Horizon Scanning in Surgery: Application to Surgical Education and Practice

Allogeneic pancreatic islet cell transplantation for the management of type I diabetes mellitus

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Disclaimer

This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

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Objective

This horizon scanning assessment provides short, rapidly completed, 'state of play' documents. These provide current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

Acronyms

ADA	American Diabetes Association
AHSCT	autologous hematopoietic stem cell transplantation
BLA	Biologics license application
BMI	body mass index
CITR	Collaborative Islet Transplant Registry
FDA	Food and Drug Administration (United States)
GFR	glomerular filtration rate
GMP	good manufacturing practice
HbA1c	glycated hemoglobin
HLA	human leukocyte antigen
HRQL	health-related quality of life
IAK	islet after kidney transplantation
ICU	intensive care unit
IND	investigational new drug
ITA	islet transplantation alone
KTA	kidney transplantation alone
NICE	National Institute of Clinical Excellence (United Kingdom)
PAK	pancreas after kidney transplantation
PTA	pancreas transplantation alone
QALY	quality-adjusted life year
SIK	simultaneous islet and kidney transplantation
SPK	simultaneous pancreas and kidney transplantation
T1DM	type I diabetes mellitus
US	United States

Introduction

Background

Allogeneic pancreatic islet cell transplantation is currently being investigated as an alternative therapy to insulin therapy and dietary regulation, or whole-pancreas transplantation, for the management of type I diabetes mellitus (T1DM). Type 1 diabetes mellitus is a chronic metabolic disorder that results from an insulin deficiency attributed to the autoimmune destruction of the pancreatic β-cells of the islets of Langerhans (Jamiolkowski et al 2012). Insulin is an anabolic hormone that controls blood glucose levels, and when glucose is absorbed into the bloodstream, the pancreas is stimulated to produce insulin. Consequently, a deficiency in the production of insulin impairs glucose control, and can result in hyperglycemia (high blood glucose levels). Acute hyperglycemia has been associated with a number of mechanisms that contribute to the development of microvascular complications, including increases in renal perfusion, oxidative stress, retinal perfusion, hyperfiltration and decreased motor and sensory nerve conduction. It can also lead to blindness, end-stage renal disease and neuropathies (Marcovecchio et al 2011). Symptoms of hyperglycemia include increased urination (polyuria) and excessive thirst (polydipsia) to reduce glucose levels. Additionally, the body begins to break down fat as an alternative source of energy, leading to the accumulation of ketones in the blood and ketoacidosis (acidic blood) (Australian Institute of Health and Welfare [AIHW] 2011). Left untreated, the disease can progress to the depression of the central nervous system, coma and death (Kelly et al 2003).

Environmental and genetic factors are both thought to contribute to the risk of developing T1DM, and it is generally believed that environmental agents trigger disease in individuals who are genetically susceptible (Kelly et al 2003). In the United States (US), individuals with a first-degree relative with T1DM have a one in 20 lifetime risk of developing the disease, compared to one in 300 for the general population (Maahs et al 2010). The principle susceptibility markers for T1DM are two haplotypes in the human leukocyte antigen (HLA) class II complex on chromosome 6. It has been estimated that 90–95 percent of young children with T1DM carry either or both of the haplotypes; however, these genes may have low penetrance, with an estimated 5 percent of individuals who are genetically at risk developing the disease (Maahs et al 2010). This may indicate the importance of environmental factors in disease susceptibility, and is further supported by seasonal and geographical variance in disease incidence (with more cases occurring in autumn and winter). Other implicated environmental agents include viral infections, dietary factors in infancy, vaccination, toxins and stress, and it has been hypothesized that T1DM has a heterogeneous etiology, with different factors promoting β-cell destruction by differing mechanisms (Kelly et al 2003).

The rate of β-cell destruction differs between patients, but tends to be more aggressive in infants and young children. The majority of cases arise during childhood or adolescence, but can additionally develop in adulthood (AIHW 2011; Kelly et al 2003). Symptoms may gradually progress over a period of months or years, however, patients with T1DM typically present with acute onset of polyuria, polydipsia and rapid weight loss. Antibodies that are directed towards the β-cell proteins (including insulin) are detectable in 85–90 percent of subjects at the time of T1DM diagnosis. While it is unclear whether they participate directly in β-cell destruction, they are good markers of the pathogenesis of the disease and can precede clinical onset of the disease by

several years (Kelly et al 2003). With increased awareness and screening, patients may be identified with sufficient residual β-cell function to be managed on low doses of exogenous insulin. However, as functionality diminishes, management of the disease becomes increasingly challenging (Maahs et al 2010).

Treatment of T1DM is most commonly glucose control by exogenous insulin injections or an insulin pump, and dietary regulation. This is supported by daily blood glucose level monitoring and measurement of longer-term glucose control by levels of glycosylated hemoglobin (HbA1c) (American Diabetes Association [ADA] 2012; Bassi and Fiorina 2011). While insulin represents a life-saving therapy, periods of hyperglycemia can still occur, and even tight blood glucose control can only partially prevent or slow the onset of chronic complications associated with T1DM (Bassi and Fiorina 2011). Many people will eventually develop long-term complications, including heart disease, blindness, kidney failure, foot ulcers, peripheral vascular disease and autonomic neuropathy (National Institute for Health and Clinical Excellence [NICE] 2007). Insulin therapy in itself can also be life threatening with an unintentional insulin overdose resulting in severe hypoglycemia (low blood glucose levels). Many T1DM patients display some degree of hypoglycemia unawareness (reduced ability to detect the symptoms of low blood glucose) (Jamiolkowski et al 2012; McCall and Shapiro 2012). Treatment alternatives to insulin therapy include allogeneic pancreatic islet cell transplantation and whole pancreas transplantation (ADA 2012; Shapiro et al 2000).

Burden of disease

The prevalence of T1DM in the US has been estimated between 1.1-1.4 million people (Tao and Taylor 2010). This number may be an underestimate, as some 10 percent of adults who are diagnosed with type II diabetes mellitus may have been misdiagnosed (Tao and Taylor 2010), with estimates of up to 2.8 million people with T1DM reported (Digon 2009). Patients with T1DM comprise approximately 5 percent of the total diabetic population. However, in the population younger than 18 years, T1DM attributes to up to 79 percent of the disease (Tao and Taylor 2010). The estimated costs attributed to T1DM are approximately 9 percent of the total costs attributed to diabetes (Tao and Taylor 2010).

Between 2002 and 2005, more than 15,000 youths aged ≤19 years were newly diagnosed with T1DM. The overall rate of new cases in those aged less than 10 years was 19.7 per 100,000 and 18.6 per 100,000 in youths aged 10–19 years, with the highest rates of new cases in non-Hispanic white youths (Table 1).

Table 1: Rates of new case of T1DM in youths, 2002–05

Population	Youths aged <10 years (per 100,000)	Youths aged 10–19 years (per 100,000)
All	19.7	18.6
Non-Hispanic white	24.8	22.6
Non-Hispanic black	15.7	15.7
Hispanic	14.1	13.8
Asian/Pacific Islander	6.4	7.4
American Indians	4.2	4.7

Source: U.S. Centers for Disease Control and Prevention (US CDC) (2011b). T1DM: type 1 diabetes mellitus.

Diabetic complications continue to be a major cause of morbidity and mortality in persons with T1DM, with cardiovascular disease the leading cause of death (Maahs et al 2010). Both type I and II diabetes are associated with complications that include heart disease, stroke, hypertension, blindness, other eye problems eye problems, kidney disease, nervous system disease, amputations and dental disease (U.S. Centers for Disease Control and Prevention [US CDC] 2011a).

It has been estimated that patients with T1DM experience 1.3 severe hypoglycemic episodes per year, with 5 percent of patients accounting for 54 percent of these episodes (Pedersen-Bjergaard et al 2004), and may result in life-threatening episodes that require assistance and emergency medical intervention. Untreated, severe hypoglycemic episodes may result in coma, seizures and death, and account for up to 10 percent of the mortality in T1DM patients (Jamiolkowski et al 2012). Such patients may require constant family or caretaker supervision.

Technology

Allogeneic pancreatic islet cell transplantation refers to the isolation of islets from a donor and transplantation into a recipient patient, usually through percutaneous infusion into the hepatic portal vein. The procedure can be used in selected T1DM patients with severe glycemic instability, recurrent hypoglycemic episodes, and hypoglycemia unawareness (de Kort et al 2011). Replacement of islet cells allows blood glucose levels to normalize without the risk of hypoglycemia, with the insulin producing β-cells able to subtly adjust insulin secretion to maintain glucose homoeostasis. While insulin independence is the primary goal of islet transplantation, in the long term, partial graft function may be more realistic, with glucose control achieved by a combination of insulin from the donor islet cells and supplementary insulin therapy (de Kort et al 2011).

Islet preparation

Pancreas procurement and preservation

To achieve transplantation success, the selection of a donor pancreas for islet isolation is a critical step. Most islets are obtained from the pancreas of a heart beating brain dead organ donor, and transplantation success may be determined by numerous donor and preservation factors, including body mass index (BMI), blood glucose levels, use of vasopressors and cold ischemia time (McCall and Shapiro 2012). Matching of donor and recipient characteristics is performed, and a recipient can receive islets from one or several donors (Bassi and Fiorina 2011; NICE 2008).

Islet isolation and purification

Islets are separated from the exocrine component of the pancreatic gland by the initial infusion of enzymes into the pancreatic duct, and subsequent sectioning of the pancreas and exposure to enzymatic and mechanic digestion within a semi-automated digestion chamber known as the Ricordi chamber. Islets then undergo density gradient centrifugation, which purifies islets based on their differential density compared to the surrounding pancreatic exocrine tissue (de Kort et al 2011; McCall and Shapiro 2012).

Most isolation centers culture the islets for several hours to days to perform rigorous quality, safety and viability tests while preparing the recipient for transfusion (de Kort et al 2011; U.S. Food and Drug Administration [FDA] 2009). To ensure a high quality drug and biological product, islets must be isolated at a facility that adheres to good manufacturing practice (GMP) guidelines (de Kort et al 2011).

Islet infusion

Islets ideally require transplantation to a site with ready access to a robust vascular supply that includes oxygen and glucose, in addition to the means to transport insulin to target tissue. For the patient, the transplantation site should confer minimal procedural risk, while allowing for long-term function (McCall and Shapiro 2012). Several islet infusions may typically be needed to achieve insulin independence (NICE 2008). The success of the graft is most commonly determined by the restoration of endogenous insulin secretion, measured by the concentration of C-peptide in the serum (Rickels et al 2007).

