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REVIEW

Effects of islet transplantation on microvascular and macrovascular complications in type 1 diabetes

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Abstract

Type 1 diabetes is associated with high morbidity and mortality from microvascular and macrovascular disease with considerable economic cost to society. Islet cell transplantation (ICT) is a treatment option recommended by National Institute for Health and Care Excellence (NICE) for people with debilitating hypoglycaemia due to type 1 diabetes, including those with renal failure where kidney transplantation may also be indicated. The primary aim of ICT is to improve glycaemic control, reduce severe hypoglycaemia, stabilise glycaemic variability and restore awareness of hypoglycaemia where this is compromised. Insulin independence, although not a primary aim, should also be considered a therapeutic goal. The impact ICT has on the progression of microvascular and macrovascular diabetes complications is derived from small studies and has not been examined in large clinical trials. Lifelong immunosuppression, which is necessary to avoid transplant rejection, has adverse effects on lipid metabolism, hypertension and renal function, which must also be considered. In this review, we discuss the role of ICT in type 1 diabetes management and the available evidence with respect to microvascular and macrovascular disease progression post-transplantation. We conclude that, following ICT, microvascular complications including retinopathy and neuropathy are stabilised or improved. Effects on nephropathy can be complicated by coexisting kidney transplantation and the impact of immunosuppression, the latter leading to an early decline in renal function; however, there is evidence to suggest stable renal outcomes in the long term. Short-term studies have demonstrated a positive impact of ICT on surrogate markers of macrovascular disease; however, long-term studies and trials in this area are lacking.

KEY WORDS

islet transplantation, macrovascular disease, microvascular disease, type 1 diabetes

What's new?

- Islet transplantation is a treatment option recommended by NICE for recurrent severe hypoglycaemia with impaired awareness of hypoglycaemia in Type 1 diabetes where conventional insulin therapy has been optimised.
- Microvascular complications including retinopathy, sensory neuropathy and long-term renal function (eGFR) are stabilised or improved following islet transplantation.

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- Benefits of islet transplantation on nephropathy and macrovascular complications may be hindered by the negative impact of immunosuppression; randomised controlled trials examining long term cardiovascular outcomes are awaited.

1 | INTRODUCTION

Diabetes affects an estimated 422 million adults worldwide¹ with high morbidity and mortality from microvascular and macrovascular complications. Microvascular complications include retinopathy, nephropathy and neuropathy. Diabetic retinopathy is the most common cause of blindness in people with type 1 diabetes (T1D); it has been estimated that a third of people with diabetes have signs of diabetic retinopathy and that 10% of those have signs of sight-threatening retinopathy, one of the leading causes of blindness in working-age people.² Up to 40% of people with T1D will develop diabetic nephropathy in their life time, of which 75% develop end stage renal disease within 10 years.³ Macrovascular complications include myocardial ischaemia, myocardial infarction and stroke.⁴ Data from the Diabetes Control and Complications Trial (DCCT) cohort has shown that those with T1D have a cumulative incidence of cardiovascular disease of 14% after 30 years of diabetes.⁵

Management of T1D focusses on structured education programmes with intensive insulin therapy via multiple daily injections or continuous subcutaneous infusion to achieve tight glycaemic control. The DCCT trial demonstrated that tight glycaemic control is beneficial in reducing long-term microvascular and macrovascular complications of diabetes.⁶ At 10-year follow-up, the risk of progression of diabetic retinopathy was reduced by 53%.⁷ Similar benefits were seen in relation to nephropathy outcomes with a reduction in the incidence of microalbuminuria and macroalbuminuria, 59% and 84%, respectively, and a 50% risk reduction on the development of impaired glomerular filtration rate (GFR).³ Follow-up at 30 years demonstrated a reduction in the incidence of any cardiovascular event and in major cardiovascular events, 30% and 32%, respectively, in the former intensive treatment group.⁴ However, for many, insulin doses are difficult to titrate, resulting in recurrent hypoglycaemia, impaired awareness of hypoglycaemia (IAH) which affects around 30% of people, impacting on their quality of life,⁸ and putting them at higher risk of seizures or coma with major economic impact.⁹ Islet cell transplantation (ICT) is a minimally invasive procedure that may be indicated in those with recurrent severe hypoglycaemia (SH) defined by the American Diabetes Association as severe cognitive impairment requiring external assistance for recovery,¹⁰ where treatment has been optimised. It can restore β -cell function, reduce hypoglycaemia and glycaemic lability, improve quality of life and can result in insulin independence.¹¹ Projected benefits of improved glycaemic control must be balanced

against the risks of long-term immunosuppression, including the risk of infection and the increased risk of cancer. Immunosuppressive drugs also have adverse effects on metabolism and blood pressure with cardiovascular disease continuing to be the leading cause of death following whole organ transplantation.¹²

In this review, we will discuss indications for ICT, the procedure and immunosuppression used, metabolic and quality of life outcomes and the evidence to date of the impact that ICT has on microvascular and macrovascular disease in the early post-transplant period, which we have considered up to 2 years post-transplant, the intermediate period between 2 and 5 years post-transplant, and, in the long term, over 5 years post-transplant.

