Nausea/ vomiting								
EG	NA	NA	NA	NA	NA	NA	NA	NA
CG	NR	NR		NR	NA	NA	NR	NA
Diarrhea								
EG	NA	NA	NA	NA	NA	NA	6	NA
CG	NR	NR	NA	NR	NA	NA	NR	NA
Ulceration of small bowel								
EG	NA	NA	NA	NA	NA	NA	NA	NA
CG	NR	NR	NA	NR	NA	NA	NR	NA
Anemia								
EG	NA	NA	NA	NA	NA	NA	4	?
CG	NR	NR	NA	NR	NA	NA	NR	?
Leukopenia								
EG	NA	NA	NA	NA	NA	NA	NA	?
CG	NR	NR	NA	NR	NA	NA	NR	?
Neutropenia								
EG	NA	NA	NA	NA	NA	NA	NA	?
CG	NR	NR	NA	NR	NA	NA	NR	?

Table T.D.3: Immunosuppression-related AEs reported in the comparative studies (cont'd)

AEs	Warnock et al. 2008[55]	Venturini et al. 2006[56]	Gerber et al. 2008[57]	Fiorina et al. 2005[58]	Fiorina et al. 2005[27]	Fiorina et al. 2003[59]	Vantyghem et al. 2009[60]	Frank et al. 2004[61]
Peripheral edema								
EG	NA	NA	NA	NA	NA	NA	3/13 pts (23%)	54%
CG	NR	NR	NA	NR	NA	NA	NR	NA
Increased sCr								
EG	NA	NA	NA	NA	?	?	1/13 pt (8%)	NA
CG	NR	NR	NA	NR	?	?	NR	NA
CrCl								
EG	NA	NA	NA	NA	?	?	NA	Mild decline in most pts
CG	NR	NR	NA	NR	?	?	NR	NA
Proteinuremia								
EG	NA	NA	NA	NA	?	?	3/13 pts (23%)	NA
CG	NR	NR	NA	NR	?	?	NR	NA
Micro-albuminuria								
EG	NA	NA	NA	NA	?	?	NA	NA
CG	NR	NR	NA	NR	?	?	NA	NA
Menstrual irregularity								
EG	NA	NA	NA	NA	NA	NA	NA	NA
CG	NR	NR	NA	NR	NA	NA	NA	NA
Ovarian cyst								
EG	NA	NA	NA	NA	NA	NA	NA	NA
CG	NR	NR	NA	NR	NA	NA	NA	NA
CMV								
EG	1	NA	NA	NA	NA	NA	NA	0
CG	NR	NR	NA	NR	NA	NA	NA	3 (10%)

Table T.D.3: Immunosuppression-related AEs reported in the comparative studies (cont'd)

AEs	Warnock et al. 2008[55]	Venturini et al. 2006[56]	Gerber et al. 2008[57]	Fiorina et al. 2005[58]	Fiorina et al. 2005[27]	Fiorina et al. 2003[59]	Vantyghem et al. 2009[60]	Frank et al. 2004[61]
EBV								
EG	NA	NA	NA	NA	NA	NA	NA	NA
CG	NR	NR	NA	NR	NA	NA	NR	NA
Cancer								
EG	Skin cancer in 1/31 pts (3%)	NA	NA	NA	NA	NA	NA	1 skin squamous cell cancer 2.5 yrs post-transplant
CG	NR	NR	NA	NA	NA	NA	NR	NA
PTLD								
EG	NA	NA	NA	NA	NA	NA	NA	NA
CG	NR	NR	NA	NR	NA	NA	NR	NA
Headache								
EG	NA	NA	NA	NA	NA	NA	NA	NA
CG	NR	NR	NA	NR	NA	NA	NR	NA
Fatigue								
EG	2/31 (6%)	NA	NA	NA	NA	NA	NA	NA
CG	NR	NR	NA	NR	NA	NA	NR	NA
Weight loss								
EG	NA	NA	NA	NA	NA	NA	5	NA
CG	NR	NR	NA	NR	NA	NA	NR	NA
IS change								
EG	NA	NA	NA	NA	NA	NA	NA	NA
CG	NR	NR	NA	NR	NA	NA	NR	NA
IS withdrawal								
EG	3/25 (12%)	NA	NA	NA	NA	NA	NA	1 pt
CG	NR	NR	NA	NR	NA	NA	NR	NA

Table T.D.4: Treatment effects of islet transplantation in non-uremic patients

Efficacy outcome	Warnock et al. 2008[55]	Venturini et al. 2006[56*]
No. of patients	N=42	N=20
Intervention No of patients No. of infusions Immunosuppressive drugs	ITA G1=31 1, 2, 3, 4 infusions: 7, 12, 9, and 3 pts, respectively ATG, SIR or MMF, and TAC	ITA G1=10 Total 18 (range 1–3) Edmonton protocol: DAC, SIR, TAC
Comparator	IIT (no details available) G2=42	IIT (no details available) G2=10
Co-intervention	Exenatide in 20 ITA pts	NA
Length of follow-up	G1 38.4±18 (range 12-58) vs. G2 34±18 (range 9-67) months (NS)	1 year
Graft function/glycemic control		
Insulin independence	Any time: 16/25 (64%) At > 1 and < 5 years: 3 pts (> 3 years: 1 pt; > 4 years: 2 pt) At ≥ 5 years: 1 pt	NA
C-peptide (ng/mL)	Fasting 448±184 (pmol/mL) in insulin independent pts vs. 241±141 in pts requiring insulin (P<0.01)	ITA: 0.20±0.06 pre- vs. 0.84±0.18 at 1 year post (P<0.01) IIT: 0.21±0.11 pre- vs. 0.14±0.08 at 1 year post (NS)
HbA1c (%)	Median value for ITA lower than IIT during all time periods Pooling all numbers during follow-up: G1: 6.6 vs. G2 7.4 (P < 0.01)	ITA: 7.95±0.29 pre- vs. 7.50±0.46 at 1 year (P=0.06); IIT: 8.28±0.36 pre-: vs. 8.15±0.22 at 1 year (NS)
Insulin requirement (U/day)	At ≤ 1 year: 38% ITA recipients returned to insulin therapy. Pts with particle graft function take 33% to 75% of pre-transplant dose	ITA: 31.1±4.2 pre- vs. 20.3±5.5 at 1 year post (P=0.06); IIT: 49.0±3.51 pre- vs. 48.0±4.05 at 1 year post (NS)
Hypoglycemia	NA	NA
HrQoL	NA	NA
Secondary complications of DM		
Cardiovascular disease	NA	No significant change in BP, cholesterol, TG, glycemia in either group
Retinopathy	Progression occurred in ITA 0/51 eyes vs. IIT 10/82 eyes (P<0.01)	Blood flow velocity of central retinal artery and central retinal vein: increased in ITA (ss) but not in IIT group (NS)
Nephropathy	Decline of GFR (mL/min/month): ITA 0.12±0.7 vs. IIT 0.45±0.7 (P=0.1). Slope of GFR decline in ITA did not differ from 0 nor from that expected in the general population while, in IIT, differed from 0 and faster than expected for general population	NA
Neuropathy	Nerve conduction velocity: no significant deterioration was observed from baseline in either group.	NA

All data are expressed as mean ± SD, unless indicated otherwise. *mean ± SE

Table T.D.5: Treatment effects of islet transplantation in uremic patients

Studies	Gerber et al. 2008[57]	Fiorina et al. 2005[58]	Fiorina et al. 2005[27]	Fiorina et al. 2005[59]
No. of patients	38 (SIK G1=13, SPK G2=25)	42 (IAK G1=17, IIT G2=25)	234 (18 IAK, 6 SIK G1=24, SPK G2=166, IIT G3=44)	241 (Successful IAK or SIK G1=24, unsuccessful IAK or SIK G2=13, SPK G3=162, IIT G4=42)
Intervention				
No. of islet infusions	1, 2, 3, 4, 5 infusions: 7, 1, 2, 2, and 1 pts, respectively	NA	NA	NA
IS regimen	Edmonton protocol (DAC, SIR, TAC)	Induction ATG, maintenance cyclosporine, MMF, and prednisone	Induction ATG, maintenance cyclosporine, MMF, and prednisone	Induction ATG, maintenance cyclosporine, MMF, and prednisone
Length of FU	SIK: mean 38 (range 12–67) months vs. SPK mean 42 (range 13–66) months	3 years	Up to 6 years At 4 yr: G1=21, G2=156, G3=41 At 6 yrs: G1=12, G2=141, G3=38	63.0±7.2 months
Graft function/glycemic control				
Primary non function	2 in SIK vs. 0 in SPK	NA	NA	NA
Early graft failure (within 6 months)	NA	10 pts	11 pts	13 pts
Insulin independence	At 1 year: 31% in SIK vs. 96% in SPK	>3 months: 12/17 At ≥1 year: NA	At 6 years: G1: 0 vs. G2 100%	NA
Insulin requirement (U/kg/day)	50% reduction in SIK group	IAK: 25.2±4.3 pre- vs. 17.3±3.4 3 years post-transplant (P<0.05), IIT 32.1±7.0 pre- vs. 35.1±4.4 3 years post-transplant (NS); IAK vs. IIT pre- and 3 years post-transplant P<0.05	Reduction of 50% from baseline at 2, 4, and 6 years in G1.	At 1 year: G1: 19.1±4.3 vs. G2: 46.0±6.2 U/day (P<0.01) At 4 years: G1: 23.0±5.3 vs. G2: 51.8±8.5 U/day (P=0.01) At 7 years: G1: 17.8±4.7 vs. 36.4±9.7 U/day (NS)
C-peptide (ng/mL)	At the end of FU: SIK 1.005±0.735 vs. SPK 2.505±0.762 nmol/L (P not reported)	At 3 years: IAK 1.7±0.2 vs. IIT 0.3±0.1 (P<0.01)	G1: 1.6±0.2 pre- vs. 1.1±0.4 at 6 years (NS)	Baseline: G1: 0.15±0.02 vs. G2: 0.15±0.03 vs. G3: 0.11±0.02 vs. G4: 0.13±0.03 At 1 year: G1: 1.64±0.25 vs. G2: 0.39±0.25 vs. G3: 1.62±0.15 vs. G4: 0.21±0.09 At 4 years: G1: 1.09±0.16 vs. G2: 0.14±0.02 vs. G3: 1.43±0.21 vs. G4:

				0.17±0.05 At 7 years: G1: 1.39±0.49 vs. G2: 0.10±0.01 vs. G3: 1.39±0.22 vs. G4: 0.15±0.04
HbA1c (%)	Baseline: SIK (n=13): 8.1±1.5 vs. SPK (n=25): 8.7±1.9 (NS) At 1 year: SIK (n=13): 6.2±0.8 vs. SPK (n=25): 6.0±0.6 (NS) At 2 years: SIK (n=9): 6.3±0.7 vs. SPK(n= 22): 5.7±0.5 (P<0.05) At 3 years: SIK (n=8): 6.7±1.0 vs. SPK (n=15): 5.8±0.4 (P<0.05) At 4 years: SIK (n=5): 6.2±0.5 vs. SPK (n=10): 5.5±0.6 (NS) At 5 years: SIK (n=1): 5.7 vs. SPK (n=3): 5.3	IAK: 7.7±0.3 pre- vs. 7.7±0.2 3 years post-transplant (NS), IIT: 8.6±0.6 pre- vs. 8.1±0.5 3 years post-transplant; Difference between the groups and before and after intervention: NS	G1: 7.4±0.2 pre- vs. 8.1±0.3 at 6 years (P<0.05) G2: 5.7±0.1 pre- vs. 5.8±0.2 at 6 years (NS) G3: 8.0±0.4 pre- vs. 7.8±0.2 at 6 years (NS)	Baseline: G1: 8.3±0.3 vs. G2: 7.7±0.6 vs. G3: 11.2±1.7 vs. G4: 11.1±2.3 At 1 year: G1: 7.35±0.29 vs. G2: 7.96±0.35 vs. G3: 5.8±0.8 vs. G4: 8.9±1.3 (NS) At 4 years: G1: 7.33±0.51 vs. G2: 8.08±0.43 vs. G3: 6.0±0.1 vs. 8.6±0.4 (NS) At 7 years: G1: 7.38±0.35 vs. G2: 8.26±0.61 vs. G3: 6.2±0.2 vs. G4: 8.7±0.5 (NS)
SH	Pre-transplant: 10/13 in SIK Post-transplant: 0 in both groups	NA	NA	NA
HrQoL	NA	NA	NA	NA
Secondary complications of diabetes				
Cardiovascular disease/risk factors	No difference between the two groups in BP, TG, total cholesterol, HDL-cholesterol, LDL-cholesterol before and after transplantation	**Cardiovascular function** Ejection fraction: improved in IAK group but not in IIT group. IAK: 68.2±3.5 at baseline to 74.9±2.1 3 years post (P<0.05); PFR (in EDV s^{-1}): IAK: 3.87±0.25 at baseline to 4.20±0.37 3 years post-transplant (P<0.05) No CV events reported	**TG:** At 2 and 4 years: lower in G1, G2 than G3 (P<0.01) At 6 years: Lower in G2 than G1, G3 **Total cholesterol:** At 2 to 6 years: no change in G1, slightly increase from baseline in G2 (P<0.01), At 2 years: slight increase in G3 (P<0.05) **SBP:** At 4 years: slight reduction in G2 (P<0.05) At 6 years: Slight reduction in G3	**Cardiovascular death:** G1: 5%, G1+G2: 18% (G2 46%), G3: 8%, G4: 19% (P-value not reported)

			(P<0.05)	
Retinopathy	NA	NA		NA
Nephropathy	No difference between the two groups at baseline. GFR 10 mL/min/1.73 m^2 higher in SPK than in SIK group during FU (NS)	NA	**Kidney graft survival** At 6 years: G1: 86%, G2: 73%, G3: 42% **sCr (mg/dl)** (pre-. Vs. 6-yr post) G1: 1.38±0.08 vs. 1.91±0.36 (NS) G2: 1.48±0.03 vs. 1.46±0.06 (NS) G3: 1.58±0.08 vs. 2.78±0.44 (vs. G2 P<0.01) **UAE (mg/dl)** Baseline: G1: 76.9±26.0 vs. G2: 22.3±3.7 (P<0.01) vs. G3: 31.4±9.0 At 2 to 4 years: lower in G2 than G1 (P<0.01) At 6 years: G1: 46.9±21.2 vs. G2: 12.0±1.2 vs. G3: 82.9±33.6 (G2 vs G3 P<0.01) **Kidney biopsy:** normal in three groups	**UAE** Increased in 1 pt in G1 vs. 6 pts in G2 (P<0.05)
Neuropathy	NA	NA		
Patient survival	NA	NA	NA	At 1 year: G1: 100% vs. G2: 84% (P=0.02) At 2 years: G1: 100% vs. G2: 75% (P=0.02) At 7 years: G1: 90% vs. G2: 45% (P=0.02)

Table T.D.6: Treatment effects of islet transplantation from studies with mixed non-uremic and uremic patients

Studies	Vantyghem et al. 2009[60]	Frank et al. 2004[61]
No. of patients	30 (7 ITA, 6 IAK G1=13, IIT G2=17)	43 (9 ITA, 4 IAK G1=13, 25 SPK, 5 PAK G2=30)
Intervention		
No. of islet infusions	2 (6 pts), 3 (7 pts)	NA
Immunosuppressive drugs	Edmonton protocol (DAC, SIR, TAC)	Edmonton protocol (DAC, SIR, TAC)
Length of follow-up	Up to 3 yrs	Median 1.4 years in G1 vs. 1.2 years in G2
Graft function/glycemic control		
Primary non-function	0	1 pt
Graft loss		G1: 4 pts; G2: 4 pts (3 immediate, 1 at 2 years)
Insulin independence	10/13 (77%) at 1 year	Any time: 11/12 (92%) in G1 At 2 years: 42% in G1 vs. 83% in G2
Insulin requirement (U/kg/day)	Baseline: G1: 46±12 vs. G2: 43±18 U/day (NS) At 1 year: G1: 4.4 ±8.5 vs. G2: 43±20 U/day (P<0.0001) At 3 years: G1: 12±16 vs. G2: 46±19 U/day (P<0.0001)	Reduced
C-peptide (ng/mL)	1.5±0.7 at 3 months	1.7 in G1 vs. 3.9 in G2 during first 600 days post-transplant (P<0.001)
HbA1c (%)	Reduced in both groups during FU. Baseline: G1: 8.2±1.1 vs. G2: 8.4±1.8 (NS) At 1 year: G1: 6.1±0.7 vs. G2: 7.9±1.0 (P<0.0001) At 3 years: G1: 6.6±1.1 vs. G2: 8.1±1.3 (P<0.01)	At 1 year: 6.3% in G1 vs. 5.0% in G2 (P ≤0.001)
SH	No. of Hypo/week: Significant reduced in G1 up to 2 yrs. Baseline: G1: 2.6±2.1 vs. G2: 2.9±2.2 (NS) At 1 year: G1: 0.3±0.5 vs. G2: 1.6±1.6 (P<0.01) At 3 years: G1: 0.7±1.1 vs. G2: 1.7±1.8 (NS)	Pre-: 100% in ITA recipients; post-transplant: none in pts with graft function
HrQoL	NA	NA
Secondary complications	NA	NA

