Islet transplantation in type 1 diabetes

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A clinical review in the *BMJ* in 2001 anticipated that by 2010 transplantation of islets of Langerhans would be the treatment of choice for most patients with type 1 diabetes.[1] Currently, islet transplantation is an option for a specific group of patients with type 1 diabetes only—those with severe glycaemic lability, recurrent hypoglycaemia, and hypoglycaemia unawareness. Patients with type 1 diabetes—who must deal with daily subcutaneous insulin injections, regular finger pricks for glucose measurements, and worries about hypoglycaemic episodes and long term complications of diabetes, hope for a cure for their disease and may ask their doctors about islet transplantation. Therefore, doctors who treat such patients should understand the potential benefits of islet transplantation as well as the hurdles that need to be overcome before it is widely used (box 1).

Why islet transplantation?

Type 1 diabetes is caused by the autoimmune destruction of insulin producing β cells in the pancreatic islets of Langerhans. A well defined worldwide population based survey showed that the incidence of childhood onset type 1 diabetes is rising rapidly, with an overall annual increase of 3.4% between 1995 and 1999.[2] A multicentre prospective registration study from Europe predicted that the number of prevalent cases of type 1 diabetes in children below the age of 15 will increase by 81% from 18 500 in 2005 to 33 500 in 2020 in the United Kingdom.[w1] For patients with type 1 diabetes, exogenous insulin administration to control blood glucose is a lifesaving treatment, but it also has a negative impact on personal and social functioning, not least because of the daily risk of hypoglycaemic episodes. In addition, normoglycaemia cannot be achieved by exogenous insulin and secondary complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease occur despite good glycaemic control.[3 4] Consequently, patients with type 1 diabetes face living with the long term debilitating consequences of their disease.

Pancreatic islets constitute only 1-2% of the pancreas. They consist of clusters of mainly hormone producing cells (fig 1), with insulin producing β cells being the most abundant cell type.[5] Replacement of β cells is the only treatment capable of normalising glycaemia without the risk of hypoglycaemia because β cells respond to changes in glucose concentrations by subtly adjusting insulin secretion to maintain glucose homoeostasis.

Whole pancreas transplantation, a form of β cell replacement that has been performed since 1966, is a major surgical procedure with considerable peri-transplant complications and post-transplant morbidity related to the transplantation of superfluous exocrine pancreatic tissue. Islet transplantation, however, is minimally invasive and has low morbidity

SOURCES AND SELECTION CRITERIA

We searched PubMed, Embase, Web of Science, Cochrane, CINAHL, Academic Search Premier, and ScienceDirect using the keyword "islet transplantation". We limited our search to the English language and to human studies. We found no randomised controlled trials, and most publications lacked an appropriate control group that was intensively managed by insulin using modern treatment regimens. Data were mainly derived from case series, follow-up studies, crossover studies, and small trials. We also consulted published reviews and expert knowledge if considered necessary.

Box 1 | What general practitioners need to know

- Most patients with type 1 diabetes do not fit the criteria for islet transplantation
- It is not a treatment option for patients with type 2 diabetes, who usually have insulin resistance and considerable remaining islet function
- Patients who have undergone successful islet transplantation usually have greatly improved hypoglycaemia awareness and experience fewer hypoglycaemic episodes
- Although insulin independence can be achieved, most patients will ultimately have to resume insulin treatment, but the frequency of hypoglycaemic episodes remains reduced
- Islet transplantation can improve glycaemic control and reduce risk of progression of vascular complications
- The clinical problems related to long term use of immunosuppressive agents include drug interactions, infections, and an increased risk of certain cancers

SUMMARY POINTS

- Islet of Langerhans transplantation is used in a select group of patients with type 1 diabetes with severe glycaemic lability, recurrent hypoglycaemia, and hypoglycaemia unawareness
- The procedure is minimally invasive, with few procedure related complications
- Two to three islet infusions are usually needed to achieve insulin independence
- Most patients need insulin by five years post-transplantation owing to declining graft function; beneficial effects on the frequency of hypoglycaemic episodes and hypoglycaemia awareness remain
- Most long term complications are related to systemic immunosuppression
- The risk-benefit ratio of islet transplantation should be carefully weighed by the treating physician and the potential recipient, who should be given adequate information

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Mabel Chew discusses diabetes