1.1 | Indications for islet cell transplant

The burden of SH on diabetes-related morbidity and mortality is well established.¹³ Since the DCCT trials, there have been advances with newer short acting insulins and technologies, including sensor technology and automated insulin delivery (AID) devices. These demonstrate that improvements in HbA1c may be possible with no increase in hypoglycaemia, an outcome that was not apparent at the time of the DCCT.⁶ However, these devices may not be suitable or readily available for all people, and in those with IAH, avoidance of hypoglycaemia may not be achievable and awareness of hypoglycaemia may not be restored.¹⁴

There are a number of islet transplantation programmes worldwide. Data from over 1000 people receiving islet transplants since 1999 has been collated via the Collaborative Islet Transplant Registry (CITR) which has served to inform best practise, including indications for ICT. The United Kingdom has a collaborative network of seven centres which together form the UK Islet Transplant Consortium (UKITC). The United Kingdom introduced this intervention free at the point of entry into its health care system; it is endorsed by National Institute for Health and Care Excellence (NICE), and we have shown that this intervention reaches all socio-economic groups in the population.⁸ It is a therapy for those with recurrent neuroglycopenia, including severe glycaemic lability with IAH where insulin therapy has been intensified as much as possible. The main aim of ICT is not insulin independence, but to restore hypoglycaemia awareness, reduce glycaemic lability and improve quality of life.

The current criteria for ICT in the United Kingdom are summarised in Table 1 and the contraindications in Table 2.

TABLE 1 Inclusion criteria for islet cell transplantation

Inclusion criteria
Type 1 diabetes:
<ul style="list-style-type: none"> • Age >18 years • Diabetes duration >5 years • C-peptide negative (<0.3 ng/ml)
Severe recurrent problematic hypoglycaemic:
<ul style="list-style-type: none"> • Impaired awareness of hypoglycaemia • ≥ 2 episodes of severe hypoglycaemia in past 2 years
Failure to achieve glycaemic targets despite intensive management and structured education:
<ul style="list-style-type: none"> • Previous trial of CSII and/or CGM or sensor augmented pump therapy preferable

TABLE 2 Contraindications to islet cell transplantation

Contraindications
Due to immunosuppression risks:
<ul style="list-style-type: none"> • A previous history of cancer, excluding completely excised nonmelanoma skin cancer • Active sepsis • Active peptic ulceration
Due to lower likelihood of successful transplant outcome:
<ul style="list-style-type: none"> • High insulin requirements (>100 units/day) • Weight >85 kg • Major psychiatric history likely to result in nonconcordance • Inability to withstand immunosuppression
Due to risks from diabetes complications:
<ul style="list-style-type: none"> • Active proliferative retinopathy • Nuclear medicine GFR <60 ml/min/1.73 m² • Excessive cardiovascular risk

Of note, in the United Kingdom, absolute insulin requirements rather than insulin doses expressed per kilogram body weight are taken into consideration. In people with significantly diminished GFRs <20 ml/min, a simultaneous pancreas–kidney transplantation would initially be considered in those with T1D with problematic glycaemic control. However, this is associated with a relatively high perioperative risk, and it necessitates people to have adequate cardiovascular fitness. If the person has multiple co-morbidities and fails cardiopulmonary function tests, usually carried out before the listing procedure, then simultaneous islet and kidney (SIK) transplant where the islet cells and kidney come from the same donor, or islet after kidney (IAK) transplant, where a new donor is used following a previous renal transplant, would be indicated.¹⁵

1.2 | Islet isolation and transplantation procedure

Islets are isolated by infusing the donor pancreas with collagenase-based enzymes; the resultant is purified using density-graded centrifugation and then assessed before being

placed in a conventional tissue culture for 24 h before being reassessed for purity, viability, sterility and yield.¹ If release criteria are met, they are infused into the sedated person via the hepatic portal vein under radiological guidance. The release criteria include (1) cell count >250,000 islet equivalents (IEQs) (approximately >5000 IEQ/kg), (2) purity >50%, (3) viability >70%, (4) sterility defined by a negative gram stain and (5) endotoxin content <5 EU/kg.