Appendix T.E: Evidence table – case series studies

Abbreviations

BP	blood pressure
D	day
DAC	daclizumab
DM	diabetes mellitus
G	group
CMV	cytomeganovirus
EBV	Epstein-Barr virus
GFR	glomerular filtration rate
HrQoL	health-related quality of life
IIT	intensive insulin therapy
IAK	islet after kidney transplantation
IPT	insulin pump therapy
ITA	islet transplantation alone
IT-s	successful islet transplantation
IT-u	unsuccessful islet transplantation
Kg	kilogram
N	number
NA	not available
NR	not relevant
NS	not significant
PFR	peak filling rate
Pt(s)	patient(s)
SIK	simultaneous islet and kidney transplantation
SIR	sirolimus
TAC	tacrolimus
Tg	triglycerid
U	unit
UAE	urinary albumin excretion

Table T.E.1: Safety profile of islet transplantation in non-uremic patients

Study	Procedure-related AEs	Immunosuppression-related AEs
Shapiro et al. 2006[10] International multicentre trial (9 centres: 6 in America, 3 in Europe) N=36	Total No. of serious events: 38 Death: 0 Intra-peritoneal bleeding: 7/77 (9%) procedures, 4 requiring blood transfusion, one requiring laparotomy PVT: partial branch-vein occlusion in 2/36 (6%) pts Liver abnormality: mild hepatic steatosis on MRI in 4/13 (31%) pts at 2 years	Renal function: sCr increased 0.007 mg/dl/mo (P= 0.001); CrCl decreased 0.45 ml/min/1.73 m^2/mo (P=0.06); 13/36 (36%) pts developed microalbuminuria during follow-up. Change in IS regimen: 9/36 (25%) pts switched to an alternative, non-SIR-based immunosuppressive regimen because of side effects. IS discontinuation: 2 pts (1 due to headache, 1 due to mouth ulcer and diarrhea) Other: mouth ulcers (92%), anemia (81%), leucopenia (75%), diarrhea (64%), headache (56%), neutropenia (53%), nausea (50%), vomiting (42%), acne (39%), and fatigue (39%); no CMV infection, no PTLD, no cancer
Ryan et al. 2005[15] Edmonton N=65	Death: 1 pt died suddenly (accidental) Intra-peritoneal bleeding: 15/65 (23%) pts; blood transfusion on required on seven occasions, laparotomy in 2 pts PTV: segmental branch thrombosis in 5/65 (8%) pts Liver abnormality: AST increased to > 2.5 times the ULN in 55% of procedures and > 5 times the ULN in 23% of procedures (usually resolved within 4 weeks); hepatic steatosis on MRI: 8/36 (22%) pts post-transplant.	Renal function (for 47 pts who completed procedure): 5 pts progressed from micro- to macroalbuminuria and 3 pts progressed from normal to microalbuminuria (17%). sCr levels increased post-transplant. No significant change in CrCl, albumin excretion rate, or 24-hr protein excretion rate post-transplant Change in IS regimen: 10/43 (23%) pts; 5 pts switched to TAC and MMF, 3 to SIR and MMF, 2 to low-dose SIR, TAC, and MMF IS discontinuation: not reported Other: mouth ulcer (89%), diarrhea (60%), acne (52%), edema (43%), ovarian cysts (very common in pre-menopausal women), pneumonia (3 pts), weight loss (common), CMV infection (2 pts had seroconversion but no overt CMV disease), cancer (1 pt had papillary carcinoma of the thyroid)
Froud et a.2005[63] Miami N=16	Death: 0 Intra-peritoneal bleeding: 2/34 (6%) procedures; 1 pt required a blood transfusion PVT: 0 Liver abnormality: a transient rise in liver transaminases—resolved within 2 to 3 weeks—followed each infusion; fatty liver on MRI: 1/13 (8%) pts	Renal function: sCr increased in 2 pts; 5 pts developed macroalbuminuria; all pts developed proteinuria Change in IS regimen: removal of TAC in 4 pts due to short-term memory loss, renal dysfunction, eczema, and insomnia/depression IS discontinuation: 3 pts due to aspiration pneumonia, parvovirus infection, and hypereosinophilia Other: leucopenia/neutropenia (9 pts), new onset or exacerbation of hyperlipidemia (14/16 pts), mouth ulcer, peripheral edema and other SIR- or TAC-related side effects (common), sub-clinical CMV disease (1 pt)

Maffi et al. 2007[66] San Raffaele Scientific Institute, Milan, Italy N=19	Death: NA Intra-peritoneal bleeding: 3 pts PVT: small portal branch in 1 pt (5%) Liver abnormality: AST & ALT increased in 10/14 pts (71%); higher elevation after the first transplant, compared with the second and third transplants; returned to normal within 2 months of transplant	Renal function: sCr increased in 2 pts and progressed to ESRD, despite withdrawal of immunosuppressive drugs; CrCl remained within normal range for pts with normal baseline CrCl, decreased in 2 pts with decreased baseline values. 24-hour UPE worsened (> 300mg/24 hrs) in 4 pts Change in IS regimen: 6 pts changed from SIR to MMF because of mouth ulcer, joint pain, or edema; 1 pt changed from TAC to cyclosporine (because of tremor) IS discontinuation: 4 pts (2 pts due to deterioration of renal function, 1 pt due to intolerance to immunosuppression, 1 pt due to graft failure) Other: NA
Badet et al. 2007[12] Swiss–French GRAGIL group N=10	Death: 0 Intra-peritoneal bleeding: 1 pt (10%) PVT: segmental branch1 in 1 pt (10%) Liver abnormality: liver transaminases increased in 1 pt (10%) and returned to normal within 1 month	Renal function: NA Change in IS regimen: TAC to MMF (1 pt, because of acute optic neuropathy) IS discontinuation: 0 Other: NA
Keymeulen et al. 2006[73] Brussels, Belgium N=24	Death: 0 Intra-peritoneal bleeding: 0 PVT: 0 Liver abnormality: ALT increased in 8/24 pts (33%)	Renal function: CrCl 16% lower, 1 year post-transplant; none presented sCr > 2 mg/dl; albuminuria decreased in 8/8 pts with pre-transplant micro- or macroalbuminuria. IS change: NA IS discontinuation: 1 pt (due to MMF-caused gastrointestinal symptoms) Other: fever (8 pts); pyrosis (heartburn) (9 pts); cerebellar ataxia (1 pt); CMV hepatitis (1 pt); leucopenia (17 pts at 3 months and 6 pts at 1 year); weight loss (22 pts)
Turgeon et al. 2010[18] Atlanta N=12 G1(Edmonton protocol): n1=8 G2 (Efalizumab): n2=4	Death: 0 Intra-peritoneal bleeding: NA PVT: NA Liver abnormality: ALT, AST higher in G1 than G2 (P=0.03)	Renal function: no clinically significant change IS change: all 8 pts in G1 converted from SIR to MMF (due to side effects) IS discontinuation: 0 Other: Mouth ulcer (G1: 5/8, G2: 0/4); diarrhea (G1 7/8, G2: 0/4); leukopenia (G1: 8/8; G2: 0/4); anemia (G1: 8/8; G2: 2/4); PTLD (0); cancer (0); opportunistic infection: 0; G2 3/4 EBV but no clinical sign; allosensitization (G1: 4/8 DSA positive; G2: 0)

Gangemi et al. 2008[24] Chicago N=10	Death: 0 Bleeding: 2 (11% of infusions, 20% of pts) PVT: 0 Liver abnormality: NA	Renal function: 3 pts increased Cr levels Change in IS drugs: 1 pt switched from SIR to MMF (due to viral stomatitis, severe anemia, elevated Cr) Discontinuation of IS drugs: 1 pt (due to side effects) Other: Mouth ulcer (0); anemia: 10 (100%) transient; cancer (2 pts developed breast cancer); weight loss: 10 (100%), from 62.3±4.5 to 59.3±5.6 kg at 1 year (NS); female reproductive system (1 pt underwent abdominal hysterectomy for irregular menstrual bleeding and ruptured ovarian cyst)
Vantyghem et al. 2009[74] France N=14	Death: 0 Bleeding: 0 PVT: 0 Liver abnormality: liver enzyme elevated in 3 pts (21%) Other: bile leak (1 pt); mechanical bowel obstruction (1 pt)	Renal function: At 3.3 years (2.8 to 4.0) sCr in normal range in all pts (100%); microalbuminuria (> 30 mg/day) persisted in 1 pt and developed in 5 pts Change in IS drugs: NA Discontinuation of IS drugs: 1 pt Other: diarrhea (4 pts, 29 %); leukopenia: (12 pts, 86%, with 1 requiring lenograstin treatment and discontinuation of IS); anemia: (5, 36 %); allosensitization (not detected in any pt); increased OA pain (3 pts)

Table T.E.2: Safety profile of islet transplantation in uremic patients

Study	Procedure-related AEs	Immunosuppression-related AEs
Fiorina et al. 2003[67,68] Milan N=36	NA	NA
Bertuzzi et al. 2002[69] Milan N=15	Death: 0 Bleeding: 2 (1 hemothorax, 1 hemoperitoneum) PVT: NA Liver abnormality: NA	NA
Benhamou et al. 2001[70] GRAGIL N=10	Death: 0 Bleeding: perihepatic hematoma in 3 pts PVT: 0 Liver abnormality: transient and reversible liver enzyme increase in some pts	Renal function: remained stable during the study period. Change in IS drugs: NA Discontinuation of IS drugs: NA Other: allosensitization (none in 7/10 pts; 1 pt had IA-2 antibody pre-transplant and persist during FU, but reached insulin independence; 2 pts developed anti-GAD and IA-2 antibodies and lost graft function)

Table T.E.3: Treatment effects of islet transplantation in non-uremic patients

Study	Patient	Intervention	Outcomes
Shapiro et al. 2006[10] International multicentre trial (nine centres: six in America, three in Europe)	**Total No.:** 36 **Age** (yr): 41 ± 2(SE) **Gender** (M/F): NA **Diabetes duration** (yr)**:** 27±2 (SE) **BMI** (kg/m^2): 22 (SE < 1) **Hypoglycemia:** 35 (97%) pts (severe, recurrent) **Labile diabetes:** 20 (56%) pts (severe) **Baseline renal function:** 2/36 (6%) pts had micro- and 1/36 (3%) pts had microalbuminuria.	**Culture of islets:** no **No. of infusions:** 1: 11 (31%) pts 2: 9 (25%) pts 3: 16 (44%) pts **Total IE/kg:** 13,473 ± 923 (range 5,189 to 22,482) **Immunosuppressive regimen:** Edmonton protocol (DAC, SIR, TAC) **Co-intervention:** NA **Follow-up:** median 41 (range 37 to 50) months after the first transplantation 1 year: 36 pts 2 years: 35 pts 3 years: 21 pts	**Insulin independence:** Any time: 21/36 (58%) pts 1 year: 16/36 (44%) pts (5 pts with one infusion, 6 pts with two infusions, 5 pts with three infusions) 2 years: 5/36 (14%) pts **Partial graft function (C-peptide ≥ 0.3 ng/ml but require insulin):** Any time: 24/36 (67%) pts 1 year: 10/36 (28%) pts Complete graft loss: 10/36 (28%) pts **Insulin requirement:** reduced in insulin independent or partial graft function pts over 2 years* **Hypoglycemia:** full protection in insulin independent group **C-peptide level:** detectable (≥ 0.3 ng/ml) in 70% of pts at 2 years** **HbA1c** (%): reduced in insulin independent (under 6.0) or partial graft function (under 7.0) pts over 2 years*** **HrQoL:** NA **Diabetic complications:** NA

* P < 0.001 for the comparison between the insulin-independence group and the partial-function group, and P < 0.001 for the comparison between baseline and each follow-up time point in both groups.

** P = 0.17 for the comparison between the insulin-independence group and the partial-function group, and P < 0.001 for the comparison between baseline and each follow-up time point in both groups.

*** Data extracted from Figure 2 in the study. P < 0.001 for the comparison between the insulin-independence group and the partial-function group, and P < 0.001 for the comparison between baseline and each follow-up time point, except at 12 months in both groups.

Table T.E.3: Treatment effects of islet transplantation in non-uremic patients (cont'd)

Study	Patient	Intervention	Outcomes
Ryan et al. 2005[15] University of Alberta, Edmonton, Canada Single centre	**Total No.:** 65 **Age** (yr): 42.9 ± 1.2 **Gender** (M/F): 28/37 (43%/57%) **BMI** (kg/m^2)**:** NA **Diabetes duration (**yr): 27.1 ± 1.3 **Hypoglycemia:** 52 (80%) pts (pragmatic*) **Labile diabetes**[#]**:** 39 (60%) pts **Baseline renal function:** microalbuminuria in 35% of pts; macroalbuminuria (> 0.2g/d) in 25% of pts	**Culture of islets:** yes (69% of the procedures) **No. of infusions:** 1: 13 pts 2: 41 pts 3: 11 pts At 1st infusion, islets from 2 donors in 8 procedures; at both 2nd and 3rd infusions, islets from 2 donors in 2 procedures **Total IE/kg:** 11,910 ± 469 (for 44 pts who achieved insulin independence) **Immunosuppressive regimen:** DAC, SIR, TAC 10 pts used infliximab, 9 pts used a lymphocyte depletion protocol (Campath-1H, ultra low-dose TAC, and higher-dose SIR) **Co-intervention:** Aspirin and enoxaparin **Follow-up:** median 35.5 (range 4.1 to 67.8) months for 47 pts who completed procedure	**Insulin independence:** One month: 44/65 pts (68%) Five yrs: 7.5% **Insulin requirement** (U/kg/d): decreased in pts who were on insulin but had persistent C-peptide secretion: 0.34 ± 0.04 post- vs. 0.66 ± 0.03 pre-transplant (P < 0.001); increased in pts who lost islet function: 0.80± 0.08 post- vs. 0.69 ± 0.08 pre-transplant (P = 0.03) **Hypoglycemia:** HYPO scores significantly improved for up to 4 yrs, some hypoglycemia episodes occurred with the use of insulin. **C-peptide level** (nmol/L): lower in pts on insulin than those off insulin both basally (0.49 ± 0.05 vs. 0.86 ± 0.05, P < 0.001) and post-stimulation (0.93 ± 0.08 vs. 1.62 ± 0.07, P<0.001) (time of measurement not reported.) **HbA1c** (%): median 6.4 (IQR 6.1 to 6.7) in pts off insulin vs. 6.7 (IQR 5.9 to 7.5) in pts who resumed insulin but C-peptide positive vs. 9.0 (IQR 6.7 to 9.3) in pts who lost graft function (P = 0.025) (most recent measurement) **HrQoL:** NA **Diabetic complications**: deterioration of eye disease in 4 pts, no change in peripheral neuropathy

Continuous variables are expressed in mean ± SE unless otherwise indicated.

* Problematic hypoglycemia was defined as frequent, recurrent episodes of hypoglycemia usually associated with hypoglycemia unawareness and more recently quantified with a hypoglycemic score (HYPO score) of ≥ 1,047.

[#] Labile diabetes was defined as frequent, wide swings in blood glucose that interfere with the patient's lifestyle and are characterized by a MAGE > 11.1 mmol/l and more frequently by a lability index of ≥ 433 mmol/l^2 · h^{-1} · week^{-1}

Table T.E.3: Treatment effects of islet transplantation in non-uremic patients (cont'd)

Study	Patient	Intervention	Outcomes
Toso et al. 2007[62] Edmonton	**Total No.:** 99 **Age** (yr): 44.3±9.6 **Gender** (M/F): 44/55 (44%/56%) **BMI** (kg/m^2)**:** NA **Diabetes duration (**years): 28.4±10.7 **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** NA	**Culture of islets:** NA **No. of infusions:** NA **Total IE/kg:** NA **Immunosuppressive regimen:** DAC, SIR, TAC **Co-intervention:** NA **Follow-up:** up to 36 months	**HrQoL:** ***Generic*** HUI2 score: at baseline: ITA 0.81±0.12 vs. IIT 0.83±0.15 (P> 0.05); remained at pre-transplant levels for up to 3 years. QoL related to pain significantly decreased after first infusion and returned to baseline level within a month. Emotion scores improved between the first and second infusions and returned to pre-transplant levels thereafter. Other domains remained stable. ***Disease-specific*** HFS score: at baseline: ITA 53.1±13.8 vs. IIT 35.8±15.6 (P<0.000001); after first infusion: 40.2±18.7 (P<0.00001); lowest level of fear observed at six (16.7±18.8), 12 (16.9±17.3), and 24 (16.8±17.4) months. At 36 months: fear increased (27.9±21.2, P<0.05 vs. six, 12, and 24 months).
Koh et al. 2010[22] Edmonton G1 (single donor): 13 G2 (multiple donors): 72	**Total No.:** 85 (who received ITA from single donor) **Age** (years): G1:48.6±2.5, G2:42.9±1.1 **Gender** (M/F): G1: 7/6 (54%/46%) G2: 28/44 (39%/61%) **BMI** (kg/m^2)**:** G1: 24.3±0.7 G2: 24.2±0.3 **Diabetes duration** (years): G1:34.5±2.9, G2:27.5±1.3 **Hypoglycemia:** no difference between the two groups **Labile diabetes:** no difference between the two groups **Baseline renal function:** N/A	**Culture of islets:** NA **No. of infusions:** 1 **Total IE/kg:** NA **Immunosuppressive regimen:** DAC, SIR, TAC **Co-intervention:** Intravenous insulin post-transplant and intravenous heparin infusion 48 hours post-transplant, then subcutaneous for seven days, aspirin for 14 days (since 2005) in 19 pts. **Follow-up:** 35 months for survival analysis	**Insulin independence:** 13/85 (15.3%) for at least four weeks after infusion if islets from a single donor, with a median duration of insulin independence of 18.1 (12.1 to 24.9) months. Pts who received insulin and heparin infusions were significantly more likely to become insulin independent (8/19, 42.1% vs. 5/66, 7.6%, P<0.001). **Insulin requirement** (U/kg/d): greater reduction in 19 pts who received insulin/heparin infusion (80.1±4.3% vs. 54.2±2.8, P<0.001). Engraft index, SUITO index, AIRa, and ACRa were significantly higher in patients who received insulin/heparin infusion.

