Islet cell transplantation: current status in the UK

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Abstract
Up to a third of patients with type 1 diabetes have impaired awareness of hypoglycaemia, putting them at a six-fold higher risk of severe hypoglycaemia, requiring third-party assistance. Following the success of a Diabetes UK funded research programme, islet transplantation is centrally funded at seven UK sites.

Islet transplantation is indicated for patients with recurrent, severe, disabling hypoglycaemia despite best medical therapy. In most patients, this includes a trial of insulin pump therapy. International data suggest five-year graft survival of between 30–50%, with those patients remaining free from hypoglycaemia and insulin-independence rates of 20–25% at five years. The UK programme is focused on hypoglycaemia protection, and UK data from 24 recipients show a reduction in the frequency of severe hypoglycaemia from 23/patient per year to 0.56/patient per year.

The main alternative to islet transplantation is whole pancreas transplantation, which also has a five-year graft survival rate of 50%, but much higher insulin independence rates. However, this is associated with significantly higher surgical morbidity. Islet transplantation is very safe, the main risks being related to immunosuppression. We have a lot of experience with these drugs in solid organ transplantation. The main risk is a 4% excess risk of skin cancers, the majority of which are curable.

It is important for hypoglycaemia status to be assessed in all patients with type 1 diabetes, so that those with problematic severe hypoglycaemia can be identified. In these patients, islet transplantation can offer potential normalisation of blood glucose with complete resolution of hypoglycaemia. Copyright © 2012 John Wiley & Sons.

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Key words
type 1 diabetes; islet cell transplantation; pancreas transplantation

Introduction
Patients with type 1 diabetes are reliant on insulin therapy. Despite advances in insulin delivery and patient education, maintaining blood glucose at levels known to reduce the risk of diabetes complications is difficult for many patients.

Whole organ pancreas transplantation has been performed successfully since the late 1960s, but transplantation of the insulin-secreting islets has only recently become a successful procedure. Historically, extracting islet cells from the pancreas was difficult, and islet function tended to deteriorate rapidly after transplantation making the whole process unviable. All this changed in 2000 following the publication of a landmark paper from James Shapiro’s group in Edmonton, Canada, describing seven patients who successfully remained insulin-free for a whole year following islet cell transplantation.1 Key factors influencing success were the use of multiple transplants of fresh islets and a new steroid-free immunosuppression regimen based on sirolimus and tacrolimus – a protocol that has become known as the ‘Edmonton Protocol’.

Although these patients were unable to maintain freedom from insulin injections in the long term, the majority enjoyed long-term graft function and symptomatic benefit in terms of avoidance of severe hypoglycaemia. This eventually led to the establishment and expansion of islet transplantation in a number of centres around the world. In the UK, Diabetes UK funded 12 islet transplants as part of a research project. This was successful, with all patients achieving complete resolution of severe hypoglycaemia. On the basis of these results, the National Specialist Commissioning Group provided central funding for the service. Islet cell transplantation is now NICE-approved,2 and the UK benefits from having one of the only government-funded islet cell transplantation services in the world. A key difference between the UK programme compared to some international programmes has been a focus on protection against severe hypoglycaemia.
hypoglycaemia rather than on insulin independence.

**Who is suitable for islet cell transplantation?**

Table 1 provides a summary of those patients with type 1 diabetes who might be suitable for islet cell transplantation, and those patients who are probably not suitable.

**How common are severe hypoglycaemia and hypoglycaemia unawareness?**

Hypoglycaemia is the most common complication of insulin therapy in patients with diabetes, and in many people this is the limiting factor in attempts to achieve good glucose control. Almost all patients with type 1 diabetes will experience episodes of mild hypoglycaemia, with blood glucose readings between 2.5 and 3.5 mmol/L. These glucose levels are typically associated with symptoms such as hunger, tremor, palpitations, sweating and anxiety. At lower glucose levels, confusion, incoordination, difficulty speaking and drowsiness can occur. At these glucose levels, the majority of patients experience symptoms and are able to treat themselves with rapidly acting carbohydrate. However, about one-third of type 1 diabetes patients each year will experience an episode of ‘severe hypoglycaemia’ in which blood glucose drops to a level that affects their conscious level to the extent that they cannot treat themselves and require assistance from someone else. In those with type 1 diabetes for >15 years, the annual proportion experiencing severe hypoglycaemia is ~45%. In about 10% of these instances, they may require assistance from paramedics or require hospitalisation and some of the most severe episodes can result in seizures, neurological impairment or even death. Every year there are 6–10 deaths in young people with type 1 diabetes, attributed to the ‘dead in bed’ phenomenon, which is thought to be caused by nocturnal hypoglycaemia.