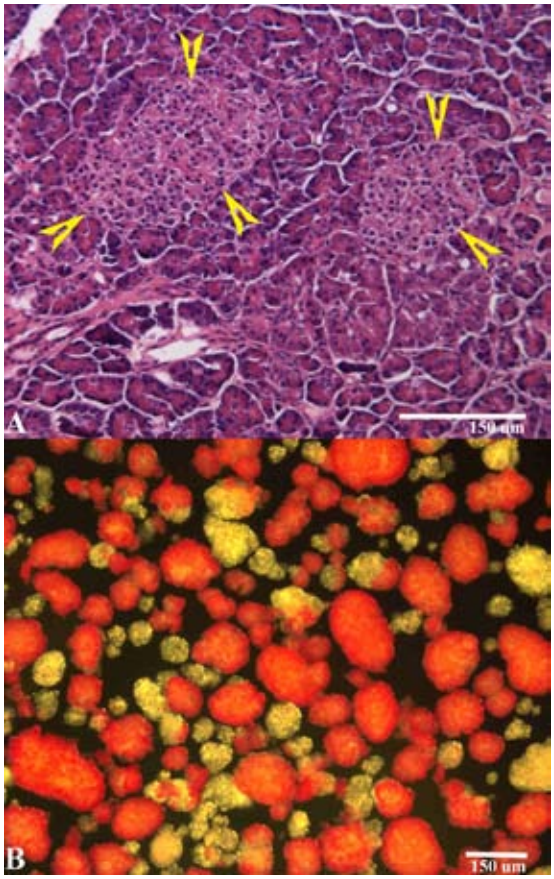

Fig 1 | (A) Histological section showing two islets (yellow arrows) in the pancreas. (B) Isolated islets stain red with dithizone; non-islet (exocrine) tissue is yellow. Image B courtesy of Marten Engelse, Human Islet Isolation Facility, Leiden University Medical Centre, Netherlands

because the islets are infused percutaneously via a catheter into the hepatic portal vein. Figures 2 and 3 illustrate the complex processes of islet isolation and transplantation.

Who is eligible?

Islet transplantation has not become a mainstream treatment for type 1 diabetes largely because of a shortage of (high quality) donor organs for islet isolation, the high costs of isolation procedures and maintenance of a specialised human islet isolation laboratory, and the need for lifelong use of immunosuppressive agents. Islet transplantation is therefore usually reserved for a highly selected group of patients with severe glycaemic lability, recurrent hypoglycaemia, and a reduced ability to sense symptoms of hypoglycaemia (reduced hypoglycaemia awareness). A cross sectional Danish-British multicentre survey found that patients with type 1 diabetes have an average of 1.3 severe hypoglycaemic episodes per patient year.[w2] However, the distribution was highly distorted, with about 5% of patients accounting for 54% of all reported episodes. Because islet transplantation improves recipients' hypoglycaemia awareness and reduces the frequency of hypoglycaemic episodes in the long term, this subgroup of patients would probably benefit most from the procedure. Islet transplantation is not a treatment option for type 2 diabetes, which is caused mainly by insulin resistance, with patients usually having considerable remaining islet function.

Most patients who undergo islet transplantation participate in clinical research studies with varying inclusion criteria. Inadequate glycaemic control with recurrent hypoglycaemia is the entry criterion most often used. However, because microvascular and perhaps macrovascular complications have stabilised in some recipients of islet transplantation, studies that focus on microvascular complications and inadequate glycaemic control rather than hypoglycaemia related problems have begun. A retrospective cohort study found that islet transplantation may also prolong the survival of a previous kidney graft.[8] For these patients, who already receive immunosuppressive agents, the clinical decision to perform islet transplantation is influenced by a different risk-benefit ratio. In the UK, islet transplantation is now funded by the NHS and is particularly indicated for patients with reduced hypoglycaemia awareness or those taking immunosuppressive drugs because of a previous kidney transplant.

How do we define success of islet transplantation?