Recipient blood glucose levels are closely monitored perioperatively and kept between 4 and 8 mmol/L using intravenous insulin infusions to reduce oxidative stress on the newly transplanted islets.¹⁶ The number of islets recovered from an individual pancreas can vary. Transplanting >10,000 total IEQ units per recipient body weight (IEQ/kg) typically from two donor pancreases is associated with insulin independence.¹⁷ Occurrence of periprocedural complications is low, with infusion-related adverse events occurring in 4.2% of islet transplants from 2015 to 2018 in the first 30 days post-transplant.¹⁸

1.3 | Immunosuppression

A major consideration in assessing people for islet transplantation is the use of induction agents and steroid-free immunosuppression which diminishes the risk of alloimmune and autoimmune rejection of islets. A previous history of cancer, excluding completely excised nonmelanoma skin cancer, is a contraindication for receiving immunosuppression and islet transplantation. The range of immunosuppression medications used in ICT is extensive and has been recently reviewed.¹⁹ A full discussion of all agents involved is out with the scope of this review; however, immunosuppressive agents at the time of ICT can impact the risk of microvascular and macrovascular complications, and this must be carefully considered.

The most common agents used at induction are alemtuzumab: a monoclonal antibody that binds to CD52 present on mature lymphocytes, in combination with etanercept: an anti-TNF- α agent. Other induction agents include antithymocyte globulin which is composed of rabbit-derived antibodies against human T cells and basiliximab: a monoclonal antibody to the α chain (CD25) of the IL-2 receptor of T cells. Maintenance immunosuppression in many programmes is with tacrolimus, a calcineurin inhibitor (CNI) in combination with mycophenolate mofetil (MMF), an inhibitor of cell division. Other immunosuppression regimens are used and include sirolimus, which inhibits IL2 via mTOR (Table 3). These are given in the absence of steroids in those receiving an islet cell transplant alone.²⁰

Although immunosuppression increases the risk of infection and malignancy, rates of these complications are relatively low. Information from the CITR showed an overall incidence of malignancy of 0.01 events/person year follow-up. Life threatening events, mainly related to infection

TABLE 3 Induction and immunosuppressive agents in islet transplantation

Immunosuppressive agent	Mechanism of action	Use
Daclizumab	IL-2 inhibitor	Early induction agent
Alemtuzumab	Monoclonal antibody to CD52	Main induction agent in current use for first islet transplant
Basiliximab	Monoclonal antibody acting as an IL-2 receptor antagonist	Potential induction agent for islet transplant
Etanercept	Anti-TNF- α inhibitor	Used in combination with Alemtuzumab or antithymocyte globulin for first transplant induction
Antithymocyte globulin	Anti-T-cell antibodies	Induction agent used in combination with etanercept
Tacrolimus	Reduces IL2 up-regulation via calcineurin inhibition	Main agent for maintenance immunosuppression
Sirolimus	Inhibits IL2 via mTOR inhibition	Alternative to mycophenolate mofetil and to tacrolimus in patients with declining renal function
Mycophenolate mofetil	Inhibits inosine monophosphate dehydrogenase	Main adjunct to tacrolimus for maintenance immunosuppression

and depleted granulocyte numbers, occurred in 5.4% of recipients between 2007 and 2018. Immunosuppression was thought to be linked with six of a total of 33 deaths reported post-ICT since the registry began in 2001.¹⁸

Immunosuppression may have an impact on microvascular and macrovascular diabetes complications. Tacrolimus is associated with hyperglycaemia, a result of inhibition of insulin secretion and increased insulin resistance which could precipitate poor glycaemic control and exacerbate diabetic complications. Tacrolimus in the therapeutic range may also be associated with peripheral nerve dysfunction and neuropathy.²¹ Of note, however, tacrolimus is anti-inflammatory and prevents early retinal neovascularisation in experimental models of diabetes.²² Many immunosuppressive agents also have adverse effects on renal function,²³ at least initially, and data from Edmonton have demonstrated that there is an initial fall in eGFR over the first year which subsequently stabilises and has been noted to remain stable over a 10-year period of follow-up.²⁴ Immunosuppression is also associated with higher rates of cardiovascular disease which could be related to known adverse effects on blood pressure and lipids.²³

1.4 | Graft assessments and outcomes

Studies have used a number of measures to reflect graft success. These in part reflect the change in the goals of islet transplantation that have evolved over time. Improvement in HbA1c, insulin independence, C-peptide secretion, reduction in insulin doses, reduction of hypoglycaemia, return of hypoglycaemia awareness and composite scoring systems which incorporate a number of these variables have all been used.