The most commonly used site is the liver, with islets percutaneously infused into the portal vein by ultrasound- or fluoroscopic-guided catheterization under local anesthesia over a period of 10 to 30 minutes. The islets embolize the small branches of the portal vein, engraft in the recipient liver, and begin to function and produce insulin (de Kort et al 2011; NICE 2007). While these sites provide access to oxygen and a near-physiologic insulin delivery environment, islets are additionally exposed to detrimental components of the blood, which can activate the coagulation and complement systems that lead to rapid islet loss. This effect may be mitigated by administration of an anticoagulant, such as heparin, post-transplant. Another disadvantage in the use of this site is that reliable monitoring of the graft has proven difficult (McCall and Shapiro 2012).

Given the disadvantages of the portal site, alternative routes, including a trans-jugular approach or intra-operative administration, have also been investigated, and may provide improved islet function and better overall safety (FDA 2009).

Immunosuppression therapy

To ensure the survival of the transplanted islets, recipients require use of an ongoing immunosuppression regimen to prevent autoimmunity and allorejection, with induction therapy used in most islet transplant protocols (McCall and Shapiro 2012).

While minimally invasive, allogeneic pancreatic islet cell transplantation is associated with both procedure- and immunosuppression-related complications, as well as the potential for islet graft rejection or decline and loss of insulin independence (Shapiro et al 2000). The benefits may be different between T1DM patients who have previously had, or are indicated for, a kidney transplant, and thus require immunosuppression regardless, to those who undertake islet transplantation alone. The latter should only be considered in patients where improvement in glycemic control outweighs the risks associated with immunosuppression (Robertson et al 2006).

Stage of development

In the US, islet transplantation is experimental and only available at sites that have received exemption from the FDA for the clinical research of islet transplantation in T1DM. The National Institute of Diabetes & Digestive & Kidney Diseases established the Collaborative Islet Transplant Registry (CITR) in 2001 to compile data from all islet transplant programs in North America to date since 1999. Between 1999 and 2009, there were 453 islet recipients in North America (Figure 1) (CITR 2011).

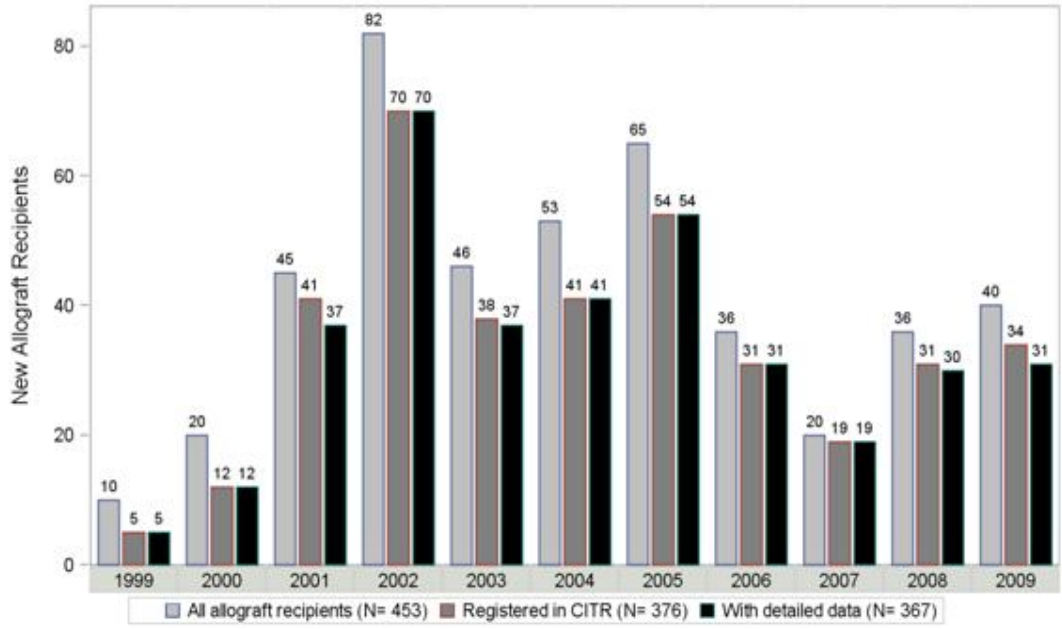

Figure 1: Islet transplant recipients 1999–2009 (CITR 2011)

Individual transplant centers may initiate their own independent research protocols or participate in the Clinical Islet Transplantation (CIT) Consortium to advance the field of islet transplantation (CITR 2011).

Regulatory approval

In the US, allogeneic pancreatic islets meet the FDA criteria for regulation both as a drug and as a biological product, in addition to the definition of somatic cell therapy, as living allogeneic somatic cells are intended for replacement therapy (Linetsky and Ricordi 2008). In consequence, allogeneic pancreatic islets cannot be clinically used without the applicable regulatory approvals (Wonnacott 2005).

While there are endeavors underway to secure a BLA for the marketing of islet transplantation as a viable therapy for selective patients with T1DM, issues such as islet safety, purity, potency and effectiveness need to be addressed (Linetsky and Ricordi 2008; McCall and Shapiro 2012). GMP guidelines outline the manufacturing controls required for the isolation of allogeneic pancreatic islets and include control of the source material, control of the isolation process and control of the final product (Wonnacott 2005).

The FDA has produced a guidance document for manufacturers, sponsors and clinical investigators involved in the clinical studies of allogeneic pancreatic islet cell products for the treatment of T1DM (FDA 2009).

Allogeneic pancreatic islets are regulated in Canada under the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* framework, and are approved for use in the United Kingdom in units with established experience in allogeneic pancreatic islet cell transplantation (Guo et al 2008; NICE 2008)

Current clinical trials

Two current comparative clinical trials have been identified (Table 2): both are randomized controlled trials that compare allogeneic islet transplantation to medical management.

Table 2: Current clinical trials

Trial ID	Title	Study design	Estimated completion date
NCT01148680	Randomized Controlled Trial Comparing the Metabolic Efficiency of Allogeneic Pancreatic Islet Transplantation to Intensive Insulin Therapy for the Treatment of Type 1 Diabetes	Randomized	June 2014
NCT00853424	A Comparison of Islet Cell Transplantation With Medical Therapy on the Risk of Progression of Diabetic Retinopathy and Diabetic Macular Edema	Randomized	June 2015

In addition, several collaborations have formed for ongoing data collection:

The Collaborative Islet Transplant Registry (CITR), founded in 2001, collect, analyse and communicate data on all islet/beta cell transplants performed in North America, as well as some European and Australian centers.
http://www.citregistry.org/

The Clinical Islet Transplantation (CIT) Consortium was established in 2004 to conduct studies of islet transplantation in patients with type 1 diabetes, and comprises a network of clinical centers throughout North America and Europe, in addition to a data coordinating center.
http://www.citisletstudy.org/

The International Islet Transplant Registry
www.med.uni-giessen.de/itr .

Current treatment and alternatives

Medical management

Insulin therapy remains the standard treatment for T1DM and the currently recommended intensive insulin therapy regime has improved glycemic control and patient outcomes (ADA 2012; The Diabetes Control and Complications Trial Research Group 1993). Intensive insulin therapy can consist of three or more injections per day of insulin, continuous subcutaneous insulin infusion or insulin pump therapy, and the use of a combination of rapid-acting and long-acting insulin analogs is also recommended (ADA 2012).

General recommendations for achieving glycemic control for adults with diabetes include achieving a pre-meal capillary plasma glucose of 70–130 mg/dL (3.9–7.2 mmol/L), a peak post-meal capillary plasma glucose of <180 mg/dL (<10.0 mmol/L), and an HbA1c level of less than 7.0 percent, although recommendations should be individualized based on the patient's situation. Children with T1DM have tailored blood glucose and HbA1c goals to avoid excessive hypoglycemia. Self-monitoring of blood glucose should be carried out three or more times a day for patients using multiple insulin injections or insulin pump therapy. Real-time continuous monitoring of interstitial glucose, which correlates with plasma glucose, is also available and can be used in conjunction with blood glucose self-monitoring (ADA 2012).

Dietary management is important to reduce the risk of hypoglycemia or hyperglycemia after a meal, and includes education for patients and relevant family members about the timing, size, frequency or composition of meals (NICE 2007).

β-cell replacement

Approximately 10 percent of patients with T1DM are sensitive to insulin and are more prone to recurrent severe hypoglycemia, without the usual warning signs of sweating, tremor, tachycardia and anxiety (Merani and Shapiro 2006). These patients are indicated for the replacement of the pancreatic β-cells of the islets of Langerhans by the transplantation of the whole pancreas or of pancreatic islet cells (discussed in Technology above). Replacement can allow for the normalization of glycaemia without the risk of hypoglycemia, with the insulin producing β-cells able to subtly adjust insulin secretion to maintain glucose homoeostasis.

Whole pancreas transplantation

Whole pancreas transplantation has been performed since 1967 (Kelly et al 1967), with subsequent improvements in the technique. Whole pancreas transplantation combined with kidney transplantation is considered the therapy of choice for T1DM patients with kidney failure and can occur at the same time as the kidney transplant (simultaneous pancreas and kidney transplantation, SPK) or in a later procedure (pancreas after kidney transplantation, PAK) (Guo et al 2008).

The ADA has recommended that in the absence of the indication for kidney transplantation, pancreas transplantation alone (PTA) should only be considered in patients for whom the benefits of glycemic control outweigh the burden of life-long use of an immunosuppression regimen to prevent rejection of the allograft, and who would consequently exhibit (Robertson et al 2006):

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

In addition to the side effects of life-long immunosuppression, the procedure of whole pancreas transplantation has significant morbidity and carries a small risk of mortality (Robertson et al 2006). Unlike allogeneic pancreatic islet cell transplantation which is minimally invasive, whole pancreas transplantation is a major surgical procedure, and is associated with considerable procedure-related complications and post-transplant morbidity (de Kort et al 2011).

Experimental means

Autologous hematopoietic stem cell transplantation (AHSCT) is an experimental treatment designed to prevent destruction and preserve the function of remaining pancreatic β-cells in newly diagnosed T1DM. This procedure includes a program of intense immunosuppression therapy, followed by the re-establishment of tolerance to pancreatic β-cells by the administration of autologous uncommitted hematopoietic stem cells (Voltarelli et al 2008). The rationale of this method is that after depletion by chemotherapy of the cells deemed to have caused the diabetes, the transplanted hematopoietic stem cells have the capacity to differentiate into β-cells. While the mechanism for this process is unclear, it has been suggested that AHSCT shifts the equilibrium from immune destruction to immune tolerance via clonal exhaustion, alterations in cytokines and changes in the types and numbers of T- and B-lymphocytes (Voltarelli et al 2008). Small Phase I/II trials have shown promising results (Gu et al 2012; Voltarelli et al 2007). However, concerns regarding both short- and long-term complications have been associated. Ongoing research in this area is required to address these concerns and to adequately determine the viability of AHSCT treatment in patients newly diagnosed with T1DM.