Observations from long term studies triggered a debate about how to define the "success" of islet transplantation. Historically, the primary goal of islet transplantation has been the ability of donor islets to maintain normal glucose control and removal of the need for exogenous insulin. "Insulin independence" is a comprehensible

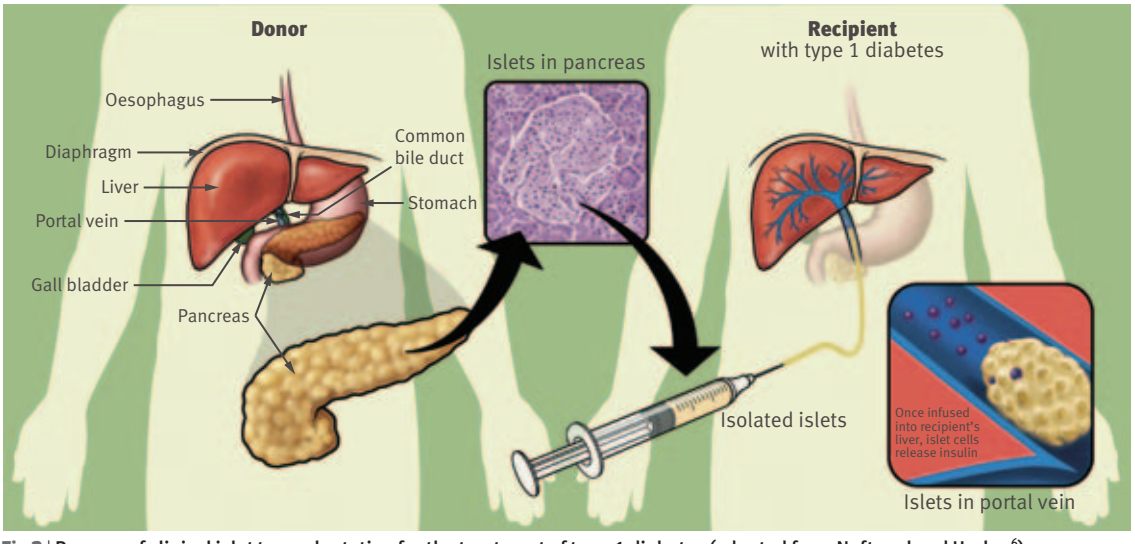

Fig 2 | Process of clinical islet transplantation for the treatment of type 1 diabetes (adapted from Naftanel and Harlan[6])