Table T.E.3: Treatment effects of islet transplantation in non-uremic patients (cont'd)

Study	Patient	Intervention	Outcomes
Froud et al. 2005[63] University of Miami, Miami, USA Single centre	**Total No.:** 16 (2 did not complete transplantation) **Age** (years)**:** 40.8 ± 9.7 **Gender** (M/F): 7/9 (44%/56%) **BMI** (kg/m^2)**:** 24.8 ± 1.7 **Diabetes duration** (years): 26.9 ± 12.4 **Hypoglycemia:** hypoglycemia unawareness in all pts **Labile diabetes:** NA **Baseline renal function:** 3 pts had nephropathy (no detail)	**Culture of islets:** 35 ± 15 (range 7.3 to 65.5) hours **No. of infusions:** 1: 3 pts 2: 13 pts (5 pts receive supplemental transplant) 4 infusions used islets from 2 donors 1 infusion used 3 donors **Total IE/kg**: 13,552 ± 2,982 **Immunosuppressive regimen:** DAC, SIR, TAC **Co-intervention:** half of the pts received a single dose of infliximab **Follow-up:** up to 3 years	**Insulin independence:** Any time: 14/16 (88%) (1 pt with one infusion and 13 pts with two infusions) 1 year: 11/16 (69%) pts 1.5 years: 6/16 (37%) pts 2 years: 5/16 (31%) pts **Insulin requirement (U/d):** 12.6 ± 5.4 post- vs. 32.7 ± 11.2 pre-transplant (a reduction of 59 ± 18%) in 8 pts **Hypoglycemia:** no severe hypoglycemia **C-peptide level:** detectable in all pts while on immunosuppression **HbA1c:** returned to normal in 8 insulin-independent pts over 3 years **HrQoL:** NA **Diabetic complications:** NA
Tharavanjil et al. 2008[64] Miami	**Total No.:** 40 (ITA 26, IAK 7, IBM 7) **Age** (years): 41±8.5 **Gender** (M/F): 19/21 (48%/52%) **BMI** (kg/m^2)**:** NA **Diabetes duration** (years): 29.3±11.8 **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** nephropathy: 12	**Culture of islets:** yes **No. of infusions:** NA **Total IE/kg:** NA **Immunosuppressive regimen:** DAC, SIR, TAC **Co-intervention:** NA **Follow-up:** 40.8±21.9 (9–72) months	**HrQoL:** ***Generic*** HSQ 2.0: A significant increase in health perception (at 1 and 6 years), physical functioning (at 3, 4, and 6 years), social functioning (at 4 and 5 years), and bodily pain (at 6 years, n=5) A transient decrease of role-limitation-physical health, role-limitation-emotional problems, and mental health at various time points, which was not sustained after adjustment for confounding factors. No significant change in energy at any time point. ***Disease–specific*** DQoL: Impact score were higher at all post-transplant time points in comparison with pre-transplantation time points. Worry scale showed a significant improvement except in the first three months after transplantation. A significant increase in satisfaction score was observed at most time points except at 3, 30 to 42, and 72 months No significant difference in three domains of DQoL among ITA, IAK, and IBM (that is, no impact of protocols on DQoL).

Table T.E.3: Treatment effects of islet transplantation in non-uremic patients (cont'd)

Study	Patient	Intervention	Outcomes
Laitao et al. 2008[65] Miami	**Total No.:** 31 (25 ITA, 6 IAK) **Age** (years): 43.8±8.7 **Gender** (M/F): 13/18 (42%/58%) **BMI** (kg/m^2)**:** NA **Diabetes duration** (years): 29.3±11.8 **Hypoglycemia:** Clark hypoglycemic score, 5.29± 1.51 **Labile diabetes:** NA **Baseline renal function:** nephropathy: 9 pts	**Culture of islets:** NA **No. of infusions:** NA **Total IE/kg:** NA **Immunosuppressive regimen:** NA **Co-intervention:** NA **Follow-up:** 47.2±21.3 months	**Hypoglycemia awareness:** SH events: none in insulin independent pts. Clarke hypoglycemic score: 5.29±1.51 pre- vs. 1.35±1.92 post-transplant (P<0.001) Proportion of pts with hypo unawareness: 87% pre- vs. 13% post-transplant (P<0.001) Glycemic threshold that resulted in symptoms: 41.4±17.6 pre- vs. 58.4±10.3 post-transplant (P=0.001)
Maffi et al. 2007[66] San Raffaele Scientific Institute, Milan, Italy Single centre	**Total No.:** 19 **Age** (years)**:** 37.2 ± 9.0 **Gender** (M/F): 10/9 (53%/47%) **BMI** (kg/m^2): NA **Diabetes duration** (years): 23.3 ± 9.0 (range 11 to 37) **Hypoglycemia:** decrease hypoglycemia awareness in all pts **Labile diabetes:** NA **Baseline renal function:** nephropathy: 2 pts (1 pt had macroproteinuria; 1 pt had elevated sCr)	**Culture of islets:** yes **No. of infusions:** 1: 2 pts 2: 11 pts 3: 6 pts **Total IE/kg:** 11,477 ± 3,970 **Immunosuppressive regimen:** DAC, SIR, TAC**,** MMF **Follow-up:** 1 year: 17 pts 2 years: 8 pts	**Insulin independence:** 1 year: 8/19 pts (42%) (interpreted from Figure 1) **Insulin requirement:** NA **Hypoglycemia:** no severe hypoglycemia post-transplant, even with insulin therapy **C-peptide level** (nmol/L): fasting C-peptide Pre-transplant: 0.01 ± 0.01 1 year post-transplant: 0.46 ± 0.07 (P < 0.001 vs. pre-transplant) 2 years post-transplant: 0.50 ± 0.03 (P < 0.001 vs. pre-transplant) **HbA1c** (%): Pre-transplant: 8.6 ± 0.03 1 year post-transplant: 6.8 ± 0.2 (P < 0.001 vs. pre-transplant) (based on 17 pts) 2 years post-transplant: 6.4 ± 0.2 (P < 0.02 vs. pre-transplant) (based on 8 pts) **HrQoL:** NA **Diabetic complications:** NA

Table T.E.3: Treatment effects of islet transplantation in non-uremic patients (cont'd)

Study	Patient	Intervention	Efficacy
Badet et al. 2007[12] Swiss–French GRAGIL group Multicentre	**Total No.:** 10 pts **Age** (years)**:** 50±3 **Gender** (M/F): 6/4 **BMI** (kg/m^2): 22.1±0.8 **Diabetes duration** (years): 29±4 **Hypoglycemia:** frequent hypoglycemia episodes in all 10 pts **Labile diabetes:** NA **Baseline renal function:** NA	**Culture of islets:** yes **No. of infusions:** 1: 2 pts 2: 8 pts **Total IE/kg:** 11,089 ± 505 (1 pt was excluded from the calculation) **Immunosuppressive regimen:** DAC, SIR, TAC **Follow-up:** median 24 (range 12 to 36, IQR 13 to 30) months	**Insulin independence:** 1 month: 8/10 pts (80%) 6 months: 6/10 pts (60%) 1 year: 3/10 pts (30%) **Insulin requirement** (U/day): 30.5 ± 2.8 pre-transplant vs. 7.8 ± 3.3 1 year post-transplant (P < 0.001) **Hypoglycemia:** number of episodes/month: 18 ± 4 pre-transplant, 2 (1 pt) at 6 months, 4 (1 pt) and 20 (1 pt) at 1 year **C-peptide level** (ng/ml)**:** basal 1.19 ± 0.22 at 1 year (P < 0.001 vs. pre-transplantation), > 0.3 in all pts, > 0.5 in 8/10 pts **HbA1c** (%): 8.58 ± 0.47 pre- vs. 6.65 ± 0.17 1 year post-transplant (P < 0.002); improved in all pts; ≤ 6.2 in 3 insulin-independent pts at 1 year **HrQoL:** NA **Diabetic complications:** NA
Benhamou et al. 2009[20] GRAGIL (10 uremic + 10 non-uremic pts)	**Total No.:** 20 (10 ITA, 10 IAK) **Age** (years): ITA: 50 (IQR 6), IAK 43 (IQR 4) **Gender** (M/F): ITA: 6/4 (30%/20%), IAK 8/2 (40%/10%) **BMI** (kg/m^2)**:** NA **Diabetes duration** (years): ITA: 29 (IQR 14) IAK: **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** NA	**Culture of islets:** NA **No. of infusions:** 1 – 2 **Total IE/kg:** NA **Immunosuppressive regimen:** DAC, SIR, TAC **Co-intervention:** NA **Follow-up:** 1 year	**HrQoL:** ***Generic*** SF-36: Significant improvement in the dimensions of physical functioning, role-physical, bodily pain, general health, and social functioning, yielding significant improvement in the Physical Component Score and health transition at six and 12 months. ***Disease-specific:*** DQoL: Significantly improved global score (dimensions of satisfaction and impact of diabetes) at six and 12 months in the ITA group.

Continuous variables are expressed as mean ± SE unless otherwise indicated

Table T.E.3: Treatment effects of islet transplantation in non-uremic patients (cont'd)

Study	Patient	Intervention	Efficacy
Lee et al. 2005[71] Huston	**Total No.:** 12 **Age** (years): median 44 (33–62) **Gender** (M/F): 3/9 (25%/75%) **BMI** (kg/m^2)**:** NA **Diabetes duration** (years): NA **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** NA	**Culture of islets:** NA **No. of infusions:** NA **Total IE/kg:** NA **Immunosuppressive regimen:** DAC, SIR, TAC **Co-intervention:** NA **Follow-up:** 1 year	**Diabetic complications**: ***Retinopathy:*** no progression when compared with pre-transplant measures in all 8 pts, improvement in 1 pt; no significant correlation between changes in HbA1C values and retinopathic changes. ***Neuropathy:*** improvement or stabilization of diabetic neuropathy in 50% of 8 pts
Barshes et al. 2005[72] Huston	**Total No.:** 10 **Age** (years): NA **Gender** (M/F): NA **BMI** (kg/m^2)**:** NA **Diabetes duration** (years): NA **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** NA	**Culture of islets:** NA **No. of infusions:** NA 2: 7 pts; 3: 3 pts **Total IE/kg:** NA **Immunosuppressive regimen:** DAC, SIR, TAC **Co-intervention:** NA **Follow-up:** 1 year	**HrQoL** ***Generic*** SF-36: Total score 60.8 (range 32 to 88) pre- vs. 77.0 (range 30 to 98) 1 year post-transplant (NS). Trend of improvement in all component scores (NS) ***Disease-specific*** HFS Questionnaire: Total score 156 (range 49 to 170) pre- vs. 69 (range 0 to 170) 1 year post-transplant (P=0.04). Fatigue Questionnaire: Overall no significant change observed in the total score.

Table T.E.3: Treatment effects of islet transplantation in non-uremic patients (cont'd)

Study	Patient	Intervention	Efficacy
Turgeon et al. 2010[18] Atlanta	**Total No.:** 12 (G1: 8 pts using Edmonton protocol; G2: 4 pts using efalizumab) **Age** (years)**:** mean 46 (range 29–61) **Gender** (M/F): 5/7 (42%/58%) **BMI** (kg/m^2)**:** 22 (15.8-24.9) **Diabetes duration** (years)**:** 29 (16–41) **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** all have preserved renal function	**Culture of islets:** NA **No. of infusions:** G1: 1: 2 pts 2: 5 pts 3: 1 pt G2: 1: 4 pts **Total IE/kg:** G1: 16636±1929 vs G2: 8179±1784 **Immunosuppressive regimen:** DAC, SIR, TAC **Co-intervention:** heparin 70 U/kg **Follow-up:** up to 3 years	**Insulin independence:** G1: 2/8 after one IT; 6/8 after completion **Insulin requirement** (U/kg/d): 0.26 – 0.36 in insulin-dependent pts **Hypoglycemia:** NA **C-peptide level** (mg/ml): Fasting: G1: 0.89±0.34 (0.7-1.5) vs. G2: 1.43±0.46 90.8-1.9); Stimulated: G1: 1.96±1.44 (0.8-5.0) vs. G2: 1.22±1.27 (1.1-4.0) **HbA1c** (%): decreased 0.2 to 1.6% from baseline in 10 pts (<6.5% in 8 pts) **HrQoL:** NA **Diabetic complications**: NA
Gangemi et al. 2008[24] Chicago	**Total No.:** 10 (G1: 4 pts using Edmonton protocol; G2: 6 pts using Edmonton protocol plus etanercept, exenatid) **Age** (years)**:** G1: 48.8±11.9 vs. G2: 44.5±9.7 (NS) **Gender** (M/F): 1/9 (10%/90%) **BMI** (kg/m^2)**:** 22.5±1.2 (G1: 21.9± 1.0 vs. G2: 21.9± 1.8) (NS) **Diabetes duration** (years)**:** G1: 30.5±9.3 vs. G2: 22.0±9.1 (NS) **Hypoglycemia:** 10 (100%) with multiple SH with unawareness **Labile diabetes:** NA **Baseline renal function:** NA	**Culture of islets:** NA **No. of infusions:** G1: 2, 2 pts; 3, 2 pts G2: 1, 4 pts; 2, 2 pts **Total IE/kg:** NA **Immunosuppressive regimen:** G1: DAC, SIR, TAC, G2: DAC, SIR, TAC, etanercept, exenatid **Co-intervention:** Heparin 5000 u during procedure followed by enoxaparin 30 mg, bid for 1 week post-transplant **Follow-up:** 1.25 years	**Insulin independence:** Any time: all (100%); at 15 months, 8 (4 in G1, 4 in G2); **Insulin requirement** (U/kg/d) **Hypoglycemia:** 0 SH during 12 mos FU; mild hypo in 2 pts **C-peptide level** (nmol/l): **HbA1c** (%):7.2±1.1 pre- vs 5.9±0.4 15 months post- (P=0.001) G1: 6.5±0.6 pre vs. 5.6±0.5 at 15 months; G2: 7.8±1.1 pre- vs. 5.8±0.3 at 15 months **HrQoL:** NA **Diabetic complications**: NA

Table T.E.3: Treatment effects of islet transplantation in non-uremic patients (cont'd)

Study	Patient†	Intervention	Outcomes
Keymeulen et al. 2006[73] Brussels, Belgium	**Total No.:** 24 pts **Age** (years): median 43 (IQR 34 to 39) **Gender** (M/F): 13/9 (59%/42%) **BMI** (kg/m^2): median 24 (IQR 22 to 26) **Diabetes duration** (years): median 24 (IQR 18 to 33) **Hypoglycemia:** not clear **Labile diabetes:** not clear **Baseline renal function:** microalbuminuria in 7 pts; macroalbuminuria in 1 pt	**Culture of islets:** yes **No. of infusions:** 1: 9 pts 2: 13 pts **Total IE/kg:** NA **Immunosuppressive regimen:** ATG, MMF, TAC **Follow-up:** 1 year	**Insulin independence:** 1 year: 10/24 pts (42%) **Insulin requirement:** significantly lower at 1 year in 8 insulin-dependent pts ($p < 0.01$) **Hypoglycemia:** no severe hypoglycaemia episodes in 18 pts with C-peptide ≥ 0.5ng/ml **C-peptide level:** ≥ 0.5ng/ml in 18 pts at 1 year **HbA1c** (%): lower than 6% in 10 insulin-independent pts at 1 year ($P < 0.01$) **HrQoL:** NA **Diabetic complications:** NA

† 24 patients received ITA and were included in the safety analysis. Patient characteristics were based on data from 22 patients who were included in a 1-year metabolic analysis

Table T.E.3: Treatment effects of islet transplantation in non-uremic patients (cont'd)