Literature review

Search criteria

Keyword/MeSH terms utilized:

Pancreatic islet*, islets of Langerhans, Islets of Langerhans [MeSH], Islets of Langerhans transplantation [MeSH], islet transplant*, Diabetes Mellitus, Type 1 [MeSH], type I diabetes

Databases utilized:

PubMed, EMBASE, Cochrane, CRD

Inclusion criteria

Inclusion criteria for eligible studies are listed in Table 3.

Table 3: Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Randomized controlled trials or non-randomized comparative studies, according to NHMRC Levels of Evidence (Appendix A)
Patient	Patients with type 1 diabetes mellitus
Intervention	Allogeneic islet cell transplantation
Comparator	Whole pancreas transplantation, medical management
Outcome	Safety: mortality, adverse events Efficacy: graft function, length of hospitalization, other system measures, quality of life
Language	English only

NHMRC: National Health and Medical Research Council.

Studies identified in the literature search that have been excluded from this assessment are listed in Appendix B.

Included studies

No randomized controlled trials were identified. A total of six non-randomized comparative studies that assessed allogeneic islet transplantation were selected for inclusion in this report (Table 4). Three compared allogeneic pancreatic islet cell implantation to whole pancreas transplantation (Frank et al 2004; Gerber et al 2008; Maffi et al 2011), two to medical management (Thompson et al 2011; Toso et al 2007) and one to whole pancreas transplantation and medical management (Fiorina et al 2003). An interim report for the Thompson et al (2011) study was additionally identified for study characteristics that were not reported (Warnock et al 2008).

Table 4: Characteristics of included studies

Study/Location	Level of evidence (Appendix A)	Intervention (number of patients)
Whole pancreas transplantation versus allogeneic islet transplantation		
Maffi et al (2011) *Italy*	Level III-2 Retrospective non-randomized comparative study	PTA (n=33) ITA (n=33)
Gerber et al (2008) *Switzerland*	Level III-2 Retrospective non-randomized comparative study	SPK (n=25) SIK (n=13) KTA (n=11)
Frank et al (2004) *United States*	Level III-2 Retrospective non-randomized comparative study	SPK (n=25) PAK (n=5) ITA (n=9) IAK (n=4)
Medical management or whole pancreas transplantation versus allogeneic islet transplantation		
Fiorina et al (2003) *Italy*	Level III-2 Retrospective non-randomized comparative study	IAK (n=37) SPK (n=162) KTA (n=42) MM[a] (n=196)
Medical management versus allogeneic islet transplantation		
Warnock et al (2008) Thompson et al (2011) *Canada*	Level III-3 Prospective non-randomized comparative study without concurrent controls[b]	MM[b] (n=45) ITA (n=32)
Toso et al (2007) *Canada*	Level III-2 Prospective non-randomized comparative study	ITA (n=99) MM (n=166)

[a] Type 1 diabetes mellitus patients on hemodialysis awaiting kidney-pancreas transplantation
[b] One way crossover study design, all patients enrolled underwent medical management until islet transplantation could be performed.
IAK: islet after kidney transplantation; ITA: islet transplantation alone; KTA: kidney transplantation alone; MM: medical management; PAK: pancreas after kidney transplantation; PTA: pancreas transplantation alone; SIK: simultaneous islet and kidney transplantation; SPK: simultaneous pancreas and kidney transplant.

Study profiles

Non-randomized comparative evidence for whole pancreas transplantation versus allogeneic islet transplantation

Maffi et al (2011)

Maffi et al (2011) aimed to analyze the risks and benefits of islet transplantation alone versus pancreas transplantation alone in T1DM, in a single center in Italy. The study was non-randomized and included patients who received PTA (n=33) or ITA (n=33) transplantation alone according to clinical indications between 1999 and 2010 with at least one year of post-transplant follow-up. Inclusion criteria for a pancreas or islet transplant included age 18 to 64 years, duration of T1DM greater than five years, unstable metabolic control with severe complications (hypoglycemia, hyperglycemia, ketoacidosis) which required hospitalization despite intensive insulin management, and progression of retinopathy and neuropathy. For islet transplantation, additional inclusion criteria included no measurable levels of stimulated C-peptide, body weight less than 75 kg for males and 70 kg for females, and cardiovascular disease excluding the patient from being listed for pancreas transplantation. Pancreas transplantation was performed with enteric diversion of exocrine secretion. Islet transplantation involved islet infusion in the liver through percutaneous transhepatic puncture with ultrasound guidance under local anesthesia. In the islet transplantation group, nine patients had a single infusion, 16 had two infusions, and 80 had three infusions. Age, diabetes duration, gender balance and hypoglycemia unawareness

appeared similar between the two patient groups. The pancreas transplantation group appeared to have more patients with retinopathy, neuropathy and arteriopathy, although a measure of significance was not provided.

Gerber et al (2008)

Gerber et al (2008) compared glucose control, renal function and procedure-related complications in patients with T1DM who underwent simultaneous islet and kidney (SIK) or SPK transplantation. This non-randomized and retrospective study included patients who underwent SIK (n=13) or SPK (n=25) at a single center in Switzerland between 2000 and 2004. Inclusion criteria for either surgery type were T1DM and end stage renal failure requiring dialysis. Mean follow-up was 42 months (range 13–66) for the SPK group and 38 months (range 12–67) in the SIK group. An additional group of patients who received kidney transplantation only (KTA) were also assessed, to assist in separating the effect of islet or pancreas transplantation from other kidney transplantation-associated effects. Pancreas transplantation was performed heterotopically (in an abnormal location) into the abdomen. Islet transplantation was performed using either infusion by gravity via a catheter placed in a mesenteric vein, or a percutaneous transhepatic approach to gain access to the portal vein under fluoroscopic guidance (Lehmann et al 2004). Gender distribution, age of T1DM diagnosis, length of time receiving pre-transplant dialysis, and time on the waiting list were similar between the islet and pancreas transplantation groups ($p>0.05$). Compared with the SPK group, the SIK group had significantly higher age at transplantation ($p=0.0001$), longer diabetes duration ($p=0.0009$), higher BMI ($p=0.03$) and more interventions for coronary heart disease ($p=0.04$). The kidney transplant-only group had an older age at T1DM diagnosis ($p=0.003$) and at transplantation ($p=0.04$), and longer duration of pre-transplant dialysis ($p=0.03$), compared with the other surgical groups.

Frank et al (2004)

Frank et al (2004) conducted a retrospective analysis of a consecutive series of patients who underwent pancreas or islet transplantation at a single center in the US between September 2001 and February 2004. The study aimed to compare a variety of parameters, including patient and graft survival, degree and duration of glucose homeostasis, procedural and immunosuppressive complications, and utilization of resources. Patients who underwent SPK (n=25), PAK (n=5), ITA (n=9) and IAK (n=4) were included. Very poor glucose control and dangerous episodes of hypoglycemia were the usual indications for islet or whole pancreas transplantation; patients indicated for IAK had stable graft function with no rejection episodes in the six months prior. Mean follow-up was 421 days for whole organ pancreas transplantation and 522 days for islet transplantation. Whole organ pancreas grafts were transplanted with systemic venous drainage in 13 cases and with portal drainage in 17 cases. Ultrasound localization and percutaneous transhepatic cannulation of portal vein branches under angiographic guidance was used for 22 of 23 islet infusions. Recipients were similar in terms of age, gender, body mass index and duration of diabetes. However, significantly more patients who received whole organ pancreas had a history of dialysis ($p<0.01$).

Non-randomized evidence for medical management or whole pancreas transplantation versus allogeneic islet transplantation

Fiorina et al (2003)

Fiorina et al (2003) conducted a retrospective analysis of a series of T1DM patients who underwent IAK (n=37), SPK (n=162), KTA (n=42), or who were on the waiting list for a kidney-pancreas transplantation (MM) (n=196). Groups were compared for patient survival, cardiovascular death rate and endothelial function (determined by skin biopsy). Exclusion criteria for transplantation included previous strokes, major amputations, severe dilated cardiomyopathy or coronary artery disease. Prior to transplantation, none of the patients had a pathologic ejection fraction or heart failure. IAK transplant patients were followed for an average of 63±7.2 months. Length of follow-up was not reported for the SPK group. The method of islet transplantation was performed as previously reported in Secchi et al (1997), where islets were transplanted into the portal vein percutaneously under local anesthesia. The authors reported that before transplantation, the groups were similar regarding clinical characteristics, although measures of significance were not provided. Islet recipients were separated according to success of the procedure, defined by fasting C-peptide secretion of greater than 0.5 ng/mL.

Non-randomized evidence for medical management versus allogeneic islet transplantation

Thompson et al (2011)

Thompson et al (2011) conducted a prospective, crossover cohort study that compared ITA with intensive medical therapy (MM) to determine the effect on the progression of diabetic nephropathy, retinopathy and neuropathy. The study entered 45 participants who received medical management, consisting of intensive glucose management, angiotensin blockade, and control of blood pressure and lipids to recommended levels. Upon availability of donor organs, patients (n=32) crossed over to the islet transplantation arm (median time 21 months). Median follow-up for medical patients was 47 months, and 66 months for patients after islet transplantation. Eight patients, five medical and three islet recipients were lost to follow-up. Baseline clinical characteristics were reportedly similar, however no comparative statistic were provided (reported in Warnock et al 2008)

Toso et al (2007)

Toso et al (2007) compared the health-related quality of life (HRQL) of nonuremic T1DM patients after ITA (n=99) to T1DM controls (n=166). Two questionnaires were administered:

- the Health Utilities Index Mark 2 (HUI2), an assessment of the overall quality-of-life which is characterized by six attributes:
    - sensation (vision, hearing, speech)
    - mobility
    - emotion (anxiety)
    - cognition
    - self-care
    - pain/discomfort

  Scores for the HUI2 range between -0.03 (worst possible health state) to 1.0 (perfect health)
- the Hypoglycemia Fear Survey (HFS) that assessed patients' concern about hypoglycemia and behaviors engaged to avoid low blood glucose, higher HFS scores indicate a greater fear of hypoglycemia.

Recipients were questioned while on the waiting list (n=99), after the first infusion (n=75), and at one month (n=77), three months (n=70), six months (n=70), 12 months (n=65), 24 months (n=53) and 36 months (n=45) after the completion of a full islet transplant. The proportion of completed questionnaires was 376/554 (68%) in the islet transplanted group and 166/277 (60%) in the control group. No significant difference was observed between the two groups for gender, age or HRQL at baseline. However, the mean duration of diabetes was significantly longer in the transplant group ($p<0.01$), and while on the waiting list, patients prior to transplantation exhibited significantly more fear of hypoglycemia than controls ($p<0.000001$).