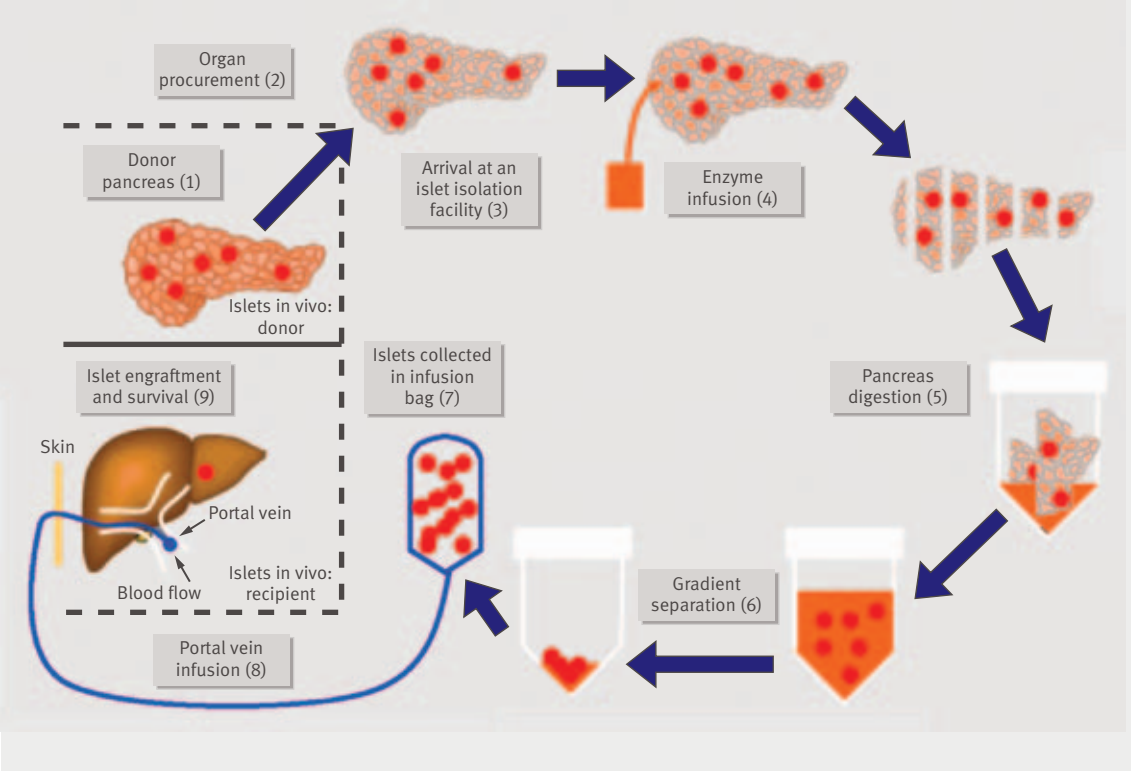

Fig 3 | The islet isolation and transplantation procedure. Islet isolation from a donor pancreas is laborious, time consuming, and costly. A donor pancreas (1) is allocated to a potential recipient on the waiting list, procured (2), and transported to an islet isolation facility (3), which adheres to good manufacturing practice guidelines (box 2). At the facility, enzyme is infused into the pancreatic duct (4) and the islets are separated from the exocrine pancreatic tissue by combined enzymatic and mechanic digestion (5), then purified by density gradient centrifugation (6). Reported numbers of isolated islets vary greatly; an estimated 300 000 to 600 000 islet equivalents (mathematical conversion of varying islet sizes to equal a standardised islet of 150 µm in diameter) can be isolated from one pancreas.[7] The actual number depends on the number of islets in the donor pancreas and the islet yield after isolation. Most centres culture the islets in incubators for several hours to several days to perform safety and viability tests and prepare the recipients. Shortly before transplantation the islets are collected in an infusion bag (7). Transplantation involves the infusion of pancreatic islets into the hepatic portal vein (8). Access to the portal vein is usually achieved by ultrasound guided percutaneous catheterisation under local anaesthesia. The islets are infused over 10-30 minutes and embolise the small branches of the portal vein. Patients usually stay in hospital for several days. The islets will engraft in the recipient liver (9) and begin to function

clinical outcome parameter for success, but success can also be measured in terms of frequency of hypoglycaemic episodes and positive effects on vascular complications or quality of life.[9] Researchers found that islet transplantation often could not achieve long term insulin independence. Patients with this "partial graft function" have persistent insulin secretion from β cells but require additional oral or subcutaneous antihyperglycaemic agents, such as insulin. A retrospective cohort study found that the hypoglycaemia score (measure of severity of hypoglycaemia) of 31 islet transplant recipients was significantly reduced from 5.29 (standard deviation 1.51) before transplantation to 1.35 (1.92) at an average 47 months after transplantation, indicating a substantial benefit even with partial graft failure and subsequent loss of insulin independence.[w3]

Box 2 | Good manufacturing practice

Good manufacturing practice is part of a quality system for the manufacturing and testing of foods, diagnostics, active drug ingredients, drug products, and medical devices. Islets of Langerhans, as a drug and biological product, are included in this quality system. In Europe, fewer than 15 islet isolation facilities currently generate islets for transplantation. Good manufacturing practice guidelines and enforcement are subject to country or continent specific legislation (see websites below).
World Health Organization (www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/)
European Union (http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/index_en.htm)
United States (www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/CurrentGoodManufacturingPracticesCGMPs/default.htm)
Canada (www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/index-eng.php)
Australia (www.tga.gov.au/docs/html/gmpcodau.htm)

Partial graft function has been shown to be associated with reduced frequency and severity of hypoglycaemic episodes and increased quality of life.[9] Today, most clinicians regard an absence of severe hypoglycaemic episodes and return of hypoglycaemia awareness as indicators of successful islet transplantation.

What results have clinical islet transplantation studies shown?

There are currently about 1000 recipients of islet transplantations worldwide. No randomised controlled trials have evaluated the effectiveness of the intervention. Small observational studies have been heterogeneous in their design. We review the best evidence from relatively large studies performed in established centres. Most studies report on patients with type 1 diabetes who had glycaemic lability, recurrent hypoglycaemia, and hypoglycaemia unawareness despite optimal self management. We focus on outcome parameters in terms of insulin independence and effects on vascular complications, quality of life, and patient survival.

Insulin independence

In 2000 a landmark case series reported on seven patients one year after islet transplantation. The seven recipients had remained insulin independent for an average of 11 months. The results of this small study were enthusiastically received.[1 10] It also became clear, however, that most patients needed two to three donor islet infusions to achieve insulin independence and that insulin independence was rarely sustained. Follow-up of a larger cohort of 65 patients reported in 2005 showed that insulin independence was present in about 69% at one year, 37% at two years, and 7.5% at five years. However, C peptide—a measure of insulin secretion (for every molecule of insulin,

Box 3 | Factors that contribute to islet loss before, during, and after transplantation

Factors affecting islet yield and quality
- Donor characteristics
- Organ procurement
- Preservation and transportation
- Isolation technique
- Culture conditions