Study	Patient	Intervention	Efficacy
Vantyghem et al. 2009[74] France	**Total No.:** 14 **Age** (years): 42 (36–51) **Gender** (M/F): 7/7 **BMI** (kg/m^2)**:** NA **Diabetes duration** (years): 27 (17–31) **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** NA	**Culture of islets:** no **No. of infusions:** 2: 4 pts 3: 10 pts **Total IE/kg:** median 12,479 (11,072-15,775) **Immunosuppressive regimen:** DAC, SIR, TAC **Co-intervention:** 35 u/kg added to islet production in all pts **Follow-up:** 3.3 (2.8 to 4.0) years	**Insulin independence:** Any time: 14 (100%) pts; at 1 year, 10 (71%) pts; at 3.3 years (2.8 to 4.0), 8 (57%) pts remained insulin-independent with HbA1c≤6.5% **Insulin requirement** (U/kg/d): NA **Hypoglycemia:** NA **Primary non-function:** 3 pts **C-peptide level** (nmol/L): Pts with suboptimal PGF (n=5): pre 0 (0-0) vs. 0.17 (0-0.53) at 2 years vs. 0 (0-0.43) (NS before vs. after). Pts with optimal PGF: pre 0 (0-0) vs. 0.5 (0.4-0.6) at 2 years (P<0.05 vs. pre-) vs. 0.5 (0.43-0.6) (P<0.05 vs. pre- and vs. suboptimal) **β score:** 1 month post-transplant, ≥7 in 9 pts (optimal); ≤6 in 5 pts (suboptimal). Suboptimal (n=5) pre- 0 (0-0), vs. 1 (0-3.8) at 2 years, vs. 2 (0-4.5) (NS). Optimal (n=9): pre- 0 (0-0) vs. 7 (0.4-0.6) at 2 years (P<0.05 vs. pre-) vs. 7 (5.8-8) (P<0.05 vs. pre- and vs. suboptimal) **HbA1c** (%): Pts with suboptimal PGF (n=5): pre- 8.7 (8.0-9.2) vs. 7.8 (7.4-8.7) at 2 years vs. 8.3 (7.4-9.4) at 3.3 (2.8-4.0) (NS before vs. after). Pts with optimal PGF: (n=9): pre 8.3 (7.3-8.6) vs. 5.8 (5.4-6.5) at 2 years (P<0.05 vs. suboptimal and vs. pre-) vs. 6.2 (5.6-6.7) at 3.3 (2.8-4.0) years (P<0.05 vs. suboptimal and vs. pre-) **HrQoL:** NA **Diabetic complications**: NA

Table T.E.4: Treatment effects of islet transplantation in uremic patients

Study	Patient	Intervention	Efficacy
Benhamou et al.2001[70] GRAGIL	**Total No.:** 10 **Age** (years): median 44 (28–62) **Gender** (M/F): 5/5 (50%/50%) **BMI** (kg/m^2)**:** NA **Diabetes duration** (years): median 29 (15–42) **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** all with previous kidney transplant	**Type of intervention:** IAK **Culture of islets:** NA **No. of infusions:** 1: 5 pts 2: 5 pts **Total IE/kg:** 9030±1090 **Immunosuppressive regimen:** Cyclosporin, MMF, steroid **Co-intervention:** NA **Follow-up:** median 16 (12 –27) months	**Insulin independence:** 20% at 1 year **Insulin requirement:** NA **Hypoglycemia:** NA **Primary non-function:** 0 **Partial function:** 50% at 1 year **C-peptide level:** >0.5 in all pts immediately after IAK; gradually lost in 5 pts; at 1 year: 5 pts remained >0.5 ng/ml **HbA1c** (%):pre: 8.6±1.6 vs. 1 year post- 6.0±0.4 in 5 pts with functioning graft (P value not reported) **HrQoL:** NA **Diabetic complications:** NA
Bertuzzi et al. 2002[69] Milan	**Total No.:** 15 **Age** (years): median 45 (31–61) **Gender** (M/F): 8/7 (53%/47%) **BMI** (kg/m^2)**:** median 22 (19–28) **Diabetes duration** (years): median 31 (12–48) **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** 100% with kidney transplantation	**Type of intervention:** IAK **Culture of islets:** yes **No. of infusions:** 1: 7 pts 2: 8 pts **Total IE/kg:** 11656±3488 in insulin-independent pts vs. 10750±2502 in insulin-dependent pts (NS) **Immunosuppressive regimen:** all had steroid and cyclosporine for KT **Co-intervention:** NA **Follow-up:** 1 year	**Insulin independence:** 6 months: 50% 1 year: 5 pts (33%) 2 years: 2 pts (13%) **Insulin requirement:** reduced more than 50% of pre-transplant doses **Hypoglycemia:** NA **Primary non-function:** 0 **C-peptide level:** >0.17 nmol/L during 1 year, median 0.8 (range 0.4 to 2.4 nmol/L) **HbA1c** (%): reduced after transplantation. 10 pts <7.0 at 1 year **HrQoL:** NA **Diabetic complications:** NA

Table T.E.4: Treatment effects of islet transplantation in uremic patients (cont'd)

Study	Patient	Intervention	Efficacy
Fiorina et al. 2003[67] Milan	**Total No.:** 36 **Age** (years): S-IK: 41.9±1.2 VS.U-IK:40.6±2.6 (NS) **Gender** (M/F): NA **BMI** (kg/m^2)**:** NA **Diabetes duration** (years): S-IK:27.2±1.9 VS.U-IK:26.7±1.7 (NS) **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** all with kidney trasnplant	**Type of intervention:** ITA, IAK, SIK **Culture of islets:** NA **No. of infusions:** 16 pts received multiple islet infusions **Total IE/kg:** S-IK: 11056±1424, U-IK:8140±1635 **Immunosuppressive regimen:** thymoglobin, cyclosporine, MMF, azathioprine, methylprednisolone **Co-intervention:** NA **Follow-up:** up to 7 years	**Insulin independence:** Any time: 12 pts; mean duration was 21.5±4.2 **Insulin requirement:** significant reduction in SIK group at 1, 2, and 4 years (p<0.05) **Hypoglycemia:** NA **C-peptide level:** NA **HbA1c** (%): No significant difference between the two groups during FU **HrQoL:** NA **Diabetic complications:** NA
Fiorina et al. 2003[68] Milan	**Total No.:** 34 **Age** (years): S-IK: 41.2±1.3 VS. U-IK:40.6±3.8 (NS) **Gender** (M/F): NA **BMI** (kg/m^2)**:** NA **Diabetes duration** (years): S-IK: 26.5±2.1 VS. U-IK:26.7±1.7(NS) **Hypoglycemia:** NA **Labile diabetes:** NA **Baseline renal function:** all with kidney transplant	**Type of intervention:** IAK **Culture of islets:** NA **No. of infusions:** NA **Total IE/kg:** NA **Immunosuppressive regimen:** thymoglobin, cyclosporine, MMF, azathioprine, methylprednisolone **Co-intervention:** NA **Follow-up:** 53.4±7.09 months	**Insulin independence:** NA **Insulin requirement:** lower in the SIK group than in the UIK group **Hypoglycemia:** NA **C-peptide level:** Higher in the SIK group than in the UIK group **HbA1c** (%): NS **HrQoL:** NA **Diabetic complications:** cardiovascular death rate higher in UIK group (4/13) than in the SIK group (1/21) **Patient survival:** significantly higher in the SIK group than the UIK group at 10 years (P=0.04)

Appendix T.F: Evidence table – safety only studies

Abbreviations

CG	control group
EG	experimental group
G	group
GFR	glomerular filtration rate
IAK	islet after kidney transplantation
ITA	islet transplantation alone
N	total number
NA	not available
NS	not significant
pt(s)	patient(s)

Table T.F.1: Adverse events reported in the safety only studies

Study	Patient/Intervention	Safety outcomes
Villiger et al. 2005[79] Edmonton	**No. of patients:** 67 **Age** (years): 43.3 ± 9.9 **Gender** (M/F): 28/39 (42%/58%) **Intervention:** ITA	**Procedure-related** Death: 0 Bleeding: 18 events (13.6% of 132 procedures) occurred in 17 pts (25.4%); 3 pts required surgical treatment PVT: 5 events (3.8% of 132 procedures)
Barshes et al. 2005[80] Houston	**No. of patients:** 11 **Age** (years): median 44 (range 33 to 62) **Gender** (M/F): 8/3 (73%/27%) **Intervention:** ITA	**Procedure-related** PTV: 0 Elevated ALT: in all 11 pts (100%)
Venturini et al. 2010[76] Milan	**No. of patients:** 36 (31 IAK, 5 ITA) **Age** (years): IAK:41.4±6.2; ITA: 35.6±9.8 **Gender** (M/F): 19/17 (53%/47%) **Intervention:** 30 IAK, 5 ITA	**Procedure-related** Liver focal fatty changes: 12 (34%) pts: 10/31 (33%) IAK, 2/5 (40%) ITA
Hafiz et al. 2005[77] Miami	**No. of patients:** 26 **Age** (years): 41.8±8.5 **Gender** (M/F): 11/15 (42%/58%) **Intervention:** 16 ITA, 4 IAK, 6 IBM	**Procedure-related** Death: 0 Bleeding: 3/26 (12%) PTV: 0/26 (0%) Elevated ALT: 26/26 (100%) Elevated AST: 26/26 (100%) **Immunosuppression-related** Mouth ulceration: 20/26 (77%) Nausea: 11/26 (42%) Vomiting: 12/26 (46 %) Diarrhea: 18/26 (69 %) Ulceration of small bowel: NA Anemia: 25/26 (96%) Leukopenia: 26/26 (100%) Neutropenia: 6/26 (23%)

		Leg edema: 12/26 (46%) Increased sCr: 10/26 (38%) Decreased CrCl: 1/26 (4%) Ovarian cyst: 9/15 (60%) Headache: 12/26 (46%) Fatigue: 8/26 (31%) IS change: 4/26 (15%) IS discontinuation: 4/26 (15%)
Senior et al. 2007[81] Edmonton	**No. of patients:** 41 **Age** (years): 43 ± 9.8 (range 24 to 64) **Gender** (M/F): 20/21 (49%/51%) **Intervention:** ITA	**Immunosuppression-related** Renal function Decline in eGFR: At 1 year: 47% (17/36) At 2 years: 64% (16/25) At 3 years: 92% (11/12) At 4 years: 80% (4/5) Compared with pre-transplant, mean eGFR was unchanged at 1 year, significantly lower at 2 and 3 years, but not statistically different from baseline at 4-year follow-up Changes in albuminuria status: Microalbuminuria: 9 pts (22%) post- vs. 4 pts (10%) pre-transplant (P<0.001) Macroalbuminuria: 6 pts (15%) post- vs. 3 pts (7%) pre-transplant (P<0.001)
Leitao et al. 2009[82] Miami	**No. of patients:** 35 **Age** (years): 42.5±8.6 **Gender** (M/F): 13/22 (37%/63%) **Intervention:** ITA	**Immunosuppression-related** Renal function Estimated GFR: remained stable during follow-up Microalbuminuria: 6 of 30 (20%) pts without albuminuria at baseline progressed to microalbuminuria Macroalbuminuria: none
Alfadhli et al. 2009[83] Edmonton	**No. of patients:** 57 **Age** (years): median 42.5 (range 36.1to 49.4) **Gender** (M/F): 0/57 (0%/100%) **Intervention:** ITA	**Immunosuppression-related** Ovarian cysts: 33 (58%) pts

Eckhard et al. 2002[78] Giessen	**No. of patients:** 48 **Age** (years): mean 40.2 **Gender** (M/F): 26/22 (54%/46%) **Intervention:** 14 IAK, 34 SIK	**Immunosuppression-related** CMV infection: 29 (60.4%) pts CMV-DNAemia
Yakubovich et al.2007[84] Vancouver	**No. Of patients:** 23 **Age** (years): NA **Gender** (M/F): NA **Intervention:** ITA	**Immunosuppression-related** CMV infection: 3 pts (13%) developed CMV antigenemia following islet transplant despite receiving prophylaxis treatment.
Gillard et al. 2009[85] Belgium	**No. of patients:** 17 **Age** (years): median 43 (range 25 to 56) **Gender** (M/F): NA **Intervention:** ITA	**Immunosuppression-related** Graves hyperthyroidism: 4 of 13 (31%) pts who discontinued immunosuppressive regimen.

Table T.G.1: Summary of findings from systematic reviews

Study	Included studies	Outcome measures	Main findings	Conclusion
Speight et al. 2010[54] **Objectives** • To identify which PROs have been used to evaluate ITA, IAK, PTA, and PAK • To report the short-, medium- and long-term outcomes of ITA, IAK, PTA, and PAK from the patient's perspective • To assess the suitability of the PRO measures for demonstrating the full impact (both positive and negative) of transplant from the patient's perspective	**No. of included studies:** 12 case series studies (9 ITA, 2 IAK, 2 PAK, 1 PTA) **No. of patients in included studies:** ranged from 7 to 205 **Length of follow-up:** > 1 year in all studies > 2 years in five studies	Generic questionnaires (8); most commonly used: 36-SF (5 studies). Diabetes specific questionnaire (2); most commonly used: DQoL (4 studies). None used transplant-specific QoL measures.	• Results were mixed but identified some benefits that remained apparent up to 36 months post-transplantation. • Improvement in fear of hypoglycemia, and in some aspects of DQoL and general health status. • Negative outcomes: short-term pain associated with the procedure; immunosuppressant side-effects and depressed mood associated with loss of graft function. • No studies assessed patient satisfaction. • Did not identify any qualitative research on the impact of islet transplantation or pancreas transplantation on QoL.	The mixed results may be attributable to limited sample size, lack of sensitivity of some PRO measures to detect actual changes, and the exclusion of key issues of potential importance to transplant patients. Therefore, the full impact of islet/pancreas transplantation (alone or after kidney transplant) on QoL is unknown.

Abbreviations: DqoL – diabetes quality of life questionnaire; IAK – islet after kidney transplantation; ITA – islet transplantation alone; PAK – pancreas after kidney transplantation; PRO – patient report outcomes; PTA – pancreas transplantation alone; PTV – portal venous thrombosis; QoL – quality of life; SH – severe hypoglycemia; T1DM – type 1 diabetes

Table T.G.1: Summary of findings from systematic reviews (cont'd)

Study	Included studies	Outcome measures	Main findings	Conclusion
Guo et al. 2008[3] **Objectives** • To assess clinical research evidence on the safety and efficacy/effectiveness of ITA for non-uremic T1DM patients with severe hypoglycemia or hypoglycemia unawareness. • To assess research evidence on the comparability of ITA with IIT or whole organ pancreas transplantation in reducing hypoglycemia episodes and restoring insulin-independence in this group of patients.	**No. of included studies:** 14 primary studies (two comparative studies; 12 case series studies) **No. of patients in included studies:**| ranged from 6 to 65 **Length of follow-up** Up to 3 years	**Safety outcomes** • procedure-related complications • immunosuppression-related complications **Efficacy/effectiveness outcomes** • insulin independence /glycemic control • hypoglycemia • HrQoL • secondary complications of diabetes	• Procedure-related complications included intraperitoneal bleeding (in up to 23% of pts) and PTV (in up to 17% of pts). • Elevated liver enzyme levels were observed in the majority of pts, but resolved spontaneously within one month after transplantation. • Decline in renal function following the use of sirolimus and tacrolimus was reported in up to 50% of the pts, leading to change/withdrawal of the original IS drugs in some cases. • Transplantation of an adequate mass of islet cells (usually from two to three pancreas donors) could restore insulin independence in the short-term (≤1 year) with adequate glycemic control in 30% to 69% of the patients; however, islet function appeared to deteriorate over time. • Partial islet function with reduced insulin requirement provides protection from SH and improves glycemic control. • Two studies with a total of 109 pts demonstrated a reduction in fear of hypoglycemia, but improvements in overall HrQoL measures were inconsistent • Two studies with a total of 22 pts showed an improvement in diabetic retinopathy and neuropathy 1 year after ITA. • No information is currently available on the comparison of ITA with IIT in patients with SH or hypoglycemia unawareness. No study directly compared ITA with PTA in non-uremic patients.	ITA is an alternative therapeutic option for a small group of highly select patients (that is, non-uremic T1DM patients with severe hypoglycemia and uncontrolled diabetes). Current clinical research demonstrated encouraging short-term efficacy results, including reduced hypoglycemia events, reduced insulin requirements, and stabilized glucose levels. ITA continues to evolve and its role in relation to other therapeutic strategies is still unknown.

SECTION THREE: ECONOMIC ANALYSIS (E)

Andy Chuck, PhD, MPH; Charles Yan, PhD

Objectives and Policy Questions

The objective of the economic analysis was to estimate the costs and cost effectiveness of islet transplantation (IT) compared to intensive insulin therapy (IIT) alone. More specifically, the objective of the analysis was:

1) to estimate the unit costs, including physician billings, hospitalization or facility operational costs, other service costs, and capital costs for the procedure and related health services
2) to estimate the costs of services avoided within a reasonable period of time
3) to provide cost-effectiveness comparisons of islet transplantation in the short term
4) to estimate patient and public demand, including prevalence and incidence of condition(s) and utilization rates of islet transplantation options, where data exist
5) to estimate the total cost for each option based on utilization estimates
6) to assess the potential for transfer of services and funds from existing services being replaced or reduced in usage, as well the impact on the health system of such transfers, if possible

These questions were addressed in both a systematic review of the economic literature and a primary economic analysis that included:

- an economic evaluation to address questions 1 through 4
- a budget impact analysis to address question 5
- a cost attribution analysis to address question 6

Review of Economic Studies

Search strategy

Selected databases were searched for economic evaluation studies of IT (see Appendix E.1). Databases searched included:

- Medline EMBASE
- CINAHL
- Cochrane Database of Systematic Reviews
- CRD Databases (DARE, NHS EED, HTA)
- Web of Science BIOSIS Previews
- Biological Sciences
- Biotechnology Research Abstracts
- Scopus
- Econlit

The date restrictions (from 2000 onward) were applied.