The main risk factors for severe hypoglycaemia are age, duration of diabetes, 'tight' glycaemic control (HbA1c <42 mmol/mol [6.0%]), prior severe hypoglycaemia, absence of endogenous insulin production and, very importantly, impaired awareness of hypoglycaemia which increases the risk of severe hypoglycaemia three- to six-fold. The typical symptoms of hypoglycaemia are mediated by protective responses of the sympathetic nervous system and counter-regulatory hormonal responses including glucagon, catecholamine and cortisol secretion. However, even a single episode of hypoglycaemia can attenuate these responses and, as patients accumulate more hypoglycaemic insults over the years, their awareness is often eroded. In the UK Hypoglycaemia Study, the incidence of impaired awareness of hypoglycaemia was 7% in those with short duration of type 1 diabetes, but 35% in those with diabetes duration >15 years.

**How can we assess the severity of hypoglycaemia and hypoglycaemia unawareness?**

The assessment of hypoglycaemia frequency, severity and awareness is an essential part of a consultation in patients with insulin treated diabetes. Questions should also relate to the timing of hypoglycaemia, any predisposing factors (e.g. exercise and alcohol) and the glucose levels at which symptoms occur. A helpful question that may identify those with impaired awareness of hypoglycaemia is whether other people detect the hypoglycaemia before the patient does. Many patients with hypoglycaemia unawareness fail to recognise the risk they are at, which creates difficulties in identifying and treating them.

There are a number of validated scores or questionnaires that can be useful in clinical practice to document and quantify the severity of hypoglycaemia and the degree of hypoglycaemia awareness. For example, the Clarke score is an easy-to-use patient questionnaire that asks questions about the frequency of severe hypoglycaemia, symptomatic and asymptomatic hypoglycaemia, and about the blood glucose threshold for the onset of hypoglycaemia symptoms. The Gold score is a simple 7-point visual analogue scale that can be used by patients to grade their awareness of hypoglycaemia.
responses to hypoglycaemia.10 The Low Blood Glucose Index (LBGI) is another score which combines the frequency and severity of recorded capillary glucose readings into a single index, and has been shown to predict those with high risk of severe hypoglycaemia.11

The pathway to islet cell transplantation
As mentioned before, islet cell transplantation is indicated for those patients with disabling recurrent hypoglycaemia despite best medical therapy. These can include the following.

Structured education in flexible insulin therapy. Courses such as DAFNE and BERTIE provide patients with self-management skills based on matching insulin and carbohydrate and adjusting for exercise and sickness. They have been shown almost to halve the number of patients who report severe hypoglycaemia, and restore awareness after a year in over half those who report hypoglycaemia unawareness before the course.12 Unfortunately, many regions in the UK do not have access to these courses.

Insulin pump therapy. Insulin pump therapy is approved by NICE for patients in whom attempts to achieve target HbA1c (<6.5 mmol/mol [8.5%]) have resulted in disabling hypoglycaemia.13 This includes those with heightened fear of hypoglycaemia with significant adverse impact on quality of life due to repeated and unpredictable hypoglycaemia. A recent meta-analysis has shown that insulin pump therapy was associated with a 0.4% improvement in HbA1c and a four-fold reduction in the incidence of severe hypoglycaemia.14 This reduction in severe hypoglycaemia was greatest in those with the most frequent episodes of hypoglycaemia at baseline, although there have not been many randomised controlled trials of multiple-dose insulin (MDI) injection therapy vs pump therapy and much of the pump data were collected against regimens not including analogue basal insulin.

Continuous glucose monitoring (CGM). These systems can be programmed to alarm if low glucose is detected, and some devices when linked to insulin pumps can even suspend insulin delivery for up to 2 hours if the patient fails to respond to the alarm. This can reduce the depth and duration of hypoglycaemia,15,16 and may help in the restoration of physiological responses to hypoglycaemia in those with hypoglycaemia unawareness.17

Ideally, patients would have had some education in carbohydrate counting and dose adjustment and would have had a prior trial of insulin pump therapy before being considered for islet cell transplantation. However, this is not essential, and patients are considered for islet cell transplantation if they are unsuitable for, or have strong views against, a trial of pump therapy.