Factors contributing to loss of transplanted cell mass during and after transplantation
- Immediate blood mediated inflammatory reaction
- Recurrence of autoimmunity
- Toxicity of immunosuppressive drugs
- Allorejection
- Glucotoxicity
- Hepatic steatosis

one molecule of C peptide is released from β cells)—was detected in 82% of subjects, indicating persistent but insufficient islet graft function at the end of this study.[11] More recently, in a cohort of 14 patients, about 64% were insulin independent and 83% had detectable C peptide at two years of follow-up.[12] The multicentre voluntary Collaborative Islet Transplant Registry (CITR) reported on 412 allograft recipients recruited from 1999 to 2008 with three year follow-up data for 257 islet transplant recipients.[w4] At three years, about 27% of recipients were insulin independent, C peptide was detected in about 57%, and 16% of the patient data were missing.[w4] Thus, long term partial graft function seems to continue and be expressed clinically by more stable glucose control and lower insulin requirements. Indicators of declining islet graft function in patients who have resumed insulin administration are worsening of glycaemic control, higher insulin demand, and a reduction in C peptide concentrations. Recent trials using a single islet infusion and new immunosuppressive protocols showed promising results at one year.[w5 w6] After one islet infusion all five patients treated with a belatacept based immunosuppressive regimen were insulin independent at one year.[w5]

Vascular complications

Islet transplantation is associated with improvement or stabilisation in microvascular complications (neuropathy, retinopathy, and nephropathy) and cardiovascular outcome parameters.[8 13 14] An important clinical question, however, is whether it reduces microvascular complications more effectively than optimal glycaemic control achieved by subcutaneous insulin administration. Because no randomised controlled trials have been performed, we report the findings of one study of 42 patients that compared the effect of islet transplantation versus intensive medical treatment on microvascular complications using a one way crossover design.[14] This study found that islet transplantation improved glycated haemoglobin (6.6 (0.7) *v* 7.5 (0.9)), halted progression of retinopathy (0/51 *v* 10/82 eyes), and stabilised glomerular filtration rate compared with intensive medical treatment. In a prospective study of 44 patients with type 1 diabetes and previous kidney transplantation, islet transplantation performed in 24 patients improved kidney graft survival at six years compared with kidney transplantation alone (86% *v* 42% kidney graft survival, respectively).[8] Improved cardiovascular function after islet transplantation was shown in the same patient group.[13]

Quality of life

Several groups have studied the effect of islet transplantation on health related quality of life.[w7 w8] Recipients of islet transplants have indicated that stable glucose control and absence of hypoglycaemic episodes are the most beneficial outcomes of the procedure, providing a feeling of reliability and improved independence.[w9]

Patient survival

Whole pancreas transplantation has been shown to improve patient survival.[w10] Because of the small number (about 1000) of patients who have undergone islet transplantation worldwide, the short length of follow-up, and the small size of individual studies, it is not yet known whether islet transplantation improves survival.

What affects outcomes?

Box 3 and fig 4 list some of the factors that can lead to the loss of islets of Langerhans before, during, and after transplantation.

Pretransplantation and peritransplantation factors

Although glucose concentrations immediately normalise after successful whole pancreas transplantation, glucose lowering after islet transplantation is delayed. This is probably because an insufficient number of functional β cells are transplanted. A single islet infusion—the islets of one donor—is often insufficient to establish normoglycaemia. Donor characteristics, the procurement of the donor pancreas, pancreas preservation during transportation, the islet isolation procedure used, and culture conditions have important effects on the number and quality of transplantable islets.[w11] A substantial loss of islets is also thought to occur during transplantation,[w12] mainly because direct contact of islets with blood components in the hepatic portal system triggers an immediate blood mediated inflammatory reaction.[w13] Thus, often an inadequate or marginally adequate islet mass reaches the liver tissue. Several measures can help avoid

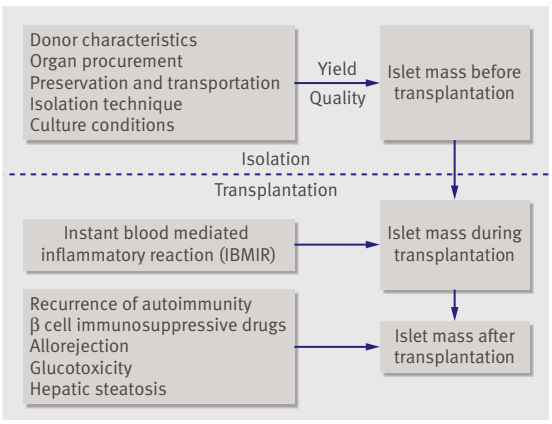

Fig 4 | Islet loss before, during, and after transplantation

this loss of functional islet mass, such as administration of heparin during and after transplantation[w14] and perioperative delivery of anti-inflammatory agents.[w15] Still, many experts believe that the best way to improve the outcome of islet transplantation would be to prevent inflammatory reactions during and immediately after islet transplantation.