Selection criteria

The search was limited to human and English-language publications. Eligible studies met the following inclusion/exclusion criteria:

Inclusion criteria

1. **Study design:** health technology assessment reports, systematic reviews, and economic evaluation studies including cost effectiveness, cost-utility, or cost-benefit analyses.
2. **Population:** adult patients with type 1 diabetes mellitus (T1DM) who are eligible for IT.
3. **Interventions and comparators:** IT versus IIT
4. **Outcomes of interest:** studies are included if they provide cost-effectiveness results that include both costs and health outcomes for each intervention; health outcomes can include health-related quality of life, quality-adjusted life years or life years.

Exclusion criteria

Excluded studies included:

1. abstracts/summaries, case studies, narrative reviews, comments, letters, and editorials
2. studies that did not conduct an incremental analysis between comparators and did not report totals for costs and outcomes of each comparator to allow for a manual calculation of incremental costs and outcomes

Quality assessment

A formal quality assessment of economic studies was conducted with the quality of health economics studies (QHES). The instrument is based on criteria adapted from Drummond et al.[3] but includes a weighting system to score and aggregate across individual criteria, thereby providing a summative index of quality. The QHES quality index ranges from 0 to 100; a score of 75 or greater indicates acceptable quality.

Data extraction

Data extracted from studies included study design, objectives, perspective, timelines, screening strategy, country, health and cost outcomes, results from the marginal analysis, and study conclusions.

Primary Economic Analysis

Economic evaluation

We developed a cohort simulation model to determine the cost effectiveness of IT. The data requirement for an economic evaluation is broad and can include (but is not limited to) epidemiological, clinical, cost, and health outcome data. The required data is rarely all available from one source (for example, published research), and is therefore derived from a variety of sources including (but not limited to) published research literature, administrative databases, and clinical program data. The advantage of a simulation model is that it allows disparate sources of information to be brought together into one intergrated cost-effectiveness analysis.

Our model compares the costs and health outcomes between IT and IIT for eligible IT patients with T1DM, to contrast the incremental gains in health benefit with the associated incremental costs, thereby providing an assessment of value for money. Whole organ pancreas transplantation is not included in the analysis because limited data is available to populate the simulation model reflecting whole organ pancreas transplantation. Including whole organ pancreas transplantation would introduce a bias into the analysis, raising issues of whether any comparisons in our results with whole organ pancreas transplantation are valid. Furthermore, prospectively collecting the required data is beyond the scope of STE reviews.

The analysis adopts the perspective of Alberta Health (AH) and considers direct health system costs including physician, inpatient, outpatient, and laboratory services. The model simulates the natural progression of T1DM under IIT and alternatively under IT, represented through a sequence of health states (see Figure E.1).

Given that diabetes is a chronic disease associated with long-term morbidity, it is important that the time horizon for the analysis allow for the capture of the relevant costs and consequences of each intervention. The model starts with a cohort of patients 19 years of age who do not have any secondary complications. The three primary health states under IIT are:

1) IIT
2) secondary complications
3) death

Over time, the patient cohort is exposed to a risk of developing secondary diabetic complications consisting of amputation, blindness, cardiovascular conditions, and renal failure or neuropathy. There is also the risk of death or of experiencing a severe hypoglycemic event (SHE) (that is, an event requiring third party assistance). Note that when an individual is in a state of cardiovascular or renal failure, they have an increased risk of mortality in addition to the baseline diabetes-related mortality risk.

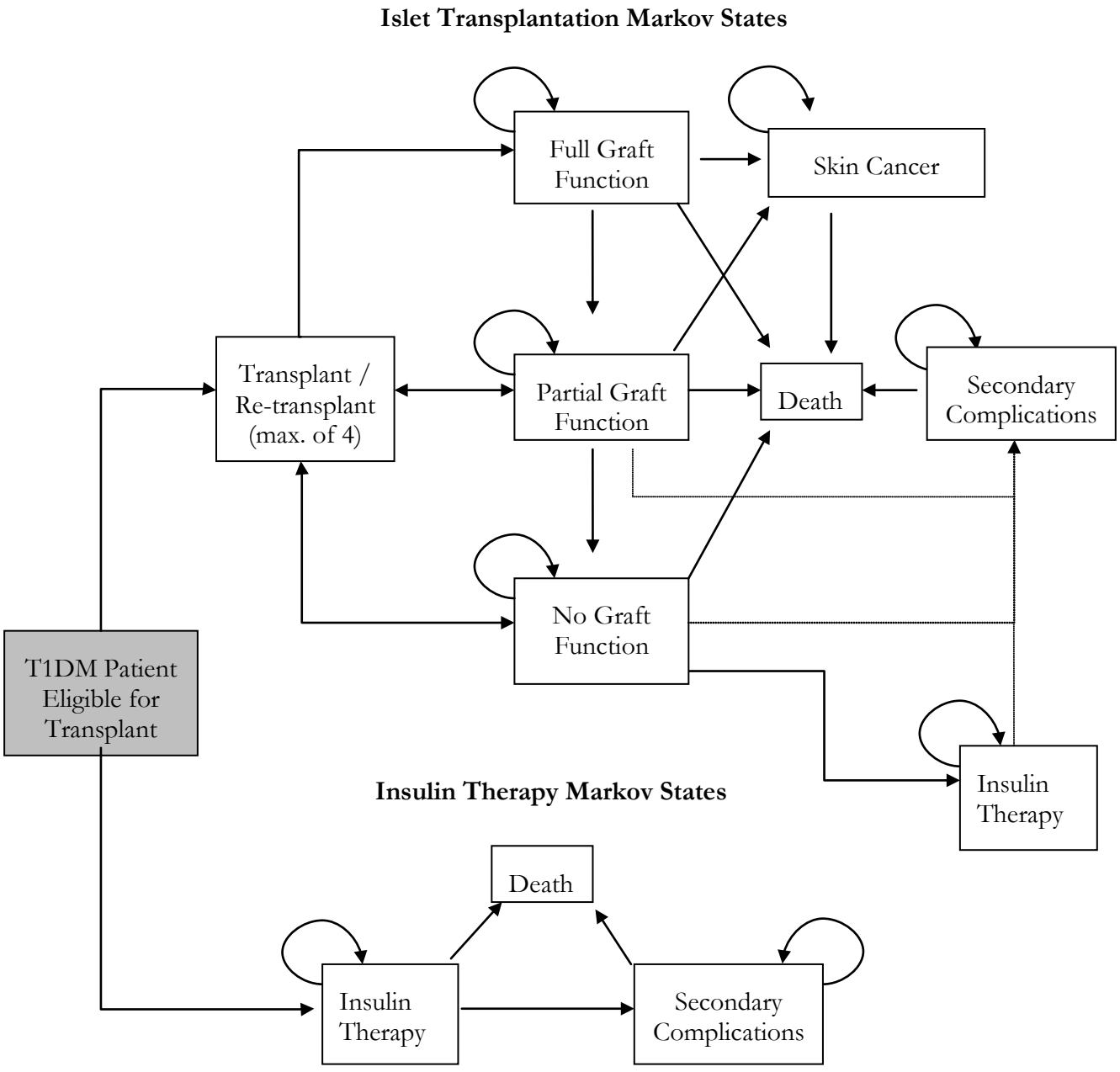
The eight primary health states under IT are:

1) IT
2) full graft function (FF)
3) partial graft function (PF)
4) no graft function (NF)
5) secondary complications
6) IIT
7) skin cancer
8) renal failure
9) death

This model starts with the same patient cohort under IIT but instead receive IT. Following transplantation, the three outcomes are FF, PF or NF. Over time, patients with FF can remain in FF (in which they are insulin-independent and are at decreased risk for death, SHE, or developing a secondary complication) or can decline to PF. Over time, patients with PF can remain in PF (in

which they are taking a reduced amount of insulin compared to when on IIT alone and are at a decreased risk of death, SHE, or developing a secondary complication), receive a subsequent IT, or decline to NF. Patients with FF or PF are at risk of developing immunosuppressant complications such as skin cancer and renal failure. Patients with NF do not receive further transplantation and return to IIT alone, where there is a higher risk of death, SHE, and developing a secondary complication. It is important to note that under IT, patients continue with IIT unless they have full graft function; IIT is shown as a separate health state only to denote that patients with failed grafts return to IIT alone. Furthermore, a maximum of four transplantations per patient is permitted. Patients who have had four ITs, and who have PF or eventually decline to NF, return to IIT alone. Each treatment will generate a separate set of associated costs and outcomes, providing the basis for the comparative economic analysis.

Figure E.1: Markov states



Model inputs

Clinical Data

Clinical data on islet transplantation were derived from the Clinical Islet Program (CIP) in Edmonton (see Table E.1). The program houses a database that tracks the clinical outcomes in 138 consecutive IT recipients who received a total of 301 islet infusions from March 11, 1999 to July 4, 2011. However, when possible, the inputs used to populate the model were based on recent data to better reflect current practice. Moreover, note that clinical data were not based on the T-section of this report for two primary reasons. First, the T-section examined only published studies and not all of the clinical data required for the economic evaluation are available in the published literature. Second, one of the main aims of the E-component of the STE review is to determine cost effectiveness in the Alberta context, and although much of the data housed by the CIP is unpublished, their data is based on the Alberta experience (refer to section 3.6, Caveats, for further discussion).

Health Outcomes

Quality-adjusted life years (QALYs) were used as the primary measure of health outcome (that is, effectiveness). In economic evaluations, QALYs are a standard measure of assessing the impact of health interventions in terms of their overall impact on health outcomes and health-related quality of life (HRQL). Note that the systematic review (see T-section) did not find any longitudinal prospective studies of IT that measured HRQL in terms of QALYs. For our economic evaluation, the impact of IIT and IT on HRQL was extrapolated via the cost-effectiveness simulation model.

Costs

Information on costs and resource utilization associated with IT were provided by Alberta Health Services (AHS) based on their financial and accounting records (this information does not include physician fees). Other cost data were generated from three provincial administrative health utilization databases for the fiscal years between 2006 and 2009. The Alberta Physician Claims database (PCD) provided information related to billing services for physicians for medically insured services in Alberta. Note that IT is currently not a medically insured service in Alberta and there is no physician fee for performing islet infusions. This fee is estimated based on a change request submitted to AH by the Alberta Medical Assocation. The Alberta Discharge Abstracts (DAD) database provided information related to hospital inpatient procedures. The Ambulatory Care Classification System (ACCS) provided information related to outpatient procedures. Note that the DAD and ACCS cost data include patient-specific drug and supply costs, functional centre direct costs such as salaries (excluding physician services), medical and surgical supplies, and functional centre indirect costs such as administration and support services.

Costs associate with diabetes management, including related comorbidities (amputation, blindness, renal failure, cardiovascular condition, neuropathy) were generated using ICD coding (see Appendix E.2). Cases were identified if an ICD code pertaining to the condition of interest was contained in any of the three databases in any diagnosis field. Furthermore, the one-time cost of lower limb amputation was identified using procedure codes (see Appendix E.2) contained in the PCD, following the method described in *Alberta Diabetes Atlas 2009*.[1] This method identifies amputation that is likely due to diabetic peripheral neuropathy and peripheral arterial disease, thereby excluding amputation due to other diseases. For each patient with the diagnoses of interest, the total costs of physician, inpatient, and outpatient services are calculated and averaged over all patients with the

diagnoses of interest, providing an estimate of the cost per patient for the condition of interest. All costs are adjusted to 2011 Canadian dollars using the Canadian Consumer Price Index.

Synthesis of cost and effectiveness

As previously mentioned, the model starts with a cohort of patients 19 years of age. The analysis was conducted at a time horizon of 20 years and lifetime (61 years, assuming a life expectancy of 80 years) to capture the relevant costs and consequences of IT and IIT on T1DM. The cycle length of the model is 1 year (that is, simulated using 1 year intervals). Costs and outcomes were discounted at 5%. All analyses were conducted using Microsoft Excel 2010 and TreeAge Pro Suite (TreeAge Software Inc; Williamstown, MA).

Criteria for cost-effectiveness

The criteria for concluding cost-effective are as follows:

1. The alternative that is more costly and less effective in comparison to the other alternative is dominated and is considered NOT cost-effective.
2. The alternative that is less costly and more effective in comparison to the other alternatives is considered cost-effective (that is, has strong dominance).
3. The alternative that is both more costly and more effective (or less costly and less effective) has a cost effectiveness that is uncertain because cost-effectiveness is dependent on whether the additional/reduced effectiveness is worth the additional/reduced cost to the health system. For technologies that are both more effective and more costly, cost effectiveness is determined by comparing the incremental net benefit associated with the technology with the opportunity cost of its adoption, which is represented by the cost effectiveness threshold. A technology that is more costly and more effective is considered cost effective if its incremental cost effectiveness ratio (ICER), that is, the cost per additional outcome gained, is less than the opportunity cost of its adoption, because it would result in a net health benefit to the health system.

Sensitivity analysis

A probabilistic sensitivity analysis was used to assess the impact of parameter uncertainty on the cost effectiveness results using the standard errors listed in Table E.1. One thousand Monte Carlo simulations were conducted to generate a distribution of the potential costs and effectiveness associated with IT and IIT. Table E.1 shows that patients with full or partial graft function who had received transplants were at no risk of developing a secondary complication. We tested the impact of this assumption on our cost-effectiveness results in a one-way sensitivity analysis where patients with partial graft function were not at decreased risk for future secondary complications.

Table E.1: Model inputs

Model Parameters	Input	SE	Distribution[a]	Ref
Epidemiology				
Secondary complications due to diabetes (zero under IT with full/partial function)				
Annual risk of amputation	1	NA	None	[2]
Annual risk of blindness	2	NA	None	[2]
Annual risk of cardiovascular event	0.43	NA	None	[2]
Annual risk of renal failure	5	NA	None	[2]
Annual risk of neuropathy	1	NA	None	[2]
1-year mortality (%)			None	
No selected comorbidities	0.41	NA	None	StatCan
Diabetes	0.43	NA	None	StatCan
Renal failure	0.44	NA	None	StatCan
Cardiovascular condition	0.55	NA	None	StatCan
Cancer	3	NA	None	PHAC
Renal + cardiovascular condition	0.56	NA	None	PHAC / StatCan
Renal + cancer	2.5	NA	None	PHAC / StatCan
Cardiovascular condition + cancer	2.6	NA	None	PHAC / StatCan
Outcomes				
Quality-adjusted life years				
Diabetes	0.72	0.32	Beta	CCHS
Added utility for full graft functioning	0.07	NA	None	[2]
Added utility for partial graft functioning	0.06	NA	None	[2]
Decreased utility for severe hypoglycemic event	0.001503	NA	None	[3]
Decreased utility for amputation	0.266	NA	None	[2]
Decreased utility for blindness	0.04979	NA	None	[4]
Decreased utility for cardiovascular condition	0.05	NA	None	[5]
Decreased utility for renal failure	0.32	NA	None	[6]
Decreased utility for neuropathy	0.19	NA	None	[6]

[a] – Refers to the mathematical distribution assigned to incorporate the likelihood of possible values (that is, inherent variance) of the input during model simulation. NONE means that input does not vary during model simulation. Distributions are fitted based on primary data.

NA – Not Available

StatCan – Statistics Canada www40.statcan.ca/l01/cst01/health30a-eng.htm (accessed July 13, 2011)

PHAC – Public Health Agency of Canada www.phac-aspc.gc.ca/cd-mc/cancer/melanoma_skin_cancer_figures-cancer_peau_melanome_figures-eng.php (accessed July 13, 2011)

CCHS – Canadian Community Health Survey Cycle 2.1

Table E.1: Model inputs (cont'd)

Model Parameters	Input	SE	Distribution [a]	Ref
Characteristics of Islet Transplantation				
Tolerate immunosuppressants	100	0	None	CIP
1-year risk of skin cancer (%)	1.3	1	Beta	CIP
Stop immunosuppressants due to Infection (%)	7	5	Beta	CIP
Severe hypoglycemic events (mean per year)				
Pre-transplant (applies to pre/no functioning)	50	8	Gamma	CIP
Post-transplant (applies to full/partial functioning)	2	0.8	Gamma	CIP
Transplant 1 (%)				
Outcome full graft function	17	3	Dirichlet	CIP
Outcome partial graft function	81	3	Dirichlet	CIP
Outcome no fraft gunction	2	1	Dirichlet	CIP
Annual probability full decline to partial function[b]	74	7	Beta	CIP
Annual probability partial decline no function[b]	8	2	Beta	CIP
Annual probability re-transplant when partial[b]	73	3	Beta	CIP
Transplant 2 (%)				
Outcome full graft function	73	4	Dirichlet	CIP
Outcome partial graft function	27	4	Dirichlet	CIP
Outcome no graft function	0	0	Dirichlet	CIP
Annual probability full decline to partial function[b]	34	5	Beta	CIP
Annual probability partial decline no function[b]	17	5	Beta	CIP
Annual probability re-transplant when partial[b]	21	5	Beta	CIP
Transplant 3 (%)				
Outcome full graft function	55	7	Dirichlet	CIP
Outcome partial graft function	40	8	Dirichlet	CIP
Outcome no graft function	5	3	Dirichlet	CIP
Annual probability full decline to partial function[b]	82	10	Beta	CIP
Annual probability partial decline no function[b]	5	2	Beta	CIP
Annual probability re-transplant when partial[b]	40	11	Beta	CIP
Transplant 4 (%)				
Outcome full graft function	86	13	Dirichlet	CIP
Outcome partial graft function	14	13	Dirichlet	CIP
Outcome no graft function	0	0	Dirichlet	CIP
Annual probability full decline to partial function[b]	82	10	Beta	CIP
Annual probability partial decline no function[b]	5	2	Beta	CIP

[a] – Refers to the mathematical distribution assigned to incorporate the likelihood of possible values (that is, inherent variance) of the input during model simulation. NONE means that input does not vary during model simulation. Distributions are fitted based on primary data.