Critical appraisal

The highest quality evidence that compares islet transplantation to either whole pancreas transplantation or medical management is limited to non-randomized comparative studies, with the majority being retrospective in design and involving a small number of patients (less than 100). One study did not include concurrent controls (Thompson et al 2011). Inclusion criteria or indications for transplantation were reported in all studies, but were in general limited. Exclusion criteria was only reported for two (Fiorina et al 2003; Thompson et al 2011; Warnock et al 2008). Islet isolation, transplantation and subsequent immunosuppression regimens were generally well reported. Transplantation procedures were performed under local anesthesia and fluoroscopic (Fiorina et al 2003; Gerber et al 2008; Thompson et al 2011; Warnock et al 2008) or ultrasound (Frank et al 2004; Maffi et al 2011) guidance for percutaneous cannulation of the portal vein. Immunosuppression regimes varied slightly between the islet and pancreas transplantation groups in at least one study (Gerber et al 2008); this could impact outcome comparison.

In the studies that compared islet and pancreas transplantation, patients were allocated to treatment groups based on patient choice or clinical indications, and those considered high risk for intra-operative complications or with cardiovascular disease were preferentially assigned to islet transplantation rather than whole pancreas transplantation (Gerber et al 2008; Maffi et al 2011). The donor pancreases used in the Frank et al (2004) study for islet transplantation were unsuitable for whole pancreas transplantation. This may also have been the case in other studies but was not reported. The case-control study conducted by Toso et al (2007) that compared islet transplantation with medical management did not appear to match controls to islet recipients for hypoglycemia unawareness. These baseline differences may reduce the validity of conclusions drawn from comparisons as the outcomes achieved by these patients may be confounded by the presence of other comorbidities. The authors of one included study argued that due to the substantial differences between the procedures of whole pancreas and islet transplantation, a randomized design would not be ethically justifiable (Gerber et al 2008).

While baseline characteristics of age and duration of T1DM for the comparative groups were reported across the six studies, comparative statistics were presented in three. One of the three studies reported significantly older patients at the time of islet transplantation (Gerber et al 2008) and two studies reported significant differences in the duration of diabetes (Gerber et al 2008; Toso et al 2007). As the comparative study conducted by Toso et al (2007) aimed to determine the effect of islet transplantation on quality of life and fear of hypoglycemia in particular, significantly shorter duration of disease may have confounded the fear of hypoglycemia at baseline. The authors of the study concede that this may have partially influenced the conclusions drawn.

Gerber et al (2008) and Fiorina et al (2003) limited their studies to patients with kidney transplants, while Maffi et al (2011) examined only patients without kidney transplants. Frank et al (2004), however, pooled results of islet patients with and without kidney transplants. This limitation may affect our ability to draw comparisons regarding the benefits of islet transplantation in patients with kidney transplantations, compared to islet transplantation alone.

Safety and efficacy

Safety

Mortality

Whole pancreas versus allogeneic islet transplantation

Mortality was reported in the three studies that compared islet transplantation with whole pancreas transplantation. In the study by Maffi et al (2011), one PTA patient (1/33; 3%) died a week after transplantectomy for acute rejection due to bleeding through an aortic-enteric fistula. Gerber et al (2008) reported that one patient in the SIK group (1/13; 8%) died one year after transplantation due to unrelated cerebral ischemia. In the study by Frank et al (2004), one whole-organ pancreas recipient died of unknown causes after SPK transplantation (1/30; 3.3%). No deaths were observed after transplantation in the islet group (0/13; 0%). There was no significant difference between the islet and whole pancreas transplant groups for mortality in this study by Frank et al (2004); the studies by Maffi et al (2011) and Gerber et al (2008) did not report significance for this outcome.

Medical management or whole pancreas transplantation versus allogeneic islet transplantation

Fiorina et al (2003) compared patient survival after islet transplantation versus whole pancreas transplantation or medical management. Patient survival was similar between the IAK and SPK groups, and was significantly higher than that of patients on the waiting list receiving medical management and dialysis ($p<0.05$). IAK and SPK groups also appeared to possibly have higher survival than the KTA patients, but this was not statistically significant. The cardiovascular death rate for the IAK group (18%) was similar to that of the KTA group (19%) and the MM group (16%); these rates appeared higher than the SPK group (8%), although statistical significance was not provided. When the IAK group was divided between successful (IAK-s) and unsuccessful (IAK-u) transplants, the cardiovascular death rate observed in the IAK-s group was similar to that in the SPK group, five and eight percent, respectively. The IAK-s group had better survival at one, four and seven years (100%, 100% and 90% respectively) compared with the IAK-u group (84%, 75% and 45% respectively) ($p=0.02$).

Medical management versus allogeneic islet transplantation

The studies that compared islet transplantation with medical management, by Thompson et al (2011) and Toso et al (2007), did not report mortality.

Complications

Whole pancreas versus allogeneic islet transplantation

The included studies that compared islet to pancreas transplantation reported other complications which are summarized in Table 5. The need for blood transfusion was significantly higher in patients who underwent pancreas transplantation in the Frank et al (2004) and Maffi et al (2011) studies ($p\leq0.025$ and $p<0.001$, respectively). Gerber et al (2008) and Maffi et al (2011) additionally reported significantly higher need for relaparotomy in pancreas recipients ($p=0.04$ and $p<0.001$, respectively). Immunosuppression-related mouth ulcers were the only significant complication observed in the islet transplantation group (Frank et al 2003, $p<0.001$).

Table 5: Complications of whole pancreas compared to islet transplantation

	Whole pancreas	Islet transplantation	p-value
Frank et al (2004)[a]			
Post-transplant surgery	7/30 (23%)	1/13 (7.7%)	NS
Transfusion	13/30 (43%)	1/13 (7.7%)	≤0.025
Abscess drainage	3/30 (10%)	0/13 (0%)	NS
Rejection	3/30 (10%)	N/A	N/A
CMV infection	3/30 (10%)	0/13 (0%)	NS
Mouth ulceration	0/30 (0%)	10/13 (77%)	<0.001
Hepatic stenosis	N/A	3/13 (23%)	N/A
Gerber et al (2008)[b]			
Pancreas or islet complications	12/25 (48%)	2/13 (15%)	NS
Kidney complications	5/25 (20%)	3/13 (23%)	NS
(Re)laparotomy due to pancreas or islet transplant	10/25 (40%)	0/13 (0%)	0.04
Revision due to kidney transplant	2/25 (8%)	2/13 (15%)	NS
Maffi et al (2011)[c]			
RBC transfusion	14/33 (42%)	2/33 (6%)	<0.001
Relaparotomy	18/33 (55%)	0/33 (0%)	<0.001
Transplanectomy	12/33 (36%)	N/A	
Thrombosis	13/33 (39%)	3/33 (9%)	
Bleeding that required intervention	5/33 (15%)	2/33 (6%)	
Acute rejection	9/33 (24%)	N/A	
Chronic rejection	1/33 (3%)	N/A	
CMV reactivation	21/33 (64%)	2/33 (6%)	<0.001
Other infections	5/33 (15%)	2/33 (6%)	
Worsening kidney function	4/33 (12%)	5/33 (15%)	
Thrombotic TP	1/33 (3%)	0/33 (0%)	
Toxic hepatitis	0/33 (0%)	1/33 (3%)	
TAC-ind optic neuritis	1/33 (3%)	0/33 (0%)	

CMV: cytomegalovirus; N/A: not applicable; NS: not significant (p>0.05); RBC: red blood cell; TAC: tacrolimus; TP: thrombocytopenic purpura.
[a] Frank et al (2004) included patients who underwent kidney transplantation simultaneous to pancreas transplant, or prior to pancreas or islet transplantation. Islet transplantation alone was additionally performed. While complications were separated according to transplantation type, p-values were combined.
[b] Gerber et al (2008) included patients who underwent simultaneous surgery for kidney transplantation.
[c] Maffi et al (2011) included patients who received only pancreas or islet transplantations.

Medical management versus allogeneic islet transplantation

Complications of islet transplantation were reported in Thompson et al (2011) and are presented in Table 6.

Table 6: Complications from islet transplantation (Thompson et al 2011)

Reason immunosuppression was stopped	Islet transplantation
Primary graft failure after first infusion[a]	2/32 (6%)
Persistent fatigue from immunosuppression drugs	2/32 (6%)
Developed malignancy[b]	2/32 (6%)
Severe CMV infection	1/32 (3%)
Lost to follow-up	2/32 (6%)

CMV: cytomegalovirus.
[a] One withdrew from the study.
[b] One skin and one breast.

Efficacy

Graft function

Graft function may be assessed by a number of means including the number of transplants required, proportion of patients who achieve insulin independence or level of insulin use required after transplantation, C-peptide levels as a proxy of insulin production, average plasma glucose levels measured by glycated hemoglobin (HbA1c) and number of hypoglycemic episodes after transplantation.

Number of islet infusions required per patient

The number of islet infusions required per patient in each of the included studies is reported in Table 7. Where reported, most islet recipients received multiple infusions.

Table 7: Number of islet infusions required

Study	Number of patients	Number of infusions required, per patient						Mean number of infusions per patient
		1	2	3	4	5	Total	
Whole pancreas versus allogeneic islet transplantation								
Frank et al (2004)	13	NR	NR	NR	NR	NR	23	1.8[a]
Gerber et al (2008)	13	7	1	2	2	1	28	2.2
Maffi et al (2011)	33	9	16	8	0	0	65	2.0
Medical management or whole pancreas transplantation versus allogeneic islet transplantation								
Fiorina et al (2003)	37	NR	NR	NR	NR	NR	NR	NR
Medical management versus allogeneic islet transplantation								
Thompson et al (2011)	32	3	12	10	7	0	85	2.6
Toso et al (2007)	99	NR	NR	NR	NR	NR	NR[b]	NR

NR: not reported.
[a] Average number of total islet equivalents (IEQ) infused per patient was 15,475 IEQ/kg.
[b] Multiple infusions were suggested.

Insulin independence and level of insulin use

The proportion of patients in each of the included studies that achieved and, where reported, maintained insulin independence is reported in Fiorina et al (2003) did not report the number of patients that achieved insulin independence. Notably, some adverse events following islet or pancreas transplantation affected the ability for patients to achieve and maintain insulin dependence. These adverse events include vascular thrombosis, infection, rejection and events related to immunosuppression. Table notes provided below indicate the nature of the adverse events which precluded patients from achieving or maintaining insulin dependence.