Post-transplantation factors

After infusion into the portal vein, the islets travel to the liver. Here they need to adjust to their new environment and also face adverse conditions. The islets are immediately exposed to drugs and nutrients, such as glucose, which are present in higher concentrations in the portal system than in the peripheral circulation, and which can negatively affect islet function. One of the obvious potential problems is acute rejection, for which immunosuppressive drugs are given. Unfortunately, some immunosuppressive drugs, such as calcineurin inhibitors and steroids, interfere with β cell function.[w16] Measures that can help to give the islets a favourable start include using immunosuppressive drugs that have little effect on glucose metabolism and strict glycaemic control to avoid glucotoxicity.[w14] In addition, alternative implantation sites are being sought to avoid triggering the immediate blood mediated inflammatory reaction and the toxic drug levels found in the liver, and at the same time optimise vascularisation of the transplanted tissue.[15] Recently, islets have also been transplanted in human forearm muscle.[w17] The omental pouch, bone marrow, and implants consisting of islets within a biomaterial structure (scaffolds). are other potential transplantation sites.[15] Islet revascularisation occurs within several weeks, but the intra-islet vascular network is less developed in islets transplanted into the liver than in eutopic pancreatic islets.[w18] Thus, if not rejected early, the islet graft may not reach maximal efficacy with respect to glucose metabolism until one to three months after transplantation.

After one to three months islet efficacy becomes apparent, but on average only half of patients remain insulin independent at 15 months.[9] Chronic allograft rejection is a potential cause of long term graft failure.[16] Autoimmunity may also recur because islet recipients with positive T cell responses to autoantigens are more likely to lose full graft function.[w19] Furthermore, the long term toxic effects of immunosuppressive drugs on β cells are probably of considerable importance.[w16]

In patients who remain insulin independent after islet transplantation, a substantial portion of β cell mass may already have been destroyed before glucose concentrations start to rise. The absence of methods to monitor β cell mass, or alloimmune and autoimmune reactivity against β cells, render the intrahepatic grafted islets a "black box." Whereas in whole organ transplantation, biopsies provide information on potential problems such as rejection, ischaemia, and immunosuppressive toxicity, it is difficult to biopsy the islets dispersed throughout the liver. Liver biopsies have been performed to evaluate transplanted islets by light microscopy.[w18] However, this is an invasive procedure with low islet sampling rates and lack of reference values, which has limited value in clinical practice. Consequently, when islet function decreases and glucose concentrations rise over time there is little basis for intervention strategies other than re-evaluating the need for immunosuppressive drugs that negatively affect glucose metabolism and the use of glucose lowering agents. Therefore, current research is focused on increasing the functional β cell mass before, during, and after transplantation and on improving the functional assessment of grafted islets.[w20]

What are the potential complications of islet transplantation?

Complications can occur early (procedure related) or late (usually related to the use of immunosuppressives). Reports of early procedure related complications have come from different centres with a variety of expertise that have performed varying numbers of transplants. We try to give an indication of how often complications arise, how to monitor them, and how to try to prevent them.

Short term procedure related complications

Islet transplantation is a minimally invasive procedure compared with whole pancreas transplantation. Few detrimental procedure related complications exist. Hepatic bleeding during transhepatic portal vein catheterisation occurs in about 12% of infusions,[11] but this has become less common with the use of fibrin sealant, Gelfoam pledgets, or coils to seal the catheter tract on withdrawal of the catheter.[17] Hepatic bleeding into the peritoneal cavity usually resolves spontaneously. Only rarely is surgery

ADDITIONAL EDUCATIONAL RESOURCES

Additional resources for healthcare professionals

Fiorina P, Shapiro AM, Ricordi C, Secchi A. The clinical impact of islet transplantation. *Am J Transplant* 2008;8:1990-7

Bretzel R, Jahr H, Eckhard M, Martin I, Winter D, Brendel M. Islet cell transplantation today. *Langenbecks Arch Surg* 2007;392:239-53

