Islet cell transplantation

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A brief history of islet transplantation

Following the first administration of insulin in man 100 years ago, there has been significant progress in the development and manufacture of insulin, and technology to monitor blood glucose levels and to deliver insulin into the body, in an attempt to mimic normal physiology in people living with diabetes. Despite these therapeutic advances, there remains a significant burden for the individual in self-management of diabetes. Current research into childhood screening for T1DM before dysglycaemia develops,[1,2] and immunological strategies to protect insulin-secreting beta cells from autoimmune destruction,[3] have the potential to delay the need for exogenous insulin therapy. However, for those with established diabetes, beta cell replacement therapy brings the possibility of a life without needing insulin treatment. A synopsis of islet transplantation presented at the ABCD meeting to commemorate the centenary of the first administration of insulin into a human is provided here; for a more extensive review, readers are directed to excellent articles from colleagues in Edinburgh,[4] and in North America.[5]

The first report of allogeneic pancreatic fragment transplantation into the subcutaneous tissue of the abdominal wall of two men with T1DM described only "temporary diminution of the sugar excretion" in one of the recipients, with degeneration of the graft noted in both men, one dying three months later, the other three years later.[6] It was not until 1980, with the introduction of immunosuppression (azathioprine, cyclophosphamide, prednisolone and antilymphocyte globulin induction, with maintenance azathioprine and prednisolone), that the first successful transplantation of allogeneic pancreatic fragments into the spleen alongside renal transplantation took place in an 11-year-old girl, with eventual insulin independence.[7] The development of the glucocorticoid-free "Edmonton protocol" of immunosuppression in 2000 revolutionised islet transplantation.[8] In the original report, seven patients with T1DM and recurrent severe hypoglycaemia or uncontrolled diabetes received sirolimus (mTor inhibitor), tacrolimus (calcineurin inhibitor) and daclizumab (non-T-cell depleting anti-CD25 monoclonal antibody, which targets the T-cell IL-2 receptor) before islet preparations of >4,000 islet equivalents (IEQ)/kg recipient body weight were infused via a percutaneous transhepatic approach into the portal vein. More than 10,000 IEQ/kg recipient body weight were found to be required to reach insulin independence. Thus, a repeat procedure with another donor was often required, resulting in reduction in average blood glucose levels and glucose excursions.

Most islet transplant centres currently use modified protocols involving T-cell depleting antibody induction regimens (e.g. alemtuzumab, anti-CD52 monoclonal antibody or anti-thymocyte globulin, ATG) with etanercept (TNF-α inhibitor) for the first transplant, and basiliximab (non-T-cell depleting anti-CD25 monoclonal antibody) for second or subsequent transplants. Tacrolimus and mycophenylate mofetil (inosine-5'-monophosphate dehydrogenase inhibitor, inhibiting T and B cell proliferation) are used as maintenance immunosuppression.[9] The donor pancreas is prepared by initial perfusion of the pancreatic duct with collagenase before being mechanically and chemically digested in a Ricordi isolation chamber, followed by centrifugation. Unlike the original Edmonton protocol, the pancreas preparation is then placed in culture medium and incubated to permit quality control.[10] In the UK, the minimum release criteria are 250,000 IEQ, purity >50% and viability >70%.[11]

Islet transplantation in the UK and beyond

Between 2008 and 2009, the UK became the first country in the world to commission a national islet transplantation programme for "routine" treatment of severe hypoglycaemia. The UK Islet Transplant Consortium (UKITC) comprises three islet isolation centres (Edinburgh, Oxford and King's College Hospital, London) and seven islet transplant centres (Edinburgh, Oxford, King's, Manchester, Newcastle, Bristol and Royal Free Hospital, London). Current indications for islet transplantation are adults aged 18-65 years with T1DM and recurrent severe hypoglycaemia that has not responded to other therapies (islet transplant alone, ITA), or suboptimal control if they are being considered for simultaneous islet-kidney (SIK) transplantation, or have had a renal transplant and are currently on immunosuppressive therapy (islet after kidney, IAK).[11] Assessment for islet transplantation therefore typically includes ensuring standard care has been optimised, which may involve structured diabetes education, optimisation of blood glucose monitoring and insulin therapy, including the use of continuous glucose monitoring, insulin pump therapy and hybrid closed loop systems, and provision of psychological support.[12] If severe hypoglycaemia remains a problem despite consideration of these educational, technolog-

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ical and psychological interventions, islet transplantation may be considered if there are no contraindications (Table 1).

An example of the benefit of islet transplantation from our own centre at King's can be seen in Figure 1, in which a patient who had been living with T1DM for more than 20 years was experiencing six episodes of severe hypoglycaemia per year despite the use of sensor augment insulin pump therapy. Prior to islet transplantation, HbA_{1C} was 8.3% and sensor data showed widely variable glucose levels with frequent, asymptomatic hypoglycaemia. Six months after islet transplantation, HbA_{1C} had fallen to 6.4%, with greater time in target and no severe hypoglycaemia.