Table 8: Proportion of patients that achieved insulin independence

Study	Islet transplantation				Pancreas transplantation		
	Follow-up (mean)	Achieved	Maintained	Partial only	Follow-up (mean)	Achieved	Maintained
Whole pancreas versus allogeneic islet transplantation							
Frank et al (2004)	522 days	11/13[a] (85%)	5/13[b] (38%)	3/13 (23%)	421 days	25/30[c] (83%)	25/30 (83%)
Gerber et al (2008)	38 months	5/13 (38%)	2/13 (15%)	NR	42 months	24/25 (96%)	24/25 (96%)
Maffi et al (2011)	NR	19/33[d] (58%)	NR	9/33 (27%)	NR	25/33[e] (76%)	NR
Medical management versus allogeneic islet transplantation							
Thompson et al (2011)	66 months	22/32[f] (69%)	12/32 (38%)	11/32 (34%)	N/A	N/A	N/A
Toso et al (2007)	36 months	69/89 (78%)	28/46[g] (61%)	NR	N/A	N/A	N/A

N/A: not applicable; NR: not reported.
[a] 1/13 developed anti-insulin autoantibodies and did not achieve insulin independence; 1/13 did not complete treatment due to a traumatic foot injury that required discontinuation of immunosuppression.
[b] Of those who achieved insulin independence, 1 experienced painful immunosuppression-related mouth ulcers, which led to graft failure due to immunosuppression discontinuation and 2 completely lost graft function.
[c] 5/30 patients experienced adverse events that led to graft failure, including 1 patient who died, 2 due to vascular thrombosis, 1 due to a persistent perigraft infection and 1 due to rejection at 24 months.
[d] 5/33 patients experienced early graft failure.
[e] 7/33 experienced surgical complications and required removal of the graft; 1/33 experienced portal venous thrombosis and achieved only partial function of the pancreas.
[f] 9/32 patients withdrew immunosuppression, including 2 patients who experienced graft failure, 1 experienced persistence fatigue, 2 developed malignancies, 1 developed cytomegalovirus infection and 2 were lost to follow-up.
[g] Of those who achieved insulin independence, 48/69 maintained insulin independence at 6 months; 48/65 at 12 months; and 33/53 at 24 months.

Whole pancreas versus allogeneic islet transplantation

Of the 11 patients who achieved insulin independence in the study by Frank et al (2004), three maintained partial function of the graft only and required small doses (4–9 units) of insulin. It was reported that this was reduced compared to pre-transplant doses; however, average pre-transplant doses and significance were not reported. Gerber (2008) reported that the average dose required after islet transplantation was nearly half of that before transplantation (decreased from 0.56 ± 0.17 units/kg/day to 0.29 ± 0.21 units/kg/day); measures of significance were not reported. Insulin requirement for the pancreas recipients was not reported in either study. Maffi et al (2011) did not report exogenous insulin use.

Medical management or whole pancreas transplantation versus allogeneic islet transplantation

Fiorina et al (2003) compared the insulin requirement of the successful islet recipients and the unsuccessful islet recipients. Insulin requirement was significantly lower in the successful group at one and four years post-transplantation ($p<0.01$ and $p=0.01$, respectively); at seven years after transplantation, the difference was no longer significant.

Medical management versus allogeneic islet transplantation

The studies that compared islet transplantation to medical management did not report level of insulin use.

C-peptide secretion

C-peptide is a byproduct of the production of insulin and can be used as a proxy measure for insulin production. Results within the range of 0.5 to 2.0 nanograms per milliliter (ng/mL) are considered normal, with lower results an indication of little to no insulin production (U.S. National Library of Medicine MedlinePlus [MedlinePlus] 2012b).

Whole pancreas versus allogeneic islet transplantation

Of the studies that compared islet transplantation to pancreas transplantation, both Frank et al (2004) and Gerber et al (2008) observed significantly higher C-peptide secretion in those who received whole organs (Table 9). The values reported in Gerber et al (2008) were the result of a C-peptide and insulin mixed meal stimulation test.

Table 9: Comparison of C-peptide secretion in whole pancreas versus islet transplantation

Study	Islet transplantation	Pancreas transplantation	p-value
Frank et al (2004)[a]	1.7 ng/mL	3.9 ng/mL	p<0.001
Gerber et al (2008)	3.018 ± 2.207 ng/mL[c]	7.523 ± 2.288 ng/mL[c,d]	p≤0.05
Maffi et al (2011)	NR	NR	NR

NR: not reported.
[a] Data presented as mean during the first 600 days after transplantation.
[b] C-peptide values were achieved through a C-peptide and insulin mixed meal stimulation test
[c] Data presented as mean ± standard deviation, converted from nmol/L into ng/mL.
[d] At the end of follow-up (mean 42 months for SPK group, 38 months for SIK), a representative sample (n=5) of SPK patients underwent a mixed-meal tolerance test to measure C-secretion, as it is not routinely measured after SPK.

Medical management or whole pancreas transplantation versus allogeneic islet transplantation

Fiorina et al (2003) reported C-peptide levels across patient groups (Table 10, Figure 2), and observed that patients with successful islet transplantations and whole pancreas transplantations had within normal C-peptide levels at one, four and seven years post-transplantation compared to

patients with unsuccessful islet transplantation or patients who received medical management for T1DM (kidney transplantation alone recipients and those on the waiting list for a transplantation). Measures of significance were not reported.

Table 10: Comparison of C-peptide secretion (Fiorina et al 2003)

	IAK-s (n=24)	IAK-u (n=13)	SPK (n=162)	KTA (n=42)[a]	MM (n=196)[b]
Baseline (ng/mL)	0.15 ± 0.02	0.15 ± 0.03	0.11 ± 0.02	0.13 ± 0.03	0.11 ± 0.01
1 year (ng/mL)	1.64 ± 0.16	0.39 ± 0.25	1.62 ± 0.15	0.21± 0.09	N/A
4 year (ng/mL)	1.09 ± 0.16	0.14 ± 0.02	1.43 ± 0.21	0.17 ±0.05	N/A
7 year (ng/mL)	1.39 ± 0.49	0.10 ± 0.01	1.39 ± 0.22	0.15± 0.04	N/A

Data presented as mean ± standard error.
IAK-s: successful islet after kidney transplantation; IAK-u: unsuccessful islet after kidney transplantation; SPK: simultaneous pancreas and kidney transplantation; KTA: kidney transplantation alone; MM: patients on the waiting list for a kidney and pancreas transplant receiving medical management; N/A: not assessed.
[a] T1DM patients who received kidney transplant alone.
[b] Uremic T1DM patients on hemodialysis on the waiting list for a kidney-pancreas transplant.

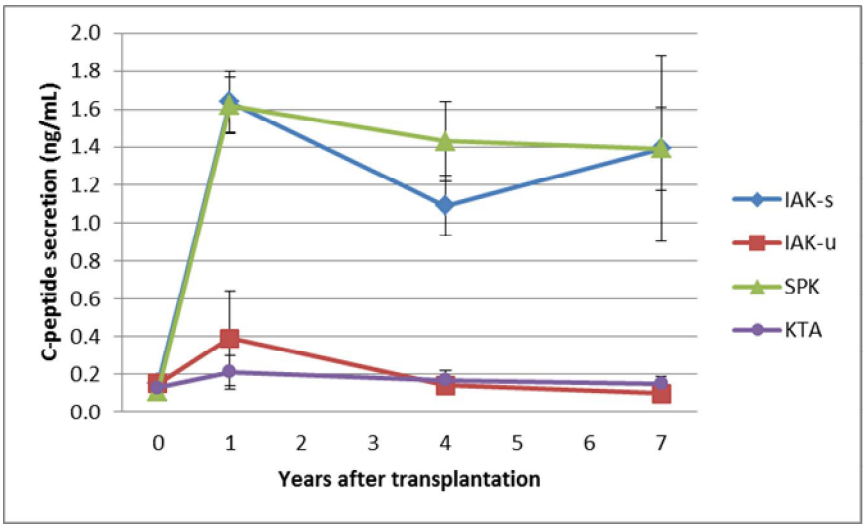

Figure 2: C-peptide secretion across transplantation groups, constructed from Fiorina et al (2003)

IAK-s: successful islet after kidney transplantation; IAK-u: unsuccessful islet after kidney transplantation; SPK: simultaneous pancreas and kidney transplantation; KTA: kidney transplantation alone.

Medical management versus allogeneic islet transplantation

Thompson et al (2011) reported that all patients who received islet transplantation that stayed on immunosuppression had detectable C-peptide secretion. All patients in the medical management group were C-peptide negative.

HbA1c levels

Glycated hemoglobin (HbA1c) is a measure of average plasma glucose levels, with levels less than 5.6 percent considered normal. Results of 5.7 to 6.4 percent are an indication of pre-diabetes, with levels exceeding 6.5 percent in patients with diabetes (MedlinePlus 2012a).

Whole pancreas versus allogeneic islet transplantation

Whole organ recipients in the Frank et al (2004) study achieved normal average plasma glucose levels which were significantly lower than those achieved by islet recipients during the first year post-transplantation (5% compared to 6.3%, p≤0.001). Maffi et al (2011) did not report HbA1c levels.

Gerber et al (2008) compared HbA1c levels between SIK and SPK groups, and SIK and KTA groups (Table 11, Figure 3). After islet or pancreas transplantation, HbA1c levels were observed to decrease and were significantly lower than in patients who received kidney transplantation alone. One year after transplantation, no significant difference was observed in the HbA1c levels of the islet and kidney transplantation groups; at two and three years, however, pancreas transplantation had significantly improved HbA1c levels (p=0.01 and p=0.03, respectively). By the fourth year, this difference was no longer significant.

Table 11: HbA1c levels (Gerber et al 2008)

	SIK (n=13)	SPK (n=25)	p-value (SIK v SPK)	KTA (n=11)	p-value (SIK v KTA)
Baseline	8.1 ± 1.5	8.7 ± 1.9	0.34	8.1 ± 1.1	0.71
1 year (%)	6.2 ± 0.8	6.0 ± 0.6	0.32	9.0 ± 1.9	0.0009
2 year (%)	6.3 ± 0.7	5.7 ± 0.5	0.01	8.5 ± 1.5	0.005
3 year (%)	6.7 ± 1.0	5.8 ± 0.4	0.03	9.1 ± 1.3	0.007
4 year (%)	6.2 ± 0.5	5.5 ± 0.6	0.11	8.8 ± 2.1	0.03

Data presented as mean ± standard deviation.
SIK: simultaneous islet and kidney transplantation; SPK: simultaneous pancreas and kidney transplantation; KTA: kidney transplantation alone.