Low G, Hussein N, Owen RJT, Toso C, Patel VH, Bhargava R, et al. Role of imaging in clinical islet transplantation. *Radiographics* 2010;30:353-66

Collaborative Islet Transplant Registry (www.citregistry.org/)—Map of affiliated transplant centres and regular updates on all recipients registered

Lecture by L Fernandez of the University of Wisconsin on islet of Langerhans transplantation. http://videos.med.wisc.edu/videoInfo.php?videoid=1112

Animation on islet cell isolation. www.youtube.com/watch?v=aMNKu-ZVUIs

European Association for the Study of Diabetes. Stem cells to cure diabetes: where do we stand? http://webcast.easd.org/Halban/index.htm

Additional resources for patients

Diabetes UK (www.diabetes.org.uk/Research/Islet_cell_transplantation/)—Comprehensive information on the islet transplantation procedure and eligibility criteria

National Institutes of Health (http://diabetes.niddk.nih.gov/dm/pubs/pancreaticislet/)—More detailed information with links to USA based clinical trials

Juvenile Diabetes Research Foundation (www.jdrf.org.au/living-with-type-1-diabetes/what-is-type-1-diabetes)—Website on what type 1 diabetes is and how you can help further research in this area

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- Preventing exacerbations in chronic obstructive pulmonary disease (*BMJ* 2011;342:c7207)
- Diagnosis and management of hereditary haemochromatosis (*BMJ* 2011;342:c7251)
- Diagnosis and management of soft tissue sarcoma (*BMJ* 2010;341:c7170)

needed and no detrimental effect on graft survival has been reported. The infusion of foreign cell material into the portal system inevitably poses a risk for portal vein thrombosis. In an experienced centre this complication occurred in less than 4% of islet infusions.[11] Low dose heparin, given prophylactically during and after transplantation, limits the risk of portal vein thrombosis and carries an acceptable increased risk of bleeding. The liver parenchyma surrounding the new islets is temporarily damaged, but this is entirely reversible probably because of the excellent regenerative capacity of the liver. Resolution of the damage can be monitored by measuring liver enzyme concentrations after transplantation.

Long term complications

Similar to other transplants, long term complications are mostly related to the side effects of systemic immunosuppressive agents. Systemic immunosuppression increases the risk of infections and cancers, particularly virus related skin cancers and certain lymphoproliferative disorders. The most widely used agents in organ transplantation are calcineurin inhibitors. Unfortunately, these agents also have a nephrotoxic effect, which increases the risk of worsening renal function, especially in patients with diabetic nephropathy. The risk of complications can be reduced and their early management ensured by monitoring drug concentrations to prevent overdosing, using measures to prevent and recognise the development of infections, having a low threshold for starting antibiotics and antivirals in transplant recipients, and regularly checking for dermatological complications.

Organ transplantation can lead to the formation of anti-HLA antibodies. Recipients of islet transplants are usually exposed to a wide range of HLA antigens from multiple donors because over time they usually receive several islet infusions matched for ABO blood group only.[18] Although antibodies to donor derived HLA antigens are detected in only a minority of islet transplant recipients taking immunosuppressive drugs, patients taken off these drugs, either because of transplant failure or immunosuppressive related toxicity, show an increase in these antibodies.[18] This is important in patients who develop end stage diabetic nephropathy and require kidney transplantation because the presence of anti-HLA antibodies limits the chance of finding an acceptable donor kidney. Currently, we have no way to prevent the development of such antibodies.

What should I tell my patient who asks about this procedure?

Islet transplantation has been shown to be beneficial for a specific group of patients with type 1 diabetes who have severe glycaemic lability, recurrent hypoglycaemia, and hypoglycaemic unawareness, although lifelong use of immunosuppressive drugs is necessary. The lack of randomised control trials prevents a thorough comparison between this procedure and best medical practice (intensive insulin treatment) or pancreas transplantation. This lack of evidence has led to scepticism about the clinical value of this procedure among some diabetologists.[19] Currently the initial goal of long term insulin independence is achieved by only a small proportion of patients—an important message to communicate to potential recipients. However, the select group of patients treated with islet transplantation has shown improved glycaemic control, reduced frequency of hypoglycaemic episodes, and reduced rate of progression of vascular complications. Researchers now need to identify factors that will lead to better graft survival and function.