An initial report of 20 patients receiving islet transplantation (16 ITA, 4 IAK) in the UK showed that 80% of recipients maintained graft function, defined as a stimulated C-peptide >50 pmol/L, with a reduction in severe episodes of hypoglycaemia from 20 to 0.3 episodes per patient year including those with graft dysfunction, improvement in hypoglycaemia awareness and HbA_{1C} (from 8.0% to 6.2%) and a reduction in insulin dose of >60%, at 24 months.[13] A more recent report of 84 islet transplant recipients (34 receiving one infusion, 50 receiving two infusions) showed uninterrupted graft survival at 12 months in 68% of single transplant recipients and 94% of two transplant recipients.[14] Of these 70 recipients with uninterrupted graft function at 12 months, graft survival was present in 64% at six years post-transplantation. For those receiving two grafts, a shorter interval between transplantations was associated with greater insulin dose reduction at 12 months.

Table 1 Contraindications to islet transplantation.[11]

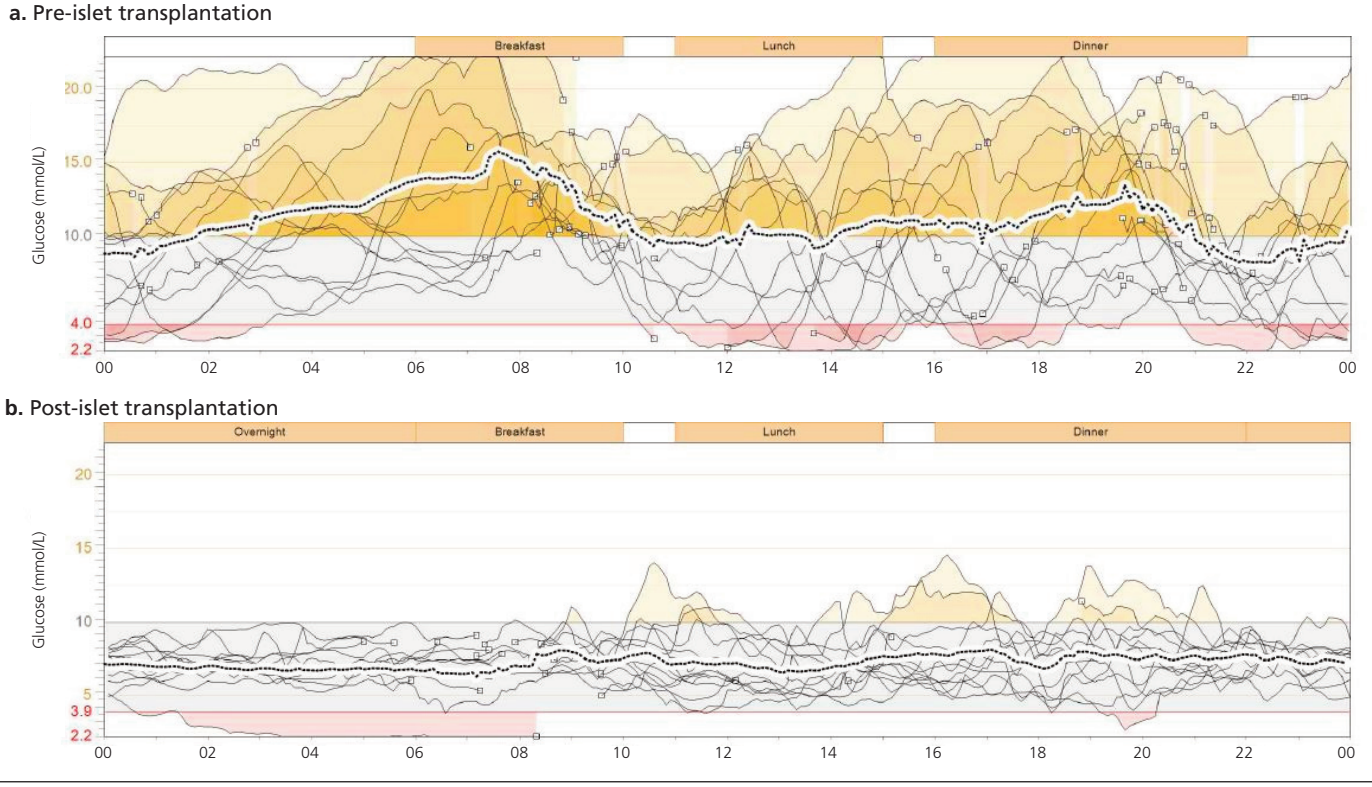
Absolute contraindications:

- Insulin requirements > 1 Unit/kg body weight/day
- Weight >85 kg
- GFR <60 mL/min/1.73m^2 (except in those being considered for SIK or IAK)
- Detectable fasting or postprandial blood C-peptide (>0.3 ng/mL) (100 pmol/L)
- Incurable malignancy
- Active sepsis
- Active peptic ulceration
- Major psychiatric history likely to result in non-concordance
- Inability to withstand immunosuppression
- Excessive cardiovascular risk

Relative contraindications:

- Substance abuse (including tobacco)
- HbA_{1C} >12% (107.7 mmol/mol)
- Body mass index (BMI) >28 kg/m^2
- Progressive, severe complications of diabetes
- Untreated coronary artery disease
- Unstable retinopathy
- Proteinuria >300 mg/day
- GFR 60-80 mL/min/1.73m^2
- Untreated hyperlipidaemia (LDL cholesterol >3.36 mmol/L)
- BP >160/100 mmHg despite maximal treatment
- Chronic infection (e.g. hepatitis B and C, Epstein-Barr virus)
- Liver changes (3x upper limit of normal enzymes, cholestasis, haemangioma)
- Calculated reaction frequency (anti-HLA antibodies) >20%
- Need for long-term oral steroid therapy

Figure 1. Continuous glucose monitoring data **a.** before and **b.** six months after islet transplantation in an individual with T1DM and severe hypoglycaemia.



The Clinical Islet Transplantation Consortium in North America has reported similar outcomes from eight centres participating in the CIT-07 single arm phase 3 clinical trial in adults with T1DM and impaired awareness of hypoglycaemia and recurrent severe episodes of hypoglycaemia.[15] Of the 48 recipients (22 receiving one infusion, 25 receiving two infusions, 1 receiving three infusions), 87.5% at year 1 and 71% at year 2 achieved the primary outcome of HbA_{1c} <7.0% and freedom from severe hypoglycaemia, with improvement in hypoglycaemia awareness. Insulin independence was achieved in 52% of recipients at 1 year and 42% at 2 years.

The Collaborative Islet Transplant Registry (CITR) currently collects data from 40 different transplantation centres in North America, Europe and Australia.[16] The latest registry report this year includes 1,108 ITA, 236 IAK, 49 SIK and 6 kidney after islet transplant recipients, with five years' post-transplantation outcome data. In the ITA recipients, approximately 50% achieved insulin independence one year post-transplant. The prevalence of insulin independence fell steadily each year to approximately 20% at five years. Factors positively associated with insulin independence were related to mass of transplanted islets (higher number of islet infusions, greater number of IEQs infused, donor weight >98 kg), recipient factors (female sex, age above 35 years, negative IA2 antibody, fewer than 43 units insulin/day and HbA_{1c} <6.5% pre-transplant) and immunosuppression (use of IL-2 receptor antagonists, TNFα inhibitor, mTor inhibitors and calcineurin inhibitors). The prevalence of graft function, defined as a C-peptide ≥0.3 ng/mL (100 pmol/L), was higher than that of insulin independence at approximately 80% at one year post-transplant, falling steadily each year to over 50% at five years. Factors associated with higher post-transplant C-peptide were similarly related to the mass of transplanted islets (greater number of islet infusions and the total number of IEQs infused), recipient factors (age 35 years or above, longer [>37 years] diabetes duration, lower diastolic blood pressure, HbA_{1c} and cholesterol levels pre-transplant, use of antihypertensive and lipid-lowering treatments pre-transplant), immunosuppression (TNFα and calcineurin inhibitors) and islets being cultured for ≥6 hours. Despite the progressive fall in insulin independence and C-peptide levels, the absence of severe hypoglycaemia remained high at around 90% during the five-year post-transplant period, with 50% of ITA recipients having both HbA_{1c} <7.0% and absence of severe hypoglycaemia. Higher fasting C-peptide levels (≥1ng/mL [330 pmol/L]) were associated with a higher likelihood of insulin independence, HbA_{1c} <7.0%, fasting blood glucose 3.3-7.8 mmol/L, absence of severe hypoglycaemia and combined HbA_{1c} <7.0% with absence of severe hypoglycaemia.

Future of islet transplantation

The UK islet transplantation programme aims to infuse a total of >10,000 IEQ/kg recipient body weight within 12 months of the first transplant. The CITR data show that the greater the mass of islets transplanted, the greater the likelihood of insulin independence and C-peptide positivity, and importantly the greater the absence of severe hypoglycaemia. The rate-limiting step in all forms of transplantation is the availability of suitable donor organs. Furthermore, good quality donor pancreases may be considered for whole organ transplantation before islet transplantation. The use of human embryonic stem cells (hESC) and induced pluripotent stem cells (iPSC) may pave a way to increase supply of islets for transplantation. Human clinical trials applying the use of hESC are currently in progress.