Many of the glycaemic targets used in diabetes stem from the DCCT, where intensively controlled participants had significantly reduced microvascular risk achieving a median HbA1c of 53 mmol/mol (7%), compared with a median

HbA1c of 75 mmol/mol (9%) in those on conventional treatment.⁶ Evidence from the CITR shows >60% of islet transplant recipients achieve and maintain HbA1c <53 mmol/mol (<7%) for up to 3 years post-transplant compared with fewer than 20% achieving this pre-transplant.¹⁸ Other studies confirm improvements in HbA1c post-transplant.^{8,25–27} Improvements in HbA1c are achieved post-transplant even in those with relatively low baseline HbA1c; a 2016 phase 3 multi-centre trial of 48 people reported a median HbA1c of 37 mmol/mol (5.6%), which was attained in the absence of SH 2 years post-transplant, from a baseline of 55 mmol/mol (7.2%).²⁸

Insulin independence post-transplant is defined as a minimum period of 14 days without the need for exogenous insulin, coupled with good glycaemic control. Several studies have shown insulin independence is achieved for at least a short period in nearly all transplanted people, but islet transplantation still falls short of a cure.^{29,30} Continued insulin independence at 1, 2 and 3 years post-islet transplant has improved over time with insulin independence rates of 66%, 55% and 44% in 2007–2010 compared with 51%, 36% and 27% in 1999–2002.²⁵ Although insulin independence is a commonly reported measure of graft success, and a beneficial outcome for ICT recipients, it is not a primary aim of islet transplantation.

Measurement of C-peptide positivity is objective and reported in the CITR. Stimulated C-peptide at 90 min using a standard mixed meal test (360-ml Ensure HP comprising 391 kcal with 8.5 g fat, 44 g carbohydrate, 17 g protein) is used and interpreted in the context of a paired blood glucose reading.³¹ Reductions in SH and a return in the awareness of hypoglycaemia post-transplantation are important outcome measures post-islet transplantation,^{25,26,28,29,32} but the latter is not well recorded. Reduction in hypoglycaemia is associated with C-peptide positivity,²⁵ independent of the restoration of autonomic function,³³ and allows people to regain adrenergic

symptoms.³⁴ Pathophysiologically, glucagon secretion in response to hypoglycaemia is partially restored following islet transplant³⁵ which is thought to be due to paracrine interactions in the transplanted islets between glucagon secreting alpha cells and insulin secreting β -cells. The benefit is sustained, with more than 90% of islet transplant recipients remaining free of SH over 5 years of follow-up,^{25,26,36} maintained with reintroduction of insulin.^{26,29} Awareness of hypoglycaemia may importantly be retained even with loss of graft function.³⁴ Notably, the Trial Comparing Metabolic Efficiency of Islet Graft to Intensive Insulin Therapy (TRIMECO) was the first randomised controlled trial to compare metabolic outcomes in people with T1D following ICT ($n = 25$) versus those managed with intensive insulin therapy ($n = 22$). After 6 months, participants randomised to receive ICT had superior outcomes including significant reductions in SH and HbA1c, with insulin independence rates of 11/25 (44%) in the ICT group.³⁷

It is now widely recognised that composite scoring systems incorporating these variables are powerful measures to assess graft function. The beta score (Table S1)³⁸ is commonly used. This gives a categorical score ranging from 0 to 8 based on fasting plasma glucose, HbA1c, daily insulin dose or oral hypoglycaemic use and stimulated C-peptide.³⁸ In the TRIMECO study, the primary end point was a modified beta score ≥ 6 , achieved by 64% of ICT versus 0% of intensively insulin-treated group.³⁷ With the advent of highly sensitive C-peptide assays, the BETA-2 score has largely superseded the beta score.³⁹ It is a continuous score (Table S2) containing the same variables as the beta score but uses a fasting rather than a stimulated C-peptide, eliminating the need for a mixed meal with the benefit of increased frequency of testing graft function and cost savings. A BETA-2 score ≥ 17 at Day 75 post-first transplant discriminates people that will not require exogenous insulin in the longer term.⁴⁰

A 2018 joint consensus report from the International and European Pancreas and Islet Transplantation Associations (IPITA/EPITA) recommends the use of clinical and metabolic factors to define islet transplant success, and the current British Transplant Society specifically highlights the use of the beta and BETA-2 scores.⁴¹ IPITA/EPITA also highlights the utility of an HbA1c < 53 mmol/mol ($< 7\%$) without SH, with $> 50\%$ reduction in insulin requirement and restoration of clinically significant C-peptide secretion.⁴¹