ONGOING RESEARCH AND UNANSWERED QUESTIONS

- How can the islet yield be improved to decrease the number of donors needed for one successful transplant?[20]
- Identifying the best islet implantation site and technique that will result in an optimally functioning graft[15]
- How can biomaterials be used to create alternative transplantation sites?
- Which in vitro tests can best predict in vivo functioning of transplanted islets?[21]
- What alternative cell sources (such as embryonic stem cells or tissue specific progenitor cells) can be used to overcome the shortage of donor organs?[22]
- What immunosuppressive strategies are less toxic to β cells?
- Can tolerance be induced by cellular immunotherapy, thereby making immunosuppressants obsolete?[23]
- What are the key factors in long term islet allograft failure?
- How can islet mass be visualised and monitored?[24]
- How can long term islet function be improved?

Conclusion

Although progression in the islet transplantation field is not as rapid as was envisaged,[1] the pitfalls and difficulties of this procedure are now clearly identified, and advances in islet isolation, transplantation, and patient management are likely to improve the clinical outcome of islet transplantation in years to come.

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CORRECTIONS AND CLARIFICATIONS

User charges require objective analysis

In the figure in this letter by Michael A Soljak (*BMJ* 2010;341:c5303, print publication 2 October 2010, p 687), the label on the left hand y axis and the key should refer to the number of consultations [not consultants, as we stated].

Non-endoscopic screening for Barrett's oesophagus

In the second paragraph of this editorial by Peter A Bampton (*BMJ* 2010;341:c4667, print publication 18 September 2010, pp 564-5), the author referred to four of the 10 principles of disease prevention described in 1968 and mistakenly attributed them to Watson and Junger (reference 5), rather than to Wilson and Jungner. The correct reference is: Wilson JMG, Jungner G. Principles and practice of screening for disease. *WHO Chronicle* 1968;22:473.

Giving it 10%

This features article about climate change by Nigel Hawkes (*BMJ* 2010;341:c5448, print publication 9 October 2010, pp 756-7) gives the NHS's carbon footprint as 18 million tonnes of carbon dioxide a year. The current estimate is in fact 21 million tonnes.

Minerva

We somehow omitted to acknowledge an author in the Minerva tomogram item by Oliver M B Bowes and colleagues (*BMJ* 2010;341:c4708, 4 September 2010, p 512). We should have included Osita N Okafor, senior house officer. Like his coauthors, at the time of his Minerva contribution he worked at Basildon Hospital.

Improve chest compressions to reduce deaths from cardiac arrest, new guidance says

In this news item by Susan Mayor (*BMJ* 2010;341:c5794, print publication 23 October 2010, p 853), we referred to Jasmeet Soar as "chairwoman of the Resuscitation Council and a consultant in anaesthesia and intensive care at Southmead Hospital, Bristol." In fact, Dr Soar is male and is chairman of the Resuscitation Council. Our apologies.

Income inequality, mortality, and self rated health: meta-analysis of multilevel studies

In this research article by Naoki Kondo and colleagues (*BMJ* 2009;339:b4471, print publication 21 November 2009, vol 339, pp 1178-81), the sample size of data used by Kravdal (2008) in the third row in table 1 (about the characteristics of selected cohort studies; this table is in the online version only) actually represents person years. Although Kravdal does not report the exact sample size, the study followed up on the entire Norwegian population aged between 30 and 79, which was about 2.5 million during that study period of 1980-2002, according to Statistics Norway. Therefore, the correct total sample size of our meta-analysis of cohort studies should be about 7.7 million. In the print issue, this affects the opening sentence of the results section of the abstract and the first paragraph of the results section. The authors state that this correction does not change any estimates reported in their paper and its conclusion.

Recognising and managing key transitions in end of life care

This Spotlight article on palliative care by Kirsty Boyd and Scott A Murray (*BMJ* 2010;341:c4863, print publication 25 September 2010, pp 649-52) contained an editorial error. In box 1 (about the supportive and palliative care indicators tool) we added a footnote to explain the abbreviation PaO2. We defined it as pulmonary artery oxygen content, whereas it is in fact the arterial partial pressure of oxygen.

Missing clinical trial data: setting the record straight

The authors of this editorial, Fiona Godlee and Elizabeth Loder (*BMJ* 2010;341:c5641, print publication 16 October 2010, pp787-8), acknowledge that they should not have included the reference to Cipriani et al's *Lancet* meta-analysis (reference 8) among the references to meta-analyses that contradicted the results of the Eyding et al meta-analysis in the *BMJ*.