Outcomes of islet cell transplantation
The Collaborative Islet Transplant Registry (CITR) collects data from a number of North American, European and Australian sites and has data on 1072 infusions in 571 patients since 1999. The latest report from 2010 shows significant improvement in rates of insulin independence and graft survival over the last decade, with insulin independence rates of 50%, 35% and 25% at one, three and five years, respectively. Graft function is defined as a C-peptide >0.3mg/ml and rates are between 50–80% at five years depending on factors such as recipient age, insulin dose at baseline and use of T-cell depletion as induction. The primary outcome for the UK programme is absence of severe hypoglycaemia and, from the CITR data, rates are 90%, 75% and 50% at one, three and five years, respectively. (Figure 1.)

Some factors such as recipient age >35 years, baseline insulin dose <0.43 units/kg and use of T-cell depletion and tumour necrosis factor-alpha (TNF-α) inhibition for

Figure 1. Proportion of patients with absence of severe hypoglycaemia. (Reproduced from the Collaborative Islet Transplant Registry [CITR] 7th Annual Report, prepared by the CITR Coordinating Center, USA)
induction can result in five-year insulin independence rates of approximately 50% that are comparable with whole-organ pancreas transplantation. Other expected outcomes are improvements in quality of life\(^{18}\) and reduced fear of hypoglycaemia.\(^{20}\) There are no randomised data to determine the effect of islet transplantation on mortality, nor on macrovascular or microvascular complications, but progression of microvascular disease appears to be slowed compared to optimised medical treatment.\(^{21}\)

**UK experience and outcomes**

To date, 54 islet transplants have been performed in 34 patients in the UK. An audit of islet transplant recipients from our seven UK centres (April 2008 to April 2011) with data from 38 transplants in 24 recipients showed primary graft function in all but one patient, and one-year graft survival in the UK is 87%, comparable to the CITR data.\(^{22}\) The frequency of severe hypoglycaemia was reduced from 66±16mmol/mol (8.2±1.5%) to 51±15mmol/mol (6.8±1.4%). Given the short duration of the UK programme, we do not yet have long-term outcome data, but it is encouraging to see that initial results are comparable to those reported internationally,\(^{16}\) and we are achieving our primary aim of protection against severe hypoglycaemia.

### Risks of islet cell transplantation

The procedure itself is generally safe, with the main risk being bleeding from the liver capsule during the

<table>
<thead>
<tr>
<th>Risks and benefits</th>
<th>Islet cell transplant</th>
<th>Pancreas transplant</th>
<th>Insulin pump</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death due to the operation or procedure</td>
<td>Less than 1 patient in 100</td>
<td>3 patients in 100</td>
<td>Close to zero</td>
</tr>
<tr>
<td>Operation to open the stomach wall</td>
<td>2 patients in 100</td>
<td>All patients</td>
<td>0</td>
</tr>
<tr>
<td>Repeat operation on the stomach</td>
<td>Close to zero</td>
<td>30 patients in 100</td>
<td>0</td>
</tr>
<tr>
<td>Serious surgical complications including colostomy</td>
<td>Close to zero</td>
<td>30 patients in 100</td>
<td>0</td>
</tr>
<tr>
<td>When treatment starts to work</td>
<td>After 3–12 weeks</td>
<td>Straight away</td>
<td>Straight away</td>
</tr>
<tr>
<td>Any infection over 6 years</td>
<td>17 patients in 100</td>
<td>17 patients in 100</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Life-threatening infection with long-term clinical effects over 6 years</td>
<td>2 patients in 100</td>
<td>2 patients in 100</td>
<td>0</td>
</tr>
<tr>
<td>Death due to infection over 6 years</td>
<td>1 patient in 300</td>
<td>1 patient in 300</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cancer, potentially life-threatening, over 6 years (except skin cancer)</td>
<td>4 patients in 100</td>
<td>4 patients in 100</td>
<td>0</td>
</tr>
<tr>
<td>Skin cancer including melanoma (often treatable) over 6 years</td>
<td>8 patients in 100</td>
<td>8 patients in 100</td>
<td>0</td>
</tr>
<tr>
<td>Freedom from insulin injections at 1 year</td>
<td>30–70 patients in 100*</td>
<td>80–90 patients in 100</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Freedom from insulin injections at 5 years</td>
<td>10–20 patients in 100**</td>
<td>50–60 patients in 100</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Major reduction in severe 'hypos' at 18 months</td>
<td>75–85 patients out of 100</td>
<td>75–85 patients out of 100</td>
<td>See below***</td>
</tr>
<tr>
<td>Reduced risk of severe 'hypos' at 5 years</td>
<td>50–70 patients in 100**</td>
<td>75 patients in 100</td>
<td></td>
</tr>
<tr>
<td>Improved HbA1c at 5 years</td>
<td>50–70 patients in 100**</td>
<td>50–70 patients in 100</td>
<td>50 patients in 100</td>
</tr>
<tr>
<td>Improved diabetes complications</td>
<td>Likely</td>
<td>Proven</td>
<td>Likely</td>
</tr>
</tbody>
</table>