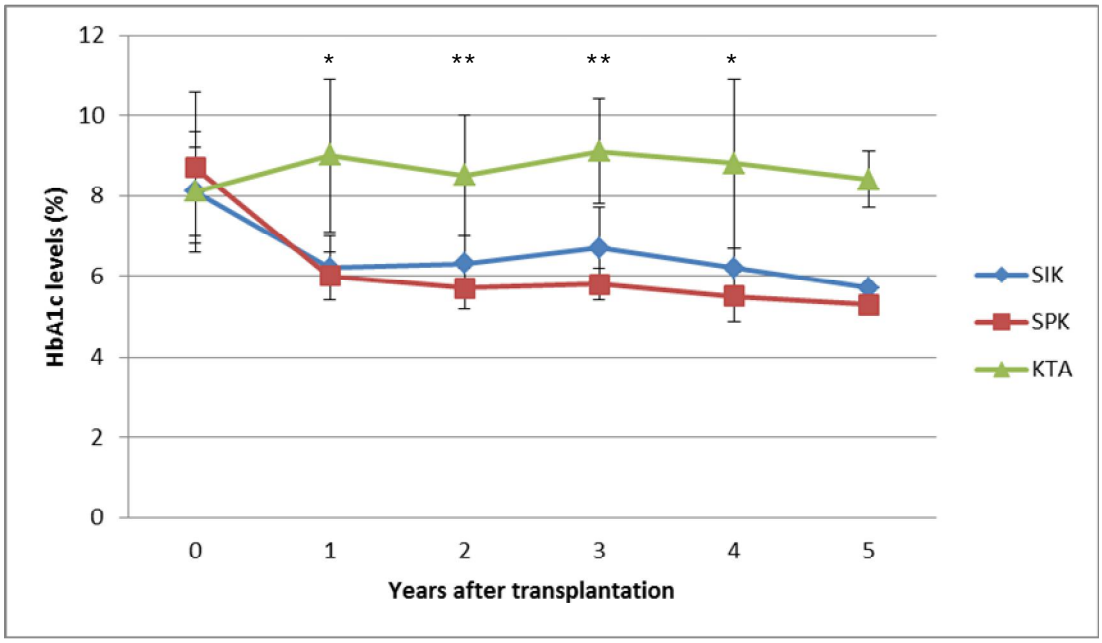

Figure 3: HbA1c levels across transplantation groups, constructed from Gerber et al (2008).

*p<0.05 SIK compared to KTA; **p<0.05 SIK compared to SPK or KTA.
SIK: simultaneous islet and kidney transplantation; SPK: simultaneous pancreas and kidney transplantation; KTA: kidney transplantation alone.

Medical management or whole pancreas transplantation versus allogeneic islet transplantation

Fiorina et al (2003) observed a decrease in HbA1c levels after successful islet transplantation (Table 12, Figure 4); however, the improvement did not appear to match that observed in patients in the pancreas transplantation group, who at baseline had higher HbA1c levels. Islet recipients appeared to have lower levels at baseline, which may affect comparisons drawn between the IAK groups and the KTA and MM groups. Measures of significance were not reported.

Table 12: HbA1C levels (Fiorina et al 2003)

Fiorina	IAK-s (n=24)	IAK-u (n=13)	SPK (n=162)	KTA (n=42)	MM (n=196)
Baseline	8.3 ± 0.3	7.7 ± 0.6	11.2 ± 1.7	11.1 ± 2.3	11.5 ± 2.2
1 year (%)	7.35 ± 0.29	7.96 ± 0.35	5.8 ± 0.8	8.9± 1.3	N/A
4 year (%)	7.33 ± 0.51	8.08 ± 0.43	6.0 ± 0.1	8.6± 0.4	N/A
7 year (%)	7.38 ± 0.35	8.26 ± 0.61	6.2 ± 0.2	8.7± 0.5	N/A

Data presented as mean ± standard error.
IAK-s: successful islet after kidney transplantation; IAK-u: unsuccessful islet after kidney transplantation; SPK: simultaneous pancreas and kidney transplantation; KTA: kidney transplantation alone; MM: patients on the waiting list for a kidney and pancreas transplant receiving medical management; N/A: not assessed.

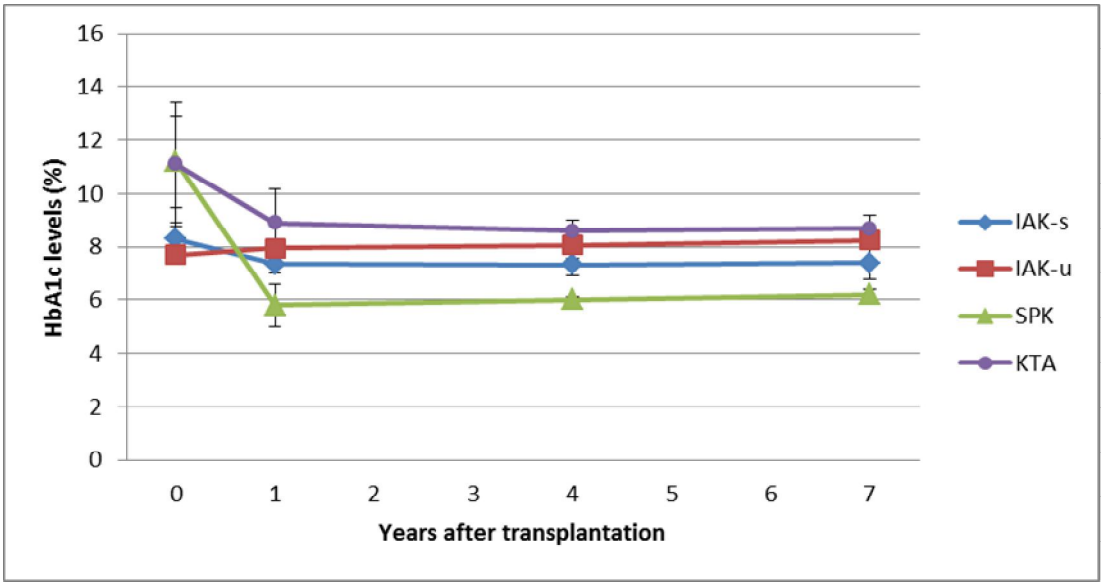

Figure 4: HbA1c levels across transplantation groups, constructed from Fiorina et al (2003)

IAK-s: successful islet after kidney transplantation; IAK-u: unsuccessful islet after kidney transplantation; SPK: simultaneous pancreas and kidney transplantation; KTA: kidney transplantation alone.

Medical management versus allogeneic islet transplantation

Compared to medical management, islet recipients were observed to have a significantly lower level of HbA1c (6.7% ± 0.2% compared to 7.8% ± 0.3%, p<0.001).

Length of hospitalization

Whole pancreas versus allogeneic islet transplantation

Length of hospitalization was reported in the three studies that compared islet transplantation with whole pancreas transplantation. Maffi et al (2011) and Frank et al (2004) both observed significantly shorter length of hospitalization in patients who underwent islet transplantation (each p<0.001). Maffi et al (2011) observed an average length of stay for patients who received islet transplant alone of 16 days (interquartile range 9-19), and for patients who received pancreas alone transplantation, 19 days (interquartile range 16-24). One islet recipient in the Frank et al (2004) study required care in an intensive care unit (ICU), compared to the routine ICU admission of pancreas recipients; significantly shorter total length of stay in ICU and all follow up hospitalizations were observed in the islet transplantation group (p<0.0001). For kidney-islet, kidney-pancreas or kidney-alone transplantation, Gerber et al (2008) reported average length of

hospitalization of 18 ± 7, 22 ± 12 and 15 ± 9 days respectively (p-values NR). Patients who underwent subsequent islet infusions were discharged within one day.

Length of hospitalization was not reported in the studies that compared islet transplantation to medical management or whole pancreas transplantation, or to medical management alone.

Other system measures

Whole pancreas versus allogeneic islet transplantation

Renal function, blood pressure and cholesterol levels were reported in Gerber et al (2008). SIK recipients did not significantly differ to SPK recipients or KTA recipients in renal function, as measured by the glomerular filtration rate (GFR); in general, blood pressure, triacylglycerol, total cholesterol and high density lipoprotein and low density lipoprotein cholesterol levels did not differ between the SPK and SIK patients. Slightly higher triacylglycerol was observed in the SIK group at 24 (p=0.03) and 36 months (p=0.03), with slightly lower diastolic blood pressure observed at 12 months (p=0.04).

Medical management or whole pancreas transplantation versus allogeneic islet transplantation

Endothelial cell lesions and hemostatic parameters were reported by Fiorina et al (2003). Scores of endothelial cell injury were significantly better in the SPK, IAK (successful only) and KTA transplant groups when compared to the IAK unsuccessful group and the MM group (p<0.05). When compared to the MM group, amelioration of pro-thrombotic markers (F_{1+2} and XDP) and the natural anticoagulant activity (protein C antigen and ATIII) were evident in the IAK group (p-values not reported).

Medical management versus allogeneic islet transplantation

Renal function, blood pressure, retinopathy and neuropathy were reported in Thompson et al (2011). GFR was observed to decline at a significantly more rapid rate in patients managed medically compared to after transplantation (p<0.0001); systolic blood pressure was also significantly lower after transplantation (p<0.001), with no differences observed in diastolic pressures. Retinopathy was significantly more likely to progress during medical management than after transplantation, with no progression observed post-transplant, compared to 10 in the managed group (p<0.01). No significant difference was observed between groups in neuropathy assessment.

Quality of life

Medical management versus allogeneic islet transplantation

Health-related quality of life (HRQL) was reported in one study that compared islet transplantation to medical management (Toso et al 2007) (
Table 13). One month after islet transplantation, the HRQL score of islet recipients significantly decreased compared to baseline (p<0.05), and was significantly poorer than the control group (p<0.01). After three months, this effect lost significance.

Toso et al (2007) additionally reported on fear of hypoglycemia (
Table 13). Prior to transplantation, islet recipients had significantly higher fear of hypoglycemia compared with the control group (p≤0.01). After the first islet infusion, fear of hypoglycemia significantly decreased (p≤0.01) and was not significantly different to the control group (p>0.05).

Between one month and 24 months, fear of hypoglycemia was significantly lower than in the control group (p<0.05), with lowest levels observed at six, 12 and 24 months. At 36 months, however, fear increased and was significantly higher than at six, 12 and 24 months (p<0.05). One year after islet transplantation, patients who were insulin independent (n=43 not reported) experienced less fear of hypoglycemia than those who required insulin (p<0.001)

Table 13: Quality of life in islet transplantation patients (Toso et al 2007)

Health-related quality of life score			
	Islet	**Control**	**p-value**
Pre-transplant	0.81 ± 0.12	0.83 ± 0.15	NS
1 month post-transplant[a]	0.75 ± 0.17		<0.01
3–36 months post-transplant			NS
Hypoglycemia Fear Survey score			
	Islet	**Control**	**p-value**
Pre-transplant	53.1 ± 13.8	35.8 ± 15.6	<0.000001
1st infusion[b]	40.2 ± 18.7		NS
6 months post-transplant	16.7 ± 18.8		<0.05
12 months post-transplant	16.9 ± 17.3		<0.05
24 months post-transplant	16.8 ± 17.4		<0.05
36 months post-transplant[c]	27.9 ± 21.2		NS

NS: not significant (p>0.05).
Data presented as mean ± standard deviation.
[a] Compared to pre-transplant, p < 0.05.
[b] Compared to pre-transplant, p ≤ 0.01.
[c] Compared to 6, 12 and 24 months, p < 0.05

Quality of life outcomes were not reported in the other included studies.