[b] – Transition probability: Original proportions were converted to annual probabilities using the formula: p=1-exp(-rt), where p is a probability and r is a constant rate of an event over a time period.

Table E.1: Model inputs (cont'd)

Model Parameters	Input	SE	Distribution [a]	Ref
Costs (2011 Canadian $)				
AHS Transplantation Services (per transplant)				
Organ retrieval	22,409	8,271	Gamma	AHS
Isolation laboratory	56,394	NA	None	AHS
Clinical program	24,692	NA	None	AHS
Pre-transplantation assessment (LAB)	1881	289	Gamma	AHS
Post-transplantation assessment (LAB)	17,743	6737	Gamma	AHS
Inpatient transplant	2633	230	Gamma	AHS
Workup but not transplanted	1227	100	Gamma	AHS
CMV prophylaxis per transplant (90% of transplants)	5000	NA	None	AHS
Immunosuppressants (per year)	10,248	NA	None	AHS
Insulin no graft function[b]	803	NA	None	AHS
Insulin graft function (33% decrease in insulin requirements)	265	NA	None	[7]
Physician transplantation fees				
Pre-transplantation assessment	1244	NA	None	AHS/ǂ
Transplant and post-transplantation assessment	6264	NA	None	AHS/ǂ
Diabetes management (DM) – annual (reference)				
Physician	177	5	Gamma	*
Inpatient	1487	329	Gamma	**
Outpatient	308	10	Gamma	***
Amputation (one-time cost)				
Physician	1691	321	Gamma	*
Inpatient	28,663	8163	Gamma	**
Outpatient	1348	275	Gamma	***
Add amputation management (AM) – annual				
Physician	177	5	Gamma	*
Inpatient	1487	329	Gamma	**
Outpatient	308	10	Gamma	***
Add blind management (BM) – annual				
Physician	177	5	Gamma	*
Inpatient	1487	329	Gamma	**
Outpatient	308	10	Gamma	***
Add renal failure management (RM) – annual				
Physician	190	5	Gamma	*
Inpatient	1738	372	Gamma	**
Outpatient	331	10	Gamma	***

[a] – Refers to the mathematical distribution assigned to incorporate the likelihood of possible values (that is, inherent variance) of the input during model simulation. NONE means that input does not vary during model simulation. Distributions are fitted based on primary data. In general, parameters estimated from larger sample sizes generate smaller ranges of possible values (consistent with statistical theory). Therefore, inputs with very small standard errors indicate they were fitted from large sample sizes.

[b] – At $2.75 per 100 units and taking 80 units of insulin per day.
NA – Not Available

ǂ – Personal Communication, Medical Director, Clinical Islet Transplantation Program
* – Alberta Health and Wellness Physician Claims Data Base 2004–2005
** – Alberta Health and Wellness Discharge Abstracts Database 2004–2005
*** – Alberta Health and Wellness Ambulatory Care Classification System 2004–2005

Table E.1: Model inputs (cont'd)

Model Parameters	Input	SE	Distribution [a]	Ref
Costs (2011 Canadian $)				
Add cardiovascular condition management (CM) – annual				
Physician	185	5	Gamma	*
Inpatient	1579	340	Gamma	**
Outpatient	315	10	Gamma	***
Add neuropathy condition management (NM) – annual				
Physician	189	5	Gamma	*
Inpatient	1611	330	Gamma	**
Outpatient	322	10	Gamma	***
DM + AM + BM – annual				
Physician	179	5	Gamma	*
Inpatient	1530	340	Gamma	**
Outpatient	306	10	Gamma	***
DM + AM + CM – annual				
Physician	179	5	Gamma	*
Inpatient	1530	340	Gamma	**
Outpatient	306	10	Gamma	***
DM + AM + RM – annual				
Physician	184	5	Gamma	*
Inpatient	1684	372	Gamma	**
Outpatient	321	10	Gamma	***
DM + AM + NM – annual				
Physician	184	5	Gamma	*
Inpatient	1567	329	Gamma	**
Outpatient	312	10	Gamma	***
DM + BM + CM – annual				
Physician	180	5	Gamma	*
Inpatient	1531	340	Gamma	**
Outpatient	306	10	Gamma	***
DM + BM + RM – annual				
Physician	184	5	Gamma	*
Inpatient	1687	372	Gamma	**
Outpatient	321	10	Gamma	***

[a] – Refers to the mathematical distribution assigned to incorporate the likelihood of possible values (that is, inherent variance) of the input during model simulation. NONE means that input does not vary during model simulation. Distributions are fitted based on primary data. In general, parameters estimated from larger sample sizes generate smaller ranges of possible values (consistent with statistical theory). Therefore, inputs with very small standard errors indicate they were fitted from large sample sizes.

‡ – Personal Communication, Medical Director, Clinical Islet Transplantation Program

* – Alberta Health and Wellness Physician Claims Data Base 2004–2005

** – Alberta Health and Wellness Discharge Abstracts Database 2004–2005

*** – Alberta Health and Wellness Ambulatory Care Classification System 2004–2005

Table E.1: Model inputs (cont'd)

Model Parameters	Input	SE	Distribution [a]	Ref
Costs (2011 Canadian $)				
DM + BM + NM				
Physician	183	5	Gamma	*
Inpatient	1561	330	Gamma	**
Outpatient	312	10	Gamma	***
DM + CM + RM				
Physician	195	5	Gamma	*
Inpatient	1,840	403	Gamma	**
Outpatient	332	10	Gamma	***
DM + CM + NM				
Physician	192	5	Gamma	*
Inpatient	1665	340	Gamma	**
Outpatient	320	10	Gamma	***
DM + RM + NM				
Physician	199	5	Gamma	*
Inpatient	1865	382	Gamma	**
Outpatient	338	11	Gamma	***
End of life				
Terminal condition	18,816	NA	None	[8]
Organ	20,508	NA	None	[8]

[a] – Refers to the mathematical distribution assigned to incorporate the likelihood of possible values (that is, inherent variance) of the input during model simulation. NONE means that input does not vary during model simulation. Distributions are fitted based on primary data. In general, parameters estimated from larger sample sizes generate smaller ranges of possible values (consistent with statistical theory). Therefore, inputs with very small standard errors indicate they were fitted from large sample sizes.

NA – Not Available

‡ – Personal Communication, Medical Director, Clinical Islet Transplantation Program

* – Alberta Health and Wellness Physician Claims Data Base 2004–2005

** – Alberta Health and Wellness Discharge Abstracts Database 2004–2005

*** – Alberta Health and Wellness Ambulatory Care Classification System 2004–2005

Cost attribution analysis

Alternative health technologies have differential resource implications to disparate health sectors (for example, costs of laboratory, physician, and outpatient services). Differentiating the resource implications of each alternative on disparate health sectors from their total system impact is important for elucidating to decision-makers how alternatives potentially impact the various sectors of the health system, because it informs questions about potential resource shifting. Information that helps identify which health sectors experience a cost increase or decrease is useful for planning and budgeting. Accordingly, a cost attribution analysis was conducted to differentiate the resource implications of IT to AHS transplantation services (inpatient, outpatient, and laboratory services directly related to the provision of IT, including administration), physician services, drugs (CMV prophylaxis, immunosuppressants, and insulin), and inpatient and outpatient services not directly related to IT (for example, diabetes care). The model was calibrated to track and categorize costs by these budgetary categories.

Budget impact analysis

The budget impact analysis (BIA) was conducted to assess the financial impact of IT. A BIA would ordinarily be estimated using the current prevalence of eligible T1DM patients in Alberta, and expanding existing IT services to meet this potential demand. However, a major constraint in the provision of IT is the availability of suitable organs for IT. The potential demand for IT in Alberta exceeds organ supply. Hence, rather than calculating the budget impact for the potential demand of IT, the BIA is calculated at the maximum number of IT procedures that can be performed given the current constraints in organ availability. Cost estimates applied in the BIA model were taken from the expected costs generated from the economic model, with the exception of the transplantation services program cost, which was obtained from the Operation and Financial Impact Analysis (OFIA) of IT conducted by AHS.

Results

Review of economic studies

The search strategy generated 163 studies between 2000 and 2010. After reviewing their titles and abstracts, 14 studies were retrieved for full text review. Of these, only four were economic studies and only one article met the inclusion/exclusion criteria. This article is discussed in the discussion section of the economic analysis.

Economic evaluation

Costs, effectiveness, and cost effectiveness

The total health system cost per patient at a 20-year time horizon is $35,769 for IIT compared to $410,373 for IT, translating into an incremental cost of $374,604. The QALYs per patient are 5.17 for IIT compared to 7.23 for IT, translating into an incremental QALY gained of 2.06 Hence, the cost per additional QALY gained for IT compared to IIT is $181,847.

The total health system cost per patient at a lifetime horizon is $50,277 for IIT compared to $429,062 for IT, translating into an incremental cost of $378,785. The QALYs per patient are 6.61 for IIT compared to 8.96 for IT, translating into an incremental QALY gained of 2.35. Hence, the cost per additional QALY gained for IT compared to IIT is $161,185.

Table E.2: Cost, effectiveness, and cost effectiveness of IT compared to IIT

Alternatives	Total Cost per Patient	QALY per Patient	Incremental Costs	Incremental QALY	$ Per QALY Gained
20-yr Horizon					
Aggressive insulin therapy	$35,769	5.17			
Islet transplantation	$410,373	7.23	$374,604	2.06	$181,847
Lifetime Horizon					
Aggressive insulin therapy	$50,277	6.61			
Islet transplantation	$429,062	8.96	$378,785	2.35	$161,185

Sensitivity analysis

A scatter plot of the 1000 Monte Carlo simulations is presented in Figures E.2 and E.3. The scatter plot illustrates the uncertainty surrounding the expected costs and expected QALYs shown in Table E.2. At both a 20-year and a lifetime horizon, 100% of the simulations show that IT is both more costly and more effective than IIT. The 95% Confidence Interval is $129,516 – $325,832 at a 20-year time horizon and $112,685 – $309,263 at a lifetime horizon.

Figure E.4 shows the cost effectiveness acceptability curve (CEAC), which shows the proportion of simulations that are cost effective at a given cost-effectiveness threshold. As previously described, the cost-effectiveness threshold represents the opportunity cost in the health system from technology adoption; a technology that is more costly and more effective is considered cost effective if its ICER (cost per additional outcome gained) is less than the opportunity cost of its adoption (that is, if it would result in a net health benefit to the health system). Between a threshold of 0 to $100,000, all simulations indicate that IIT is more cost effective than IT. Above $100,000 the probability that IT will be cost effective is greater than 0% and reaches 50% at a threshold of $182,584. Above a threshold of $250,000, the probability that IT will be cost effective is greater than 90%.

When assuming that secondary complications are not completely prevented for individuals with partial graft function, the incremental costs and outcomes of IT compared to those associated with IIT were $374,604 and 0.74 QALYs, respectively, giving an incremental cost effectiveness ratio of $506,222 per additional QALY gained at a 20-year time horizon. At a lifetime horizon, the incremental costs and outcomes of IT compared to those associated with IIT were $297,111 and 0.78 QALYs, respectively, giving an ICER of $380,912 per additional QALY gained.

Figure E.2: Distribution of incremental costs and effectiveness between IT and IIT: 20-year horizon based on 1000 Monte Carlo simulations

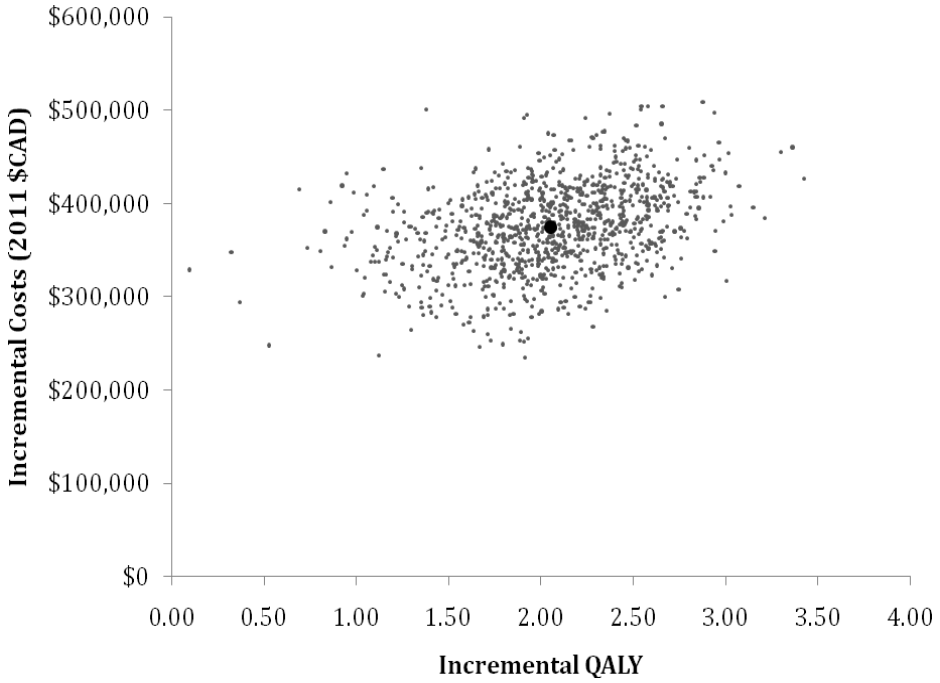


Figure E.3: Distribution of incremental costs and effectiveness between IT and IIT: Lifetime horizon based on 1000 Monte Carlo simulations

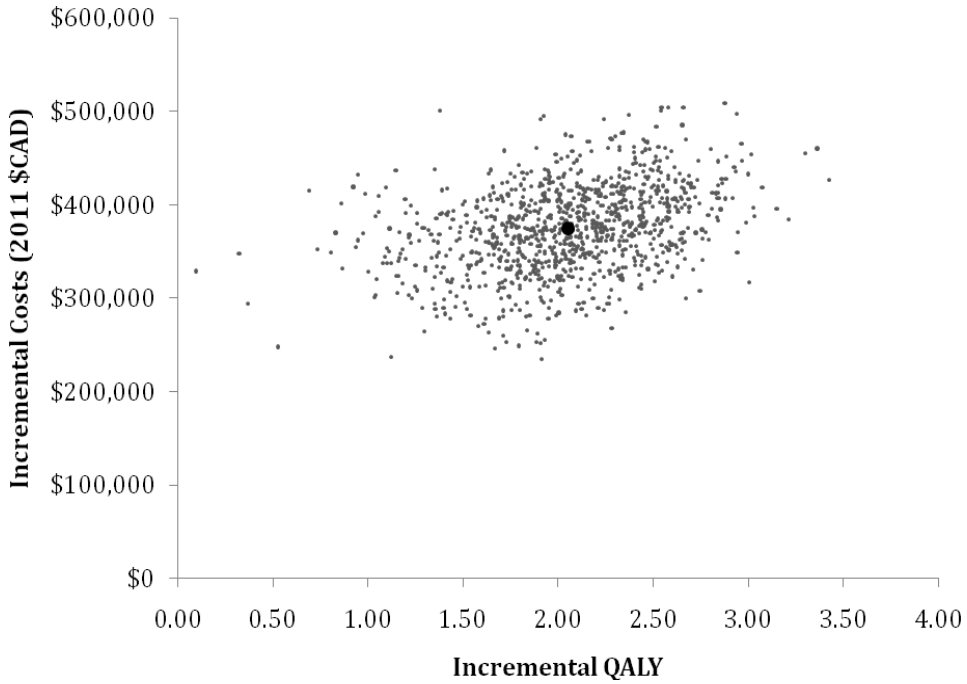
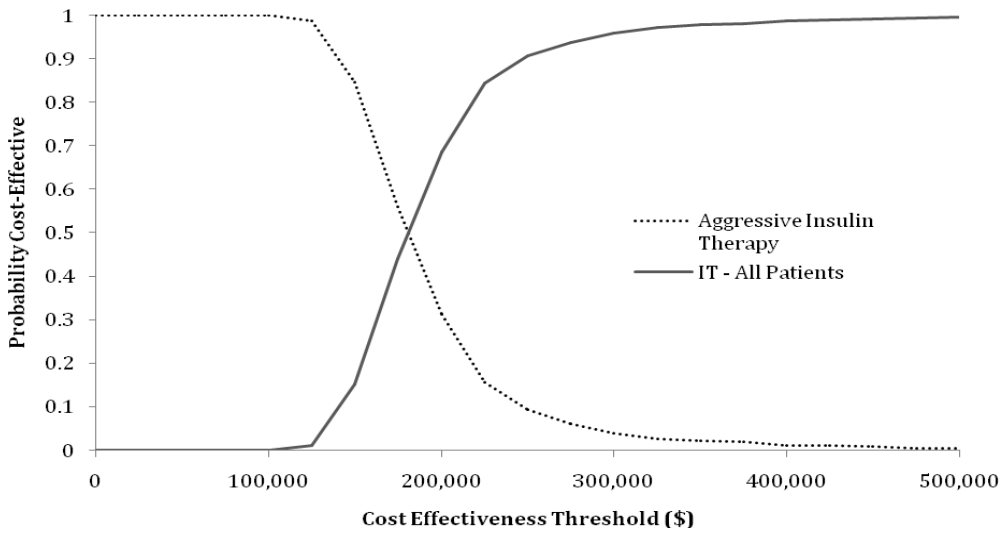