Vertex pharmaceuticals' phase 1/2 clinical trial is assessing the safety, tolerability and efficacy of VX-880, allogeneic stem cell-derived, fully differentiated insulin-producing islet cells. These islet cells are infused intraportally, similar to conventional islet transplantation,[17] with recipients receiving ATG at induction and tacrolimus and sirolimus maintenance immunosuppression. Data from two individuals with T1DM, impaired awareness of hypoglycaemia and recurrent severe hypoglycaemia, receiving half the target dose of VX-880, were presented in abstract form at the ADA and EASD this year.[18,19] One recipient was insulin-independent by day 241-270, with time in range increasing from 40.1% to 99% and a fall in HbA_{1c} from 8.6% to 5.2%. A second recipient had a 30% reduction in insulin by day 121-150, with time in range increasing from 35.9% to 51.9% and HbA_{1c} falling from 7.5% to 7.1%. No adverse events related to VX-880 occurred in either recipient.

ViaCyte Inc. have taken a different route in their phase 1/2 studies, placing pluripotent stem cell derived pancreatic endoderm progenitor cells in microencapsulation devices that are then implanted subcutaneously. VC-01 is a combination of these endoderm cells in immunoprotective devices such that immunosuppression is not required but transfer of nutrients and oxygen to the enclosed cells occurs. Data from a safety, tolerability and efficacy trial using subtherapeutic doses in 19 recipients with T1DM have been published in abstract form only.[20] Cell survival at explantation was demonstrated for as long as two years but was inconsistent due to foreign body response to the device, with insulin and glucagon detectable on immunohistochemical staining but no reports of insulin secretion. No evidence of immune rejection or sensitisation was found. The study was terminated due to insufficient engraftment.[21] A 26-week study to assess safety and engraftment, and efficacy by means of C-peptide response to a mixed meal, is reported to be ongoing.[22]

VC-02 utilises an encapsulation device that allows direct vascularisation of the endoderm cells, therefore requiring immunosuppression. In a safety, tolerability and efficacy study, individuals with T1DM and hypoglycaemia unawareness received up to four larger dose-finding devices (9cm x 3cm x 1mm) containing 90-120 million cells and up to 10 smaller devices (1.5 cm x 1 cm x 1 mm) containing 6-8 million cells for histological assessment, with ATG induction and tacrolimus and mycophenylate mofetil immunosuppression.[23] Improvements in HbA_{1c}, time in range and hypoglycaemia awareness were observed over the 1-year follow-up period. Total daily insulin requirements fell but insulin independence was not achieved. C-peptide increased in response to a mixed meal, with no difference in response at 26 and 52 weeks. The explanted devices had more glucagon- than insulin-staining cells, with the latter appearing to have a mature beta cell phenotype. However, two out of 15 recipients with-

Key messages

- Islet transplantation is an established treatment in the UK for adults with refractory type 1 diabetes and severe hypoglycaemia
- Whilst 50% of islet transplant recipients achieve insulin independence at 1 year, falling to 20% at five years, over 90% of recipients are free from severe hypoglycaemia.
- Research in the application of human stem cells in transplantation has the potential to address the limited supply of donor organs for islet transplantation.

drew during the first year due to complications from the immunosuppression, and five were withdrawn after nine months due to unfavourable risk-benefit assessment, based on undetectable C-peptide, histology and clinical state of diabetes. In an accompanying report of 17 recipients (six of whom were included in the previous report), six were deemed "responders" with positive C-peptide responses to a mixed meal.[24] Greater numbers of insulin-staining cells were detected in the explants of responders compared to non-responders. Insulin content and secretion per beta cell increased over time. Devices were infiltrated by host-derived fibroblasts, with graft cells comprising 40% of the total cell population in responders and 26% in non-responders.

Lastly, working with CRISPR Therapeutics, ViaCyte Inc. have announced the dosage of the first patient in a Phase 1 clinical trial of VCTX210, which comprises similar devices used in VC-02 to encapsulate gene-edited, stem cell-derived pancreatic endoderm cells that can evade the immune system.[25]

Conclusion

Advances in diabetes technology have produced hybrid closed-loop systems that demonstrate significant improvements in HbA_{1c}, time in range and hypoglycaemia. However, these systems still require a high level of user involvement, and commercially available fully closed-loop "artificial pancreases" are eagerly anticipated. Islet transplantation is an established, safe and effective NHS treatment for recurrent, severe hypoglycaemia in T1DM, offering the individual the opportunity to lead a life closer to that of someone without diabetes. Limitations of islet transplantation include the limited supply of donated islets and the low level of insulin independence at five years post-transplantation. Developments in human stem cell transplantation and encapsulation may help address these limitations, with the potential to avoid the need for immunosuppression.

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