Cost impact

Currently, research covers the costs of all islet isolations in the US and includes up to US$35,000 pancreas procurement fees, in addition to islet processing fees of up to US$40,000. An approved BLA for islet transplantation would enable much of the routine costs associated with islet preparation and patient care to be assumed by reimbursable sources, such as Medicare and Medicaid (McCall and Shapiro 2012).

Canadian provincial governments consider islet transplantation as standard clinical care in carefully selected indications and, as such, the cost of islet processing is covered by the public healthcare system. Similarly, NICE have recently granted full funding of islet transplantation in the UK (McCall and Shapiro 2012).

Whole pancreas versus allogeneic islet transplantation

One study was identified that compared whole pancreas transplantation to islet transplantation in the US context (Frank et al 2004). Frank et al (2004) observed significantly lower costs associated with whole pancreas transplantation (both adjusted for costs associated with kidney transplantation, and unadjusted), when compared to islet transplantation ($p \leq 0.001$ and $p \leq 0.005$, respectively) (Figure 5). The increase in costs observed for islet transplantation is associated with the use of multiple organs and islet isolation, with the cost of the isolation process slightly more than the cost of the organ itself, about US$20,000 in 2001 to 2004. As islet isolation and procurement costs are incurred regardless of whether the isolated cells were transplanted, ineligible 'intent to transplant' islets posed an estimated additional cost per recipient of more than US$40,000 in 2001 to 2004 (23 processed organs for 12 patients).

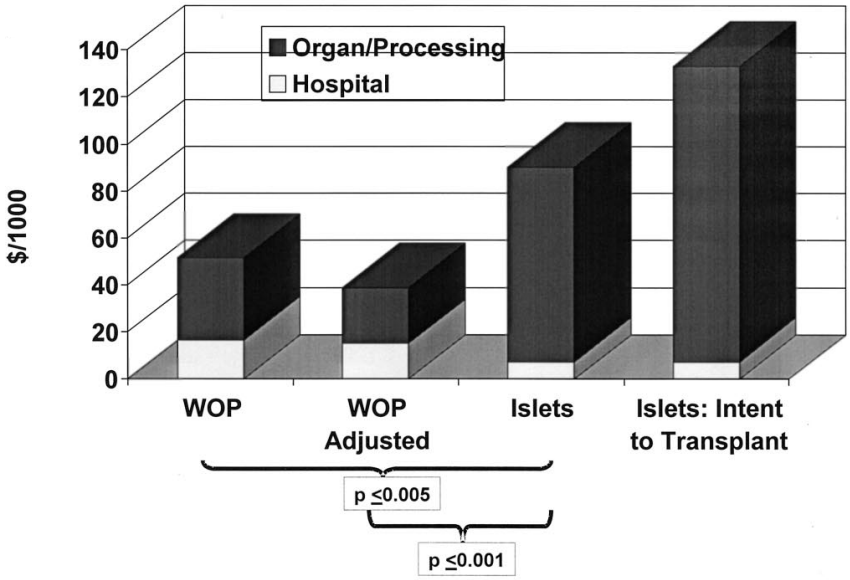

Figure 5: Direct cost of whole pancreas transplantation compared to islet transplantation per patient (Frank et al 2004)

Costs are reported in US dollars.
WOP: whole organ pancreas transplantation; WOP adjusted: costs adjusted for the cost of a kidney transplant; Islets intent to transplant: total cost of islets isolated from procured pancreases regardless of eligibility for transplantation.

Gerber et al (2008) additionally reported costs for kidney-pancreas, kidney-islet or kidney-alone transplants from a single center in Switzerland. However, due to differences in the organization of healthcare in Europe and the US, differences in the costs of organ procurement, processing and transplantation are expected and, in consequence, the costs reported in this study may not be reflective of those in the US context; these costs have not been reported.

Medical management versus allogeneic islet transplantation

An economic evaluation conducted by Beckwith et al (2012) compared costs and benefits (measured in terms of quality-adjusted life years [QALYs]) of islet transplantation to medical management by using Markov modeling and Monte Carlo simulation. The model was based on a 20-year-old patient with T1DM and hypoglycemia unawareness, and estimated complication and graft survival probabilities from literature and small clinical trials, and US based costs. Over the 20-year period, it was observed that a single islet transplantation was more effective and less costly than medical management, while transplantation was initially more costly, with break-even in cost-effectiveness achieved at nine years (transplantation US$40,200; medical management US$42,800) (Table 14, Table 15). Similar results were observed in the Monte Carlo simulation. These savings were attributed to a lower incidence of diabetes-associated complications.

Table 14: Costs and benefits of islet transplantation compared to medical management (Beckwith et al 2012)

	QALYs gained	Cumulative cost	Cost per QALY
Medical management	9.3	$663,000	$71,000
Islet transplantation			
One transplantation	10.9	$519,000	$47,800
Two transplantations	10.9	$612,500	$56,400

Costs are reported in US dollars.
QALY= quality-adjusted life year.

Table 15: Comparisons of average costs per year for treatment groups (Beckwith et al 2012)

	Medical management	Islet transplantation
First-year costs	$3,000	$103,000
Second-year costs	NR	$18,000
Twentieth-year costs	$40,000	$15,000

Costs are reported in US dollars.
NR: not reported.

The model was analyzed for sensitivity to changes in the graft survival probabilities in the first year after transplantation. No effect was observed to cost-saving and cost-effectiveness when all full functioning graft recipients were replaced by those with partial graft function; increases in the partial graft function rate and graft failure rate in the first year were cost-saving and cost-effective up to a threshold (Table 16). The sensitivity analysis did not attempt to vary the graft survival probabilities after the first year, and as graft survival may be poorer than estimated, this would likely impact the observed cost-effectiveness.

The initial model assumed that recipients with full and partial graft function were not susceptible to diabetic complications; when the diabetic complication probabilities were applied to those with partial function, the model was sensitive only to increases in the probability of end-stage renal disease. Transplantation was cost-saving up to a 1.1 percent probability of end-stage renal disease and cost-effective up to 2.4 percent, of the five percent estimated for the medical management group.

Cost-effectiveness and cost-savings were maintained when recipients received two transplantations (Table 146); however, more than two were not investigated. As the studies included for safety and efficacy report average number of infusion of two or more, three or more infusions may impact the cost-effectiveness of islet transplantation.

Table 16: Results of sensitivity analysis (Beckwith et al 2012)

	Cost-saving	Cost-effectiveness[a]
Accuracy of outcome of graft survival probabilities in the first transplant year:		
Full graft function rate[b]	0%	0%
Partial graft function rate	≤23%	≤39%
Graft failure rate	≤62%	≤78%
Diabetes-related complications in patients with partial function[c]		
End-stage renal disease[d]	<1.1%	<2.4%

[a] Cost-effective when cost per QALY gained is less than US$100,000.
[b] Full graft function replaced by partial graft function.
[c] The probabilities of amputation, blindness, cardiovascular events, neuropathy and end stage renal disease complications were applied as for the medical management group. The model was sensitive only to end-stage renal disease.
[d] Probabilities of 0-5% were applied.

Clinical practice guidelines and consensus statements

The ADA has provided a position statement for the Association's recommendations for pancreas and islet transplantation in patients with T1DM (Robertson et al 2006). The key recommendations are:

- Pancreas, pancreas-only and islet transplants require lifelong immunosuppression to prevent graft rejection and recurrence of autoimmune destruction of islet cells, with severe and frequent side effects that restrict use to patients who have serious progressive complications of diabetes or whose quality of life is unacceptable.
- Pancreas transplantation is an acceptable therapeutic alternative to insulin therapy in T1DM patients with imminent or established end-stage renal disease who have, or who plan to have, a kidney transplant. Pancreas transplantation may be performed simultaneously to, or subsequent to, a kidney transplant.
- In the absence of indications for kidney transplantation, pancreas transplantation alone should only be considered in patients who have:
    - a history of frequent, acute and severe metabolic complications (hypoglycemia, marked hyperglycemia, ketoacidosis) requiring medical attention
    - clinical and emotional problems with exogenous insulin therapy that are so severe as to be incapacitating
    - a consistent failure of insulin-based management to prevent acute complications.

  Programs that undertake pancreas transplantation alone should establish and follow guidelines to ensure that an objective multidisciplinary evaluation and assessment for transplantation is undertaken.
- While pancreatic islet transplantation may confer advantages over whole-organ transplantation, it still requires systemic immunosuppression and should only be performed within the setting of controlled research studies.

Training and education impact

The NICE interventional procedure overview of islet transplantation (2007) indicated that:

- The majority of the training and facilities required would be involved in the islet isolation process, and would require a purpose built and accredited laboratory. Islet isolation is challenging and has a significant impact on the eligibility of islet use.
- In addition, the procedure requires interventional radiologists who are competent in percutaneous portal vein cannulation, and clinicians experienced in the use of immunosuppressive medications.

NICE guidance (2008) recommends that patient selection for this procedure involves a multidisciplinary team, and that further audit and research should address the effect of the procedure on quality of life and its long-term efficacy, particularly in relation to the complications of diabetes.

Summary

Recurrent severe hypoglycemia, without the usual warning signs of sweating, tremor, tachycardia and anxiety, affects approximately 10 percent of patients with T1DM. Hypoglycemia unawareness may result in coma, seizures, and death if left untreated, and accounts for up to 10 percent of the mortality observed in T1DM patients (Jamiolkowski et al 2012; Merani and Shapiro 2006). Beta-cell replacement is indicated in these patients, and can be performed by whole pancreas transplantation or, more recently, by allogeneic islet cell transplantation.

Evidence that compares islet transplantation to either whole pancreas transplantation or medical management is limited to studies of non-randomized comparative design; six studies were identified.

Safety

Safety outcomes were reported in five of the included studies. The three studies that compared islet to whole pancreas transplantation concluded that islet transplantation was typically safer, with fewer complications observed due to the transplantation procedure. In two of the three studies, pancreas recipients were significantly more likely to require blood transfusions and relaparotomies; in the islet transplantation group, one study reported significantly higher incidence of mouth ulcers, due to immunosuppression. Patient survival was similar between islet and pancreas recipients in one study, and this was found to be significantly higher than patients receiving medical management.

The studies that compared islet transplantation to medical management alone indicated that islet transplantation is less safe, as medical management patients require no surgical procedure (which is the method for implantation in some islet cell patients), nor the need for immunosuppression, which alone is associated with adverse events. However, one outcome which was not addressed in these studies was the number of hypoglycemic events—islet transplantation would be expected to decrease the frequency and severity of these episodes, in addition to other long term diabetes-related complications.