Figure E.4: Acceptability curve of IT and IIT: 20-year horizon based on 1000 Monte Carlo simulations



Cost attribution

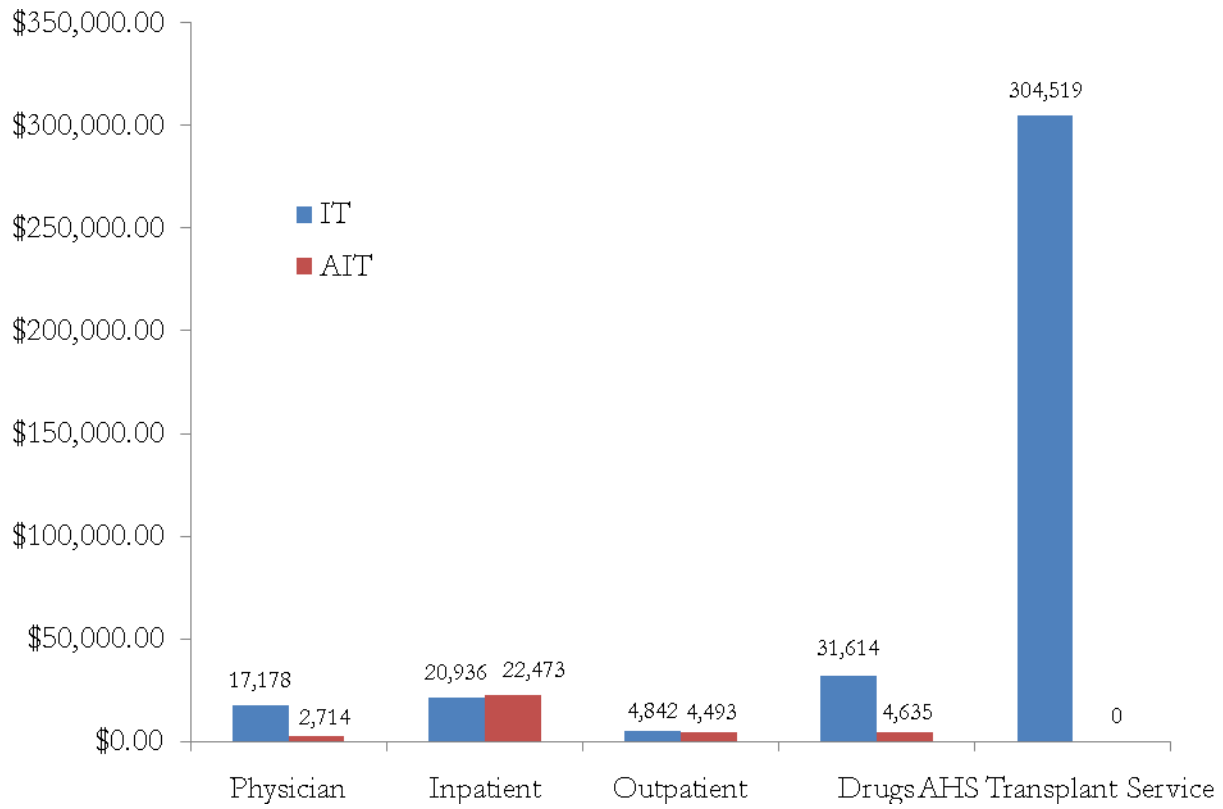
Figure E.5 shows the costs of IT and IIT separated into cost categories of physician, inpatient, outpatient, drugs, and AHS transplant services (20-year time horizon). The cost driver of IT is AHS transplant services. This is followed by drugs (CMV prophylaxis, immunosuppressants, and insulin), inpatient services (not directly related to IT), physician services, and outpatient services (not directly related to IT).

Compared to IIT, there is a cost increase per patient of:

- $14,463 in physician services
- $348 in outpatient services
- $26,979 in drugs (immunosuppressants)
- $304,519 in AHS transplant services (none in IIT)

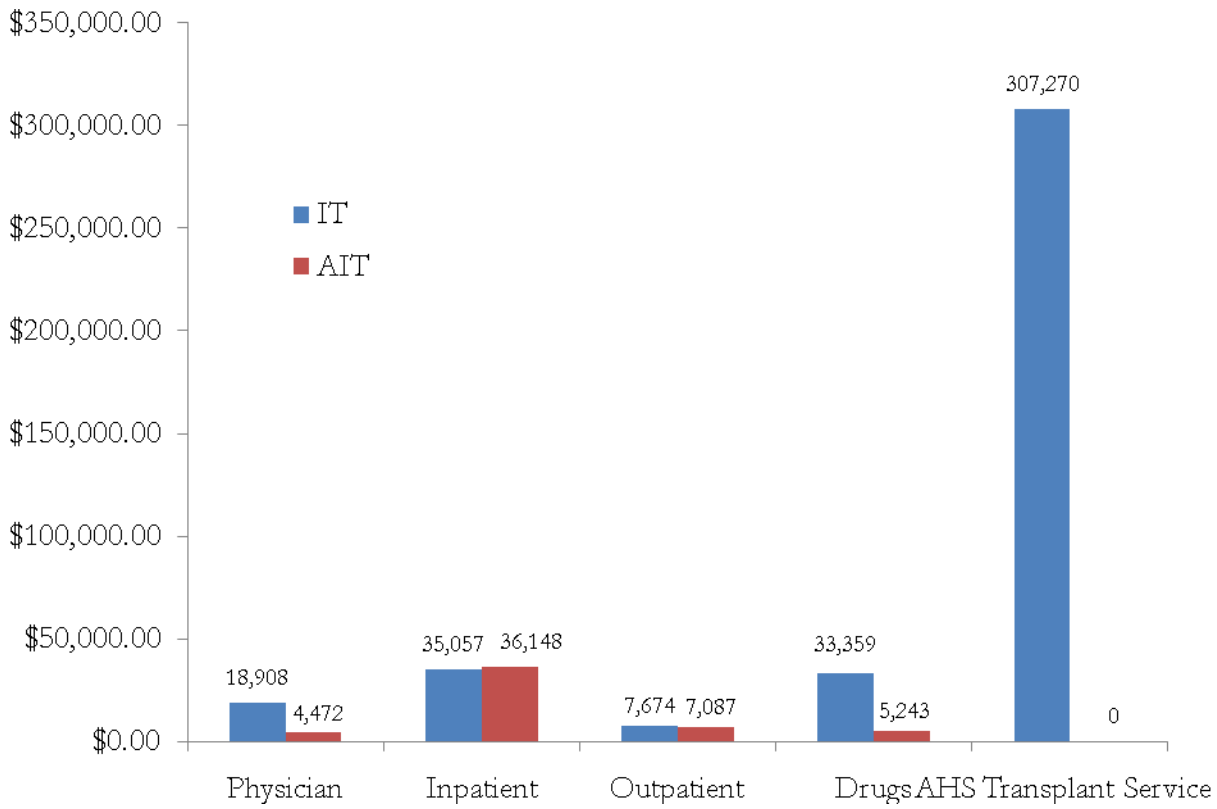
Compared to IIT, there is a cost saving of $1,537 per patient in inpatient services.

Figure E.5: Cost impact of IT and IIT to health sectors within a health system at a 20-year horizon



Note: Inpatient and Outpatient Costs are unrelated to transplantation services

Figure E.6: Cost impact of IT and IIT to health sectors within a health system at a lifetime horizon



Note: Inpatient and Outpatient Costs are unrelated to transplantation services

Budget impact analysis

Table E.3 shows the results from the BIA. With the available supply of pancreata, it is estimated that approximately 65 IT procedures can be performed per year, with 27 procedures being conducted out of province. At 65 procedures, the budget impact is $5,216,302 for in-province patients and $3,687,386 for out-of-province procedures, giving a total of $8,903,687. However, the program currently performs 22 procedures per year. Hence, the budget impact for the additional 43 procedures is $3,450,784 for in-province patients and $2,439,348 for out-of-province procedures, giving a total of $5,890,132.

Table E.3: Budget impact analysis results

Components	In-province	Out-of-province*	Total
	38	27	65
Physician costs	$284,635	$201,207	$485,842
Inpatient costs (unrelated to transplant services)	$1042	$737	$1,779
Outpatient costs (unrelated to transplant services)	$433	$306	$739
Drug costs (immunosupression and insulin)	$328,526	$232,234	$560,759
AHS Transplant Services	$4,603,751	$3,254,376	$7,858,126
Total	$5,216,302	$3,687,386	$8,903,687

Note: The budget impact includes the cost of the current volume of 22 IT procedures per year

* Estimated from AHS OFIA data

Discussion

Value for money

Cost and health outcomes were evaluated between IT and IIT for eligible IT patients with T1DM in Alberta. Compared to IIT, IT generated an additional 2.06 QALYs (that is, years worth of perfect health) at a 20-year horizon and 2.35 QALYs at a lifetime horizon. This difference in QALYs is clinically significant and large in magnitude given that a change of 0.03 QALYs is an indicator of clinical importance.[9] As previously mentioned, the systematic review in the T-section did not find any longitudinal prospective studies of IT that measured HRQL in terms of QALYs that we could compare with our results.[a] However, compared to IIT, IT was associated with an incremental cost of $374,604 at a 20-year horizon and $378,785 at a lifetime horizon, corresponding to a cost per additional QALY gained of $181,847 and $161,185, respectively. This suggests that the opportunity cost (that is, the cost effectiveness threshold) associated with IT must be greater than $181,847 or $161,185 for IT to be considered cost effective. In other words, at a lifetime horizon, if the amount of foregone net health benefit from investing the resources in the next best alternative is greater than $181,847, then IT is cost effective because it would result in a net health benefit to society.

[a] The T-section examines published empirical studies while the economic results are extrapolated (that is, output of the model). It should be recognized that extrapolated results are not as valid as results generated from published, prospective empirical studies.

The probabilistic sensitivity analysis indicates that the results are not significantly impacted by parameter uncertainty but are significantly impacted by the prevention of secondary complications. The improvements in health outcomes were primarily driven by the prevention of secondary complications such as amputation, blindness, renal failure, cardiovascular conditions, and neuropathy. The one-way sensitivity analysis shows that if secondary complications are not prevented, incremental costs and outcomes associated with IIT were $374,604 ($380,850 at a lifetime horizon) and 0.74 QALYs (0.78 QALYs lifetime), respectively, giving an ICER of $506,429 per additional QALY gained at a 20-year time horizon ($380,850 at a lifetime horizon). While the impact on health outcomes is still clinically significant, driven by the improvement on the frequency of severe hypoglycemic events, the value for money is significantly less if IT has no impact on secondary complications. While evidence shows that IT may hinder the progression of secondary complications,[7,10,11] the impact of IT on secondary complications from a long term perspective is less certain.

The literature search identified one study with which our results can be compared. Beckwith et al.[2] conducted an economic evaluation comparing IT with IIT. They found that over a 20-year horizon, IIT was associated with $663,000 USD and 9.3 QALY while IT was associated with $519,000 USD and 10.9 QALY. The authors did not perform an incremental analysis between IT and IIT but rather calculated the average cost effectiveness within each treatment of $71,000 per QALY for IIT and $47,800 per QALY for IT. The authors concluded that IIT is cost effective compared to IT. Both this study and our results show that IT is associated with clinically important improvements in health outcomes. Costs (and, more specifically, the cost of IT) drive the differences between these two analyses. In the study conducted by Beckwith et al.,[2] the costs of IT were assumed to be a one-time cost of $93,500 with annual follow-up costs of $19,000 per year. Over a 20-year time horizon, this is an underestimate of the total cost of IT given that re-transplant is common among IT recipients.

In our analysis, the high total cost of IT is what causes its high incremental cost per QALY gained (despite the clinically important improvements in health outcomes). This raises two important issues.

The first relates to how the cost effectiveness results may be impacted if IT were compared to whole organ pancreas transplantation (WOPT). WOPT can be considered as an alternative therapy to IT, although it should be acknowledged that WOPT would only apply to a select group of T1DM patients, with most IT patients being ineligible (personal communication, Medical Director Clinical Islet Transplant Program, November 15, 2010). WOPT was not included due to the lack of reliable and readily available Alberta data from which a valid comparative economic assessment could be performed. Without this data, it is uncertain how the long-term results in terms of both morbidity and mortality would differ between the two treatments.

The second issue relates to the fact that IT is an evolving procedure. For instance, new immunosuppressant regimens have shown a greater proportion of patients remaining insulin-independent for a longer duration (based on information about 22 patients contained in the CIP data). While these results are based on a small sample, it remains important to consider that if future advancements in IT result in a greater proportion of patients retaining full or partial graft function while minimizing the number of transplants to achieve these outcomes, this would result in reducing the total cost of IT (and would also improve health outcomes), improving its associated cost effectiveness.

Cost attribution analysis

A cost attribution analysis was conducted to provide insight into the resource implications on the various sectors of the health system that are impacted by IT. Not surprisingly, AHS transplantation services are associated with the highest cost impact (that is, the cost of transplant is not applied to IIT). Other sectors significantly impacted by IT are physician services and drugs. Over a 20-year time horizon, there is a net cost increase of $14,463 per patient to physician services and $26,979 per patient to drugs (immunosuppressants). There was a net cost increase of $384 per patient to outpatient services but a cost savings of $1,537 to inpatient services. This suggests that IT does have a small impact on reducing health service costs associated with general diabetes care (outpatient and inpatient categories account for costs associated with diabetes care and not those related to IT), but the costs associated with IT, including physician costs and immunosuppression, offset any health system savings in diabetes management. Note that AHS funds all these services with the exception of physician services, which are funded by AH.

Budget impact

In 2011, approximately 16,445 Albertans between the ages of 18 and 65 had T1DM without renal failure. This represents over 90% of the estimated Albertans with T1DM (see appendix E-3 for calculation details). It is uncertain what proportion would be eligible for IT. The CIP estimates that approximately 10% of those referred to the program are eligible for IT. However, considerations of demand may be unnecessary given that demand will exceed organ supply. Several issues relate to the supply of pancreata for use in IT including:

- whole organ transplants being given priority over IT
- the ability to match organs to suitable patients
- the yield of viable islets for transplantation

The current waiting list consists of 5 to 10 patients at any given time (personal communication, Manager, Transplant Services, AHS, October 12, 2011). At this volume of patients, matching available organs to suitable patients while also considering islet requirements of patients and yield of viable islets can be challenging. If the waiting list were to increase to 30 to 40 patients, there would likely be no issues of matching available organs to a suitable patient. Furthermore, islet isolation processes have improved over time so that yield has increased by over 100,000 units since 2009. With no issues of patient matching and islet requirements for transplant, the maximum number of ITs that can be conducted is approximately 65 per year.

Excluding the 22 ITs currently being conducted per year, the budget impact for the additional 43 ITs is approximately $3,450,784 for in-province patients and $2,439,347 for out-of-province procedures giving a total of $5,890,131. It is important to note that physician fees for performing islet infusions are not currently reimbursed in Alberta. This would add $77,000 to the current 22 IT procedures and $157,500 for the 43 additional procedures. It should be acknowledged, however, that the BIA does not include the maintenance cost of immunosuppression for transplantees. The weighted average for immunosuppression is approximately $8,627 per patient per year. Consequently, as more patients receive IT, there will be an associated cumulative increase in maintenance costs over time.