*Limited information due to small numbers from UK at present (70% is achieved in Edmonton, Canada); **In Edmonton, Canada. ***No data for direct comparison, but on average ~50% reduced (some more, some less) compared to using subcutaneous insulin.


**Caution:** comparisons are provided as a guide only. No randomised controlled trials have been performed to compare these therapies, and baseline risk factors may be different and influence outcome.
procedure. The major risks are those of cancer and infection caused by long-term immunosuppression required to prevent rejection.

Experience from solid organ transplant registries suggests that use of immunosuppressive agents used in islet transplantation leads to an excess risk of cancer of ~4% over a six-year period (this excludes skin cancers which occur in ~8% over six years).23 Although the UK programme has not been in place for long enough to provide meaningful numbers of patients with malignancy, international data from CITR suggest that the risks of immunosuppression in islet transplant recipients are comparable or slightly lower than those seen in other organ transplants (Table 2). A total of 29 neoplasms, two-thirds being cutaneous squamous or basal cell carcinomas, have been reported in 27/571 islet transplant recipients. Of the 12 patients with non-skin cancers, six recovered completely, three recovered with sequelae, three did not recover – including one who died from lung cancer.18

Over a mean six-year follow-up approximately 1 in 6 islet recipients had an episode of infection related to immunosuppression, although in almost all cases this was successfully treated. Only 2/100 islet transplant recipients have had any long-term sequelae as a result of these infections, or have had to stop immunosuppression.18

Work-up and admission for islet cell transplantation

There are seven UK islet transplantation centres (Table 3) that are centrally funded to assess potential islet recipients and to perform islet cell transplantation. As mentioned before, most patients will undergo initial assessment, including screening for other causes of hypoglycaemia such as coeliac disease and adrenal insufficiency, and optimisation of their current therapy with trial of insulin pump therapy with or without continuous glucose monitoring if deemed appropriate. During this time, they will be counselled on the risks and benefits of islet transplantation and will complete further work-up, including isotope assessments of renal function

Table 3. List of centres performing islet cell transplantation in the UK

<table>
<thead>
<tr>
<th>Centre</th>
<th>Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bristol</td>
<td>Dr Richard Smith, Richard Bright Renal Unit, Southmead Hospital, Southmead Road, Westbury-on-Trym, Bristol BS10 5NB; <a href="mailto:Richard.Smith@bristol.ac.uk">Richard.Smith@bristol.ac.uk</a>; tel: 0117 3253434</td>
</tr>
<tr>
<td>Edinburgh</td>
<td>Mr John Casey, Transplant Unit, Royal infirmary of Edinburgh, 51 Little France Crescent, Old Dalkeith Road, Edinburgh EH16 4SA; <a href="mailto:jcasey@staffmail.ed.ac.uk">jcasey@staffmail.ed.ac.uk</a>; tel: 0131 242 1714</td>
</tr>
<tr>
<td>London</td>
<td>Dr Pratik Choudhary, Department of Diabetes, King’s College Hospital, Denmark Hill, London, Greater London SE5 9RS; <a href="mailto:pratik.choudhary@nhs.net">pratik.choudhary@nhs.net</a>; tel: 0203 299 1737</td>
</tr>
<tr>
<td>London</td>
<td>Dr Miranda Rosenthal, Diabetes Department, Royal Free Hospital, Pond Street, London NW3 2QS; <a href="mailto:miranda.rosenthal@nhs.net">miranda.rosenthal@nhs.net</a>; tel: 020707794 0500 x 33325</td>
</tr>
<tr>
<td>Manchester</td>
<td>Dr Martin Rutter, Manchester Diabetes Centre, 193 Hathersage Road, Manchester M13 0JE; <a href="mailto:martin.rutter@cmft.nhs.uk">martin.rutter@cmft.nhs.uk</a>; tel: 0161 276 6709</td>
</tr>
<tr>
<td>Newcastle</td>
<td>Prof James Shaw, Institute of Transplantation, Freeman Hospital, Freeman Road, High Heaton, Newcastle upon Tyne NE7 7DN; <a href="mailto:Jim.Shaw@newcastle.ac.uk">Jim.Shaw@newcastle.ac.uk</a>; tel: 0191 222 7019/8129</td>
</tr>
<tr>
<td>Oxford</td>
<td>Prof Paul Johnson, Nuffield Department of Surgical Sciences, Level 6, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU; <a href="mailto:paul.johnson@nds.ox.ac.uk">paul.johnson@nds.ox.ac.uk</a>; tel: 01865 221291</td>
</tr>
</tbody>
</table>

±myocardial blood flow, a liver ultrasound scan and extensive blood work including tissue typing. For most patients, the average time on the waiting list is ~6–9 months.