Efficacy

Efficacy outcomes were reported in each of the included studies. When compared to whole pancreas transplantation, islet transplantation appears less effective, as typically fewer patients achieved and maintained insulin independence, produced less insulin (measured by C-peptide secretion as a proxy), and had higher glycated hemoglobin levels (HbA1c). However, length of hospitalization was typically longer for whole pancreas recipients, and was significantly so in two of the studies that compared islet transplantation to whole pancreas transplantation.

When compared to medical management, C-peptide secretion was typically higher in islet transplant recipients, with HbA1c levels typically lower. While exogenous insulin requirement was not compared in the studies that compared islet transplantation to medical management, across the six studies in general it was reported that patients required less insulin than prior to transplantation. Significant improvements in renal function, retinopathy, blood pressure and quality of life (particularly a decreased fear of hypoglycemia) were additionally observed.

Cost impact

Compared to whole pancreas transplantation, islet transplantation is more costly, due to the expense of organ processing, need for multiple donor organs for each recipient, and the costs of procurement and isolation that are incurred regardless of whether the islets are suitable for transplantation or not.

Compared to medical management, islet transplantation may be cost-saving due to a lower incidence of diabetes-associated complications. There is, however, uncertainty surrounding these conclusions due to the use of small clinical trial data to inform survival graft probabilities, and because the model did not include costs for more than two islet transplantations.

Other considerations

In addition to the high costs and uncertain benefits, islet transplantation technology is further associated with regulatory, economic and technical challenges, with future research and development of the technology restricted by the limited supply and increasing demand for donor organs. However, islet transplantation may be able to use donor organs that are unsuitable for whole pancreas transplantation.

The benefits of islet transplantation may additionally vary depending on whether a patient has received, or will also receive, a kidney transplant, as immunosuppression and the accompanied associated risks would already be indicated. In patients who receive islet transplantation alone, immunosuppression is indicated to prevent rejection of the islets alone and it is unclear if the benefits of transplantation in these cases outweigh the risks associated with the adverse events of immunosuppression. A small trial conducted by Benhamou et al (2009) drew comparisons between the quality of life of patients who underwent islet transplantation alone, compared to those who underwent islet after kidney transplantation. While the quality of life of islet alone recipients improved significantly after transplantation, and was maintained until 12 months after the procedure, no significant differences were observed in quality of life of islet after kidney recipients; however, these patients did not have a history of severe hypoglycemia and pre-transplantation quality of life may have been higher, with the effects of transplantation not as pronounced.

Previously reported systematic reviews and health technology assessments have been summarized in Table 17. Case-series studies (level IV, Appendix A) formed the bulk of the evidence used to inform these reviews. The general conclusions were that the procedure is relatively safe; however, it is associated with serious procedure- and immunosuppression-related complications. In the short term, the procedure was generally considered efficacious; however, conclusions regarding the long-term efficacy varied. The findings of this report were consistent with those previously published, and provide further contributions to the evidence by including the most recently published comparative evidence that allows some comparisons to be drawn between islet transplantation and either whole pancreas transplantation or medical management.

The small non-randomized and, in many cases, retrospective study design of the evidence base restricts the ability to draw firm conclusions regarding the safety, efficacy and cost impact of islet transplantation compared to pancreas transplantation or medical management.

Table 17: Summary of previously published systematic reviews and health technology assessments on islet transplantation

Study	Number of included studies	Comparisons	Conclusions
Speight et al (2010) Systematic review of patient reported outcomes of islet or pancreas transplantation (alone or after kidney)	12	Case series (n=11) Medical Management (n=1)	Results were mixed; benefits included improvements to fear of hypoglycemia, aspect of diabetes-specific quality of life and general health status. Negative outcomes included short-term pain related to the procedure, side-effects of immunosuppression and depressed mood associated with loss of graft function. The sensitivity of the questionnaires used in the included studies may not be sufficient enough to detect changes in domains important for quality of life post-transplantation and satisfaction with the procedure.
Guo et al (2008) Institute of Health Economics, Canada Health Technology Assessment (2008)	14	Case series (n=12) Medical Management (n=1) Whole pancreas transplantation (n=1)	Safety: Islet transplantation alone is relatively safe; however, it is associated with procedure- and immunosuppression-related complications, including: intraperitoneal bleeding, portal vein thrombosis (partial), liver abnormalities, deterioration of kidney function, and other hematological, cardiovascular, respiratory and immune system complications. Efficacy: Islet transplantation alone is effective in achieving insulin independence over a short period of time (less than 1 year), however, it appears to deteriorate over time: insulin independence at 1 year ranged from 30–60%, 14–33% at 2 years and 7.5% at 5 years. HbA1c levels were reduced after islet transplantation, even with partial graft function and episodes of hypoglycemic episodes did not occur in insulin independent patients, and were reduced in severity, due to decreased insulin requirement, in those with partial graft function. The comparative studies included in the HTA did not compare islet transplantation alone to whole pancreas transplantation or medical management in a comparable patient population; thus comparable safety and efficacy is uncertain.
NICE Interventional Procedural Overview (2007) Guidance (2008)	8	Case series (n=6) Case reports (n=2)	Safety: Serious complications may occur as a result of the procedure. Long-term immunosuppression is required and is associated with a risk of adverse events. Efficacy: The evidence presented indicates that islet transplantation shows short-term efficacy, with some evidence of long-tern efficacy. Selection criteria should take into account patient indications of hypoglycemic unawareness and/or those already on immunosuppression therapy because of renal transplantation.
Piper et al (2004) Blue Cross and Blue Shield Association (2004)	12	Case series (n=10) Case reports (n=2)	Safety: Infrequent but serious adverse events, including portal vein thrombosis and hemorrhage, have occurred, but it is not possible to estimate the frequency from the data. Efficacy: Insufficient data to conclude a high rate of technical success of islet transplantation alone.

HbA1C: glycated hemoglobin; HTA: health technology assessment.

Recommendation

The evidence base, currently limited to the non-randomized comparative studies presented in this report, conclude that islet transplantation appears to be safer than whole pancreas transplantation, as fewer complications result from the surgical procedure. However, may be less efficacious than whole pancreas transplantation in the treatment of T1DM, as fewer patients achieve and maintain the graft. Due to the less invasive nature of the procedure, islet transplantation may be indicated for patients who may be unable to tolerate whole pancreas transplantation, and may additionally be used with organs that are unsuitable for transplantation of the whole organ. Large, prospective and randomized studies would be required to draw firmer conclusions regarding the safety and efficacy of islet transplantation compared to transplantation of the whole pancreas.

Compared to medical management, islet transplantation is less safe, as it is associated with procedure- and immunosuppression-related adverse events. However, it appears to be more efficacious, with increased insulin production and improved glycemic control. These may lead to a lower incidence of diabetes-associated complications, and long-term cost-savings. Two randomized controlled trials that compare islet transplantation to medical management are currently in progress; these will enable more firm conclusions to be drawn regarding the safety and efficacy of islet transplantation compared to medical management.

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Appendix A

NHMRC Evidence Hierarchy: designations of 'levels of evidence' according to type of research question

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Aetiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilized.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6 Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 At study inception the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

8 All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C with statistical adjustment for B).

10 Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C, to determine A vs. C but where there is no statistical adjustment for B).

11 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.

Appendix B

Additional papers not included in this assessment

Article reference	N=	Conclusions	Reason for exclusion
Girman P & Saudek F. The IKEM pancreas and islet transplant program as part of healthcare for type 1 diabetes patients: Retrospective analysis of outcome from 1983 to 2010. *Review of Diabetic Studies* 2011; 8 (1)35-43.	SPK n=390 PTA n=34 ITA n=15 SIK n=5 SIL n=3	Islet transplantation is currently provided in selected indications; however, the technology may be applied to broader indications with improvements to isolation techniques and methods of transplantation.	Did not draw comparisons between treatment groups
Rickels MR, Schutta MH, Mueller R, Kapoor S, Markmann JF, Naji A & Teff KL. Glycemic thresholds for activation of counterregulatory hormone and symptom responses in islet transplant recipients. *J Clin Endocrinol Metab* 2007; 92(3): 873-879.	MM n=6 IT n=7 Non-diabetic controls n=8	Islet transplantation appears to restore normal glycemic thresholds for the activation of counter-regulatory hormone and symptom responses.	Did not report outcomes of interest
Paty BW, Senior PA, Lakey JR, Shapiro AM & Ryan EA. Assessment of glycemic control after islet transplantation using the continuous glucose monitor in insulin-independent versus insulin-requiring type 1 diabetes subjects. *Diabetes Technol Ther* 2006; 8(2): 165-173.	MM n=8 IT n=8 Non-diabetic controls n=8	Successful islet transplantation (measured by positive C-peptide secretion) provides stable blood glucose control and leads to a reduction in hypoglycemia when exogenous insulin is required.	Did not report outcomes of interest

IT: islet transplantation; ITA: islet transplantation alone; MM: medical management; PTA: pancreas transplantation alone; SIK: simultaneous islet and kidney transplantation; SIL: simultaneous islet and liver transplantation; SPK: simultaneous pancreas and kidney transplant.

Studies excluded from this assessment

Del Carro U, Fiorina P, Amadio S, De Toni Franceschini L, Petrelli A, Menini S, Martinelli Boneschi F, Ferrari S, Pugliese G, Maffi P, Comi G & Secchi A. 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.	Meier JJ, Hong-McAtee I, Galasso R, Veldhuis JD, Moran A, Hering BJ & Butler PC. Intrahepatic transplanted islets in humans secrete insulin in a coordinate pulsatile manner directly into the liver. *Diabetes* 2006; 55(8): 2324-2332.
Fiorina P, Venturini M, Folli F, Losio C, Maffi P, Placidi C, La Rosa S, Orsenigo E, Socci C, Capella C, Del Maschio A & Secchi A. Natural history of kidney graft survival, hypertrophy, and vascular function in end-stage renal disease type 1 diabetic kidney-transplanted patients: beneficial impact of pancreas and successful islet cotransplantation. *Diabetes Care* 2005; 28(6): 1303-1310.	Fiorina P, Gremizzi C, Maffi P, Caldara R, Tavano D, Monti L, Socci C, Folli F, Fazio F, Astorri E, Del Maschio A & Secchi A. Islet transplantation is associated with an improvement of cardiovascular function in type 1 diabetic kidney transplant patients. *Diabetes Care* 2005; 28(6): 1358-1365.
Paty BW, Ryan EA, Shapiro AM, Lakey JR & Robertson RP. Intrahepatic islet transplantation in type 1 diabetic patients does not restore hypoglycemic hormonal counterregulation or symptom recognition after insulin independence. *Diabetes* 2002; 51(12): 3428-3434.	