Caveats

Findings should be evaluated in light of the following caveats:

1. Although WOPT can be considered an alternative therapy to IT in select patients, it was not included as a comparator in our analysis due to lack of data on WOPT. If WOPT were to be more similar in cost to IT, with IT showing better health outcomes, the associated cost per additional QALY gained of IT would be significantly lowered (that is, more cost effective). The fact that IT has a high ICER when compared to IIT but a low ICER when compared to WOPT would suggest that IT is cost effective for the sub-population of patients eligible for WOPT (Note: patients eligible for WOPT represent a more severely affected patient group). However, this remains unknown, and the exclusion of WOPT remains a significant limitation.
2. The available Alberta data did not permit differentiation of the clinical effectiveness of IT by specific subpopulations. For purposes of parsimony, and to provide an objective assessment of the value for money associated with IT, the economic model begins with a cohort of 19-year-old patients without secondary complications. However, the exclusion criteria for IT eligibility only include renal failure and the average age of patients at the time of transplant is 47 years. Given that cost effectiveness was observed to improve at longer time horizons (for example, a 20-year horizon versus a lifetime horizon) and that the presence of secondary complications decreases the potential clinical benefit of IT (that is, decreases the potential to prevent future morbidity/mortality), the cost effectiveness of IT on a cohort of older patients with multiple comorbidities would result less cost effectiveness.
3. Clinical data were primary derived from the CIP because the required data were not available in the published literature (see T-section), but to also improve the relevance of the economic results to the Alberta environment. However, the majority of the data received from the CIP was unpublished and the validity and quality of the data is uncertain.
4. Other immunosuppressant complications (excluding cancer and renal failure) such as post-transplant lymphoproliferative disorder, mouth ulcers, liver abnormalities, and so on, were not explicitly modelled. No data on these complications was found in the more recent data housed by the CIP or in the review of the diagnostic coding data contained in the provincial administrative health databases for IT recipients. The Collaborative Islet Transplant Registry 2009 report, which includes patients from the CIP, does indicate that IT is associated with severe complications due to the islet infusion procedure and immunosuppressant therapy. However, because the data reports on all adverse events dating back to 1999 and does not differentiate their data by specific IT centres, it is uncertain how representative the data is to the current Alberta context, particularly because IT is an evolving procedure. A study published in 2005 on CIP patients did report the occurrence of acute complications such as major bleeds, blood transfusions, and thrombosis, but it also reported that some of these risks have been ameliorated by further refinement of the surgical technique.[13] Furthermore, the cost data provided by AHS represents an average cost for IT recipients, which would have included the costs of intraprocedural complications and associated sequelae. Nevertheless, it is important to reiterate the limitation pointed out in caveat #3.
5. Allosensitization refers to an exposure to an alloantigen that induces immunological memory cells. Allosensitization may impact the ability to receive future transplants/treatment for IT

patients who have developed an immunologic response. Costs and health outcomes for patients who may not be able to receive transplants/treatment (for example, whole organ pancreas transplants) in the future was not accounted for in the analysis.

6. Implementation considerations, such as infrastructure requirements and capital purchases, were beyond the scope of this analysis. Thus, the analysis does not consider the investment requirements associated with technology implementation nor does it assess the capacity within existing services to meet the demand for services.
7. Fixed costs could not be separated from variable costs for AHS program administration. However, separating fixed from variable costs for the program would not significantly affect the budget impact analysis because it represents a small proportion of total overall costs.
8. A cost attribution analysis was conducted to elucidate the resource implications of each alternative on the various sectors of the health system that are impacted by IT. This information is generated from an overall perspective, which is not the same as information generated from a detailed, local level microcosting.

Conclusion

IT is associated with clinically significant improvements in health outcomes but it is not cost saving compared to IIT. Hence, IT does not dominate IIT (that is, IT is not less costly and more effective) and its cost effectiveness depends on whether its associated health benefit is worth its additional cost. A prohibitive factor in the value of IT is its high associated cost per additional QALY gained. It is important to identify the services that have been displaced, expanded, or contracted in the health system to support IT (that is, the opportunity costs), and to evaluate the net impact of these actions in terms of their net health benefit. If the opportunity costs for the health system are greater than the value for money associated with IT (>$181,847 per additional QALY gained), IT would be considered cost effective. While IT is associated with cost savings from reduced health service utilization for general diabetes management, savings are dominated by the cost increases associated with transplantation. The budget impact of IT is approximately $5.9 million per year.

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Appendices

Appendix E.1: Search strategy

The IHE research librarian conducted an update search and retrieved articles published between 2000 and November 2010. Searches were limited to human studies where possible. Reference lists of relevant articles were also browsed to find more studies. The search strategy was created and carried out prior to the study selection process.

Table E.A.1: Search strategy

Database	Edition or date searched	Search Terms ††
Core Databases		
Cochrane Library Licensed Resource (Wiley Interface)	November 12, 2010	islet* AND (transplant* OR allotransplant*) **in Title, Abstract or Keywords** , from 2000 to 2010
MEDLINE (includes in-process citations) (Ovid interface)	November 12, 2010	**Islet cost SR** 1. "Islets of Langerhans Transplantation"/ 2. (islet* adj4 (transplant* or allotransplant*)).tw. 3. diabetes mellitus/ or diabetes mellitus, type 1/ 4. diabet*.tw. 5. (1 or 2) and (3 or 4) 6. limit 5 to animals 7. limit 6 to humans 8. 5 not (6 not 7) 9. limit 8 to yr="2000 - 2011" 10. exp "Costs and Cost Analysis"/ 11. (cost or (cost* not costimulat*) or economic* or expenditures or price or fiscal or financial or burden or pay or valuation or spending).tw. 12. 10 or 11 13. 9 and 12 **Additional searching for economic models** 14. *Pancreas Transplantation/ 15. (pancreas and transplant*).ti. 16. (14 or 15) and (3 or 4) 17. limit 16 to animals 18. limit 17 to humans 19. 16 not (17 not 18) 20. 12 and 19 21. limit 20 to yr="2000 - 2011" 22. 21 not 13 23. exp clinical trial/ 24. meta-analys*.pt,mp. 25. ((systematic* adj2 review*) or Medline or pubmed or psychinfo or psycinfo or search*).tw. 26. 19 and (23 or 24 or 25) 27. limit 26 to yr="2000 - 2011" 28. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or cross-sectional studies/ 29. 19 and 28 30. limit 29 to yr="2000 - 2011"

CRD Databases (DARE, HTA, & NHS EED) www.crd.york.ac.uk/crdweb	November 12, 2010	Islet* AND (transplant* OR allotransplant*) AND (cost* OR economic*) RESTRICT YR 2000 2010
EMBASE Licensed Resource (OVID Interface)	November 12, 2010 (to 2010 Week 44)	1. pancreas islet transplantation/ 2. (islet* adj4 (allotransplant* or transplant*)).tw. 3. diabet*.mp. 4. (1 or 2) and 3 5. limit 4 to yr="2000 - 2011" 6. (exp vertebrate/ or animal/ or exp experimental animal/ or nonhuman/ or animal.hw.) not (exp human/ or human experiment/) 7. (rat or rats or pig or pigs or porcine or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cats or bovine or sheep or murine or primate*).mp. not (exp human/ or human experiment/) 8. 5 not (6 or 7) 9. "COST"/ 10. exp Economic Evaluation/ 11. "health care cost"/ 12. (cost or (cost* not costimulat*) or economic* or expenditures or price or fiscal or financial or pay or valuation or spending).tw. 13. or/9-12 14. 8 and 13
Web of Science SCI-EXPANDED, SSCI Licensed Resource (ISI Interface)	November 12, 2010	#1 TS=((islet* SAME (transplant* OR allotransplant*)) AND diabet*) #2 TS=(rat OR rats OR rodent OR mice OR mouse OR sheep OR murine OR lamb OR lambs OR dog OR dogs OR cats OR monkey OR primate* OR pig OR pigs OR piglet* OR porcine OR rabbit* OR bovine OR hamster*) #3 #1 NOT #2 #4 TS=(cost or (cost* not costimulat*) or economic* or expenditures or price or fiscal or financial or pay or valuation or spending) #5 #3 AND #4
CINAHL Licensed Resource (EBSCO Interface)	November 12, 2010	S1 (MH "Islets of Langerhans") and (transplant* OR allotransplant*) S2 islet* cell* transplant* or islet* transplant* or islet* allotransplant* and islet* cell* allotransplant* S3 (S1 OR S2) and diabet* S4 cost or (cost* not costimulat*) or economic* or expenditures or price or fiscal or financial or pay or valuation or spending S5 S3 AND S4 Limit to 2000–2010
SCOPUS Licensed resources (Sciverse interface)	November 12, 2010	TITLE-ABS-KEY((islet* W/4 transplant*) OR (islet* W/4 allotransplant*)) **AND** TITLE-ABS-KEY(diabet*) **AND** TITLE-ABS-KEY(cost OR (cost* AND NOT costimulat*) OR economic* OR expenditures OR price OR fiscal OR financial OR pay OR valuation OR spending)

		AND NOT TITLE-ABS-KEY(rat OR rats OR rodent OR mice OR mouse OR sheep OR murine OR lamb OR lambs OR dog OR dogs OR cats OR monkey OR primate* OR pig OR pigs OR piglet* OR porcine OR rabbit* OR bovine OR hamster*) **AND** PUBYEAR AFT 1999 AND PUBYEAR BEF 2011
Library Catalogues		
NEOS Library Catalogue www.library.ualberta.ca/catalogue		Islet$ AND transplant$
Guidelines		
US National Guideline Clearinghouse www.guideline.gov/		Islet* AND transplant*
Canadian Diabetes Association www.diabetes.ca		Browsed site for guidelines
Clinical Trials		
US Clinical Trials.gov www.clinicaltrials.gov		(islet OR islets) AND (transplant OR transplantation) AND diabetes
Regulatory and Licensing Sites		
Alberta Health and Wellness www.health.gov.ab.ca		Islet transplant
Health Canada (used google.ca)		islet* AND transplant* site: hc-sc.gc.ca
United States Food and Drug Administration www.fda.gov		Islet* transplant*
United States Medicare Coverage Database www.cms.hhs.gov/mcd/search.asp?		Islet* transplant* (National coverage and local coverage—all words in title)
Aetna Clinical Policy Bulletins (used google.ca)		Islet transplantation site: aetna.com
BlueCross Blue Shield www.bcbs.com		Islet* transplant*
HTA Websites		
AETMIS www.aetmis.gouv.qc.ca/site/home.phtml		Islet; islets
CADTH www.cadth.ca/index.php/en/hta/reports-publications/search		Islet; islets
ICES www.ices.on.ca		Islet; islets
Health Technology Assessment Unit at McGill www.mcgill.ca/tau/publications/		Browsed 2002–2008 reports and work in progress
Medical Advisory Secretariat www.health.gov.on.ca/english/providers/program/ohtac/tech/techlist_mn.html		Browsed list of reviews

ECRI www.ta.ecri.org/Topics/prod/home/current.aspx		Islet (used "Find on this page" to browse quickly)
NICE (UK) www.nice.org.uk/page.aspx?o=ourguidance		Islet; islets
NZHTA http://nzhta.chmeds.ac.nz		Browsed publications list (ceased June 2007)
Search Engine		
Google www.google.ca		Islet transplantation diabetes—Pubmed Blackwell Ingenta Wiley Karger Elsevier Springer (first 50 results)

Note: ††, *, and $ are truncation characters that retrieve all possible suffix variations of the root word; e.g., surg* retrieves surgery, surgical, surgeon, etc. Semi-colons separate searches that were entered separately.

Appendix E.2: ICD and CCI coding

ICD-10	ICD-9	Description
	250	Diabetes mellitus
E10. ×[a]	250. ×1	Insulin-dependent diabetes mellitus
	250. ×3	
N18, N19	585, 586	Chronic renal failure
H54	369	Blindness and low vision
E10.4	250.6	Diabetic neuropathy
I21-I22	410	Acute myocardial infarction
I20, I24	411, 412, 413	Ischemic heart disease
I50	428	Heart failure
I60–I69, G45	430–438	Stroke
CCI code	**Description**	
1OJ85GRXXK	Islet cells from deceased donor using percutaneous transluminal venous approach	
1OJ85HAXXL	Xenogenic islet cells using percutaneous needle approach	
1OJ85WKXXK	Islet cells from deceased donor using small incisional approach	
1OK85TNXXK	Whole pancreas with duodenum	
1OK85TLXXK	Whole pancreas with duodenum	
1OK85TMXXK	Whole pancreas with duodenum	
1OK85XUXXK	Multi organ: pancreas with duodenum and kidney	
1OK85XVXXK	Multi organ: pancreas with duodenum and kidney	

[a]: The symbol × refers to any possible digit.

Table E.A.2: Procedure codes of lower limb amputation and excluded diagnostic code

Procedure Code	Description
96.11A	Amputation and disarticulation of one toe
96.12A	Amputation and disarticulation of foot: metatar sal- whole ray
96.12B	Amputation and disarticulation of foot: transmetatarsal
96.13	Amputation and disarticulation of ankle: Symes, Pirogoff
96.14	Amputation of lower leg below knee
96.15	Amputation of thigh or disarticulation of knee: supracondylar thigh through femur
ICD-9*	**Description**
170	Malignant bone tumor
171	Malignant connective tissue tumor
213	Benign neoplasm of bone
730	Osteomyelitis
740–759	Congenital abnormalities
800–900	Trauma
901–904	Arterial injury
940–950	Burns
*: any procedure code with one of the ICD code is excluded	

Appendix E.3: Budget impact analysis calculation steps

The prevalence of T1DM was estimated using the provincial administrative health databases described in the body of this report. The large majority of ICD codes contained in the PCD does not differentiate type 1 from type 2 diabetes mellitus. As a result, T1DM was estimated using two approaches.

In the direct approach, patients were diagnosed as having T1DM if they had an ICD code that directly corresponded to T1DM in any of the three administrative databases in any diagnosis field. In the indirect approach, for the remaining patient population patients are first defined as having undifferentiated diabetes using the National Diabetes Surveillance System definition[12] for diagnosing general diabetes. According to this definition, patients are diagnosed as having diabetes if they have at least two general ICD diabetes codes (for example, ICD code 250) within 2 years. Within this population, data contained within the Canadian Community Health Survey 3.1 are applied to estimate the proportion that has T1DM. According to the Canadian Community Health Survey 3.1, 12.6% of Albertans who reported having diabetes were taking insulin therapy within one month after diagnosis. It is assumed that patients with type 1diabetes initiate insulin therapy at the time of diagnosis, whereas those with type 2 diabetes do not.

Patients with T1DM (aged 18 to 65 years)

	2007			2008			2009		
	F	M	Overall	F	M	Overall	F	M	Overall
T1DM	6950	8309	15,259	7075	8766	15,841	7189	8753	15,942
T1DM without renal failure	6877	8228	15,105	6995	8658	15,653	7123	8654	15,777

Step	Description			Source/calculation
1	Patients with T1DM without renal failure (aged 18 to 65 years) in 2011 (projected based on observed incidence in table above)			Health administrative databases
	16,445			
2	Proportion of patients eligible for transplant			Assumption
	5%	10%	15%	
3	Number of eligible patients			1 × 2
	822	1644	2467	
4	Number of patients already in program			*
	138			
5	Number of patients to enter the program			3 - 4
	684	1506	2329	
6	Incremental number of transplant procedures over 5 years (estimated need for transplants)			**
	1481	3260	5039	
7	$7,474.49 per patient	Incremental physician costs		Economic model
	-$27.37 per patient	Incremental inpatient costs		Economic model
	$11.36 per patient	Incremental outpatient costs		Economic model
	$8,627.06 per patient	Incremental drug costs		Economic model
	$120,894.25 per transplant	Incremental AHS Transplant Services		AHS FOIA
8	Financial impact, physician			5 × 7
	Financial impact, inpatient			5 × 7
	Financial impact, inpatient			5 × 7
	Financial impact, outpatient			5 × 7
	Financial impact, drugs			5 × 7
	Financial impact, AHS Transplant Services			6 × 7

* – Clinical Islet Program
** –11%, 65%, 20%, and 4% of patients underwent one, two, three, and four transplants, respectively, over a 5-year period (AHS OFIA). Applying these percentages patients in Step 5 generates the number of transplants.

AUTHOR CONTRIBUTION STATEMENTS

Paula Corabian contributed to study conception and design, data analysis and interpretation, and approved the final version for publication.

Bing Guo contributed to study conception and design, data analysis and interpretation, and approved the final version for publication.

Christa Harstall contributed to study conception and design, revision of manuscript for critical content, and approved the final version for publication.

Charles Yan contributed to study conception and design, statistical analysis, economic expert review of the literature, revision of manuscript for critical content, and approved the final version for publication.

Anderson (Andy) Chuck contributed to study conception and design, statistical analysis, economic expert review of the literature, manuscript preparation, and approved the final version for publication.

This report is an update of the 2010 report on islet transplantation for Type 1 diabetes. Section One of this analysis was intended to describe the profile of T1DM (definition, progression, epidemiology, and population dynamics of affected adults in Alberta, in Canada, and worldwide) and patterns of care for this condition in adults (focusing on recommendations from evidence-based guidelines), as well as to identify potential inequities in health status or care across adult population groups. Social, ethical, and legal issues associated with the provision of IT as a treatment for adults with T1DM were also considered. Section Two of the analysis was to determine, for the treatment of patients with T1DM in Alberta, the potential role of islet transplantation compared to whole pancreas transplantation or intensive insulin therapy. The objective of the economic analysis in Section Three was to estimate the costs and cost effectiveness of islet transplantation (IT) compared to intensive insulin therapy (IIT) alone.

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