Suitable donor pancreata are sent to one of three UK islet isolation laboratories (at Oxford, King’s College Hospital, London, and in Edinburgh) where islets are extracted from the organ. The isolated islets are cultured for 12–24 hours before being transported to the local islet transplant centre. During this time, the patient is admitted to hospital for assessment and induction treatment. This can be with a combination of IL-2R antagonists such as basiliximab (original Edmonton protocol) or more recently with more aggressive T-cell depleting agents such as alemtuzumab or anti-thymocyte globulin.

Increasingly, patients also receive TNF-α antagonists such as etanercept. The islets are then infused transcatheterly into the portal vein under radiological guidance. Most patients will then receive a second transplant within three months. Maintenance immunosuppression is usually with tacrolimus and mycophenolate mofetil.

What is the main alternative to islet cell transplantation?

The main alternative to islet transplantation is whole organ pancreas transplantation. As of 2011, 35 000 pancreas transplantation operations have been reported to the International Pancreas Transplant Registry. The majority of these (93%) were performed with, or following, a kidney transplant, and only 7% were ‘pancreas transplant alone’.

In the UK, the criteria for whole pancreas transplantation are similar to those for islet cell transplantation, namely recurrent disabling and life-threatening hypoglycaemia in the context of hypoglycaemia unawareness. However, this is a much more complex procedure, and many patients are not suitable for this procedure. Contraindications include poor cardiac reserve with severe coronary artery disease or ejection fraction <50%. Relative contraindications include aortic, iliac or other peripheral vascular disease. Up to a third of patients may require re-laparotomy for surgical complications, and the mortality associated with the procedure is around 3%. One-year graft survival is lower for pancreas transplant alone (PTA) than for simultaneous kidney pancreas (SPK) transplant (85% vs 79%),23 and at five years the graft has failed in 40–50%, leaving the patients back on insulin.25,26

Pancreas transplantation does have some advantages over islet cell transplantation: it can be used in patients who have a high insulin requirement; and it can more reliably deliver insulin independence rather than just protection against hypoglycaemia, although graft survival rates at five years are becoming comparable as results from islet transplantation improve. There are some data
demonstrating stabilisation and sometimes reversal of some complications of diabetes, although similar data are now also emerging with islets. Risks due to immunosuppression are similar for pancreas or islet transplant recipients. Direct comparison of data relating to islets and PTA is problematic because there have been no randomised controlled trials comparing these therapies, and baseline patient characteristics may be different. That said, the chance of being free from severe hypoglycaemia at five years may be similar comparing these therapies.

The future of islet cell transplantation

The results of islet cell transplantation have been steadily improving in the UK and internationally. Most of this improvement has come from changes in immunosuppression and a better understanding of the management of patients after the transplant. Current research areas include research on protecting the organ during transportation to the isolation site, improving the islet yield during isolation, and work on minimising loss of islets to ‘immediate blood mediated inflammatory reaction’ immediately post-transplant. Novel immunosuppression regimens are also being trialled, as are alternative anatomical sites for the transplantation of islets. Given the scarcity of donor organs, there is also a lot of interest in xenotransplantation, but at present this is in very early stages. However, as long as islet transplantation is reliant on scarce donor organs and toxic immunosuppression, it will remain a treatment that is restricted to the few severely symptomatic patients in whom conventional therapies have failed.

Conclusion

A significant proportion of patients with type 1 diabetes have problematic hypoglycaemia, and it is important that all patients with type 1 diabetes are screened for hypoglycaemia frequency and hypoglycaemia awareness status, ensuring that we identify those who may benefit. Current data support islet transplantation as a proven therapy for those with disabling hypoglycaemia and this remains life-changing, and in many cases a potentially life-saving, treatment for these patients. All UK leads are very happy to discuss possible referral informally.

Declaration of interests

There are no conflicts of interest declared.

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