Glycaemic variability as assessed by continuous glucose monitoring (CGM) has been studied post-ICT, but the literature is limited. There are reductions in mean glucose, time spent in hyperglycaemia and hypoglycaemia and coefficient of variation (CV) of glucose.^{36,42,43} Higher levels of C-peptide are required to reduce time in hyperglycaemia versus time in hypoglycaemia.⁴⁴ Our own work has related BETA-2 scores to CGM indices; at 1 year post-transplant, 39 ICT recipients had lower time in hypoglycaemia and decreased CV glucose

versus those on open loop continuous subcutaneous insulin infusion (CSII) therapy.⁴³ Over time post-transplant, glycaemic variability increases as graft function falls. An area of intensive research currently is how glycaemic variability per se contributes to microvascular and macrovascular complications as well as quality of life measures independently from HbA1c.

Factors associated with a favourable metabolic outcome include induction immunosuppression with T-cell depletion and/or a TNF- α inhibitor, maintenance immunosuppression with an mTOR inhibitor and CNI, recipient age > 35 years (associated with reduced autoimmunity) and a transplanted mass $> 325,000$ IEQs.¹⁸

1.5 | Quality of life

Quality of life (QoL) is an important outcome measure. Studies have shown that the psychosocial burden of T1D pre-transplant is significant.^{8,45} The score most frequently used to measure QoL is the EQ-5D-3L which is not specific or sensitive with respect to diabetes. Post-transplant studies show improvements in QoL scores following ICT compared with pre-transplant.^{37,46,47} The TRIMECO study showed significant improvement in questionnaire scores, the Diabetes Quality of Life questionnaire and Short Form³⁶ Health Survey (SF-36), at 6 months in those randomised to receive immediate transplantation compared with those randomised to continue with medical therapy.³⁷ Similarly, a recent single-arm phase 3 study of IAK recipients found significantly reduced diabetes distress and fear of hypoglycaemia scores up to 3 years post-transplant compared with pre-transplant scores.⁴⁸ Improvement is particularly seen for diabetes specific QoL assessments and those relating to hypoglycaemia fears, anxiety scores and depression scores in islet transplant alone (ITA). While improvements in QoL scores were clear for those receiving ITA, there were no significant differences in QoL scores in SIK/IAK recipients. QoL scores were higher (better perceived QoL) at baseline in SIK/IAK groups, which may be related to the fact that they did not have a history of SH.⁴⁷

There is a need to use sensitive QoL assessments, and we propose that as this outcome measure is so important, weight is given both to this assessment and the metabolic assessment including glycaemic variability.

2 | MICROVASCULAR AND MACROVASCULAR DIABETES COMPLICATIONS

There is evidence that ICT has a positive impact on the microvascular complications associated with T1D, such as retinopathy, sensory neuropathy and nephropathy. There is less evidence with respect to macrovascular complications.

TABLE 4 Summary of current evidence for effects of ICT on diabetic retinopathy

Author and year	Study type	Number of ICT subjects included (and baseline DR grading)	Control group	Follow-up post-transplant	Main findings	Retinopathy outcomes post-islet transplant
Short-term follow-up						
Lee et al 2005 (S5)	Cohort	8 included (3 no DR, 2 mild DR, 1 minimal NPDR, 2 PDR)	None	1–2 years	No progression in retinopathy compared with pre-transplant baseline	Stable
Ryan et al 2005 ²⁹	Cohort	65 included (30 PDR, 18 NPDR) 47/65 completed procedure (defined as insulin independence for >4 weeks) and were assessed at follow-up	None	5 years (retinal outcomes only reported for 5-months post-transplant)	Assessment within early post-transplant period showing progression in 4/47 patients, who required photocoagulation or vitrectomy within 5 months of transplant	Worsening
Venturini et al 2006 (S7)	Prospective case control	10 included (2 no DR, 5 mild NPDR, 3 moderate NPDR)	10 medically treated subjects on islet transplant waiting list 3 no DR, 5 mild NPDR, 2 moderate NPDR	1 year	Significantly increased retinal artery and vein blood flow on colour Doppler in transplanted patients versus controls	Improved
Long-term follow-up						
Thompson et al 2008 (S1) and Thompson et al 2011 ³⁰	Prospective crossover cohort	27 included (51 eyes—8 mild NPDR, 12 moderate DR, 3 severe NPDR, 28 PNPDR)	44 medically treated subjects on islet transplant waiting list—27/44 later transplanted, 17/44 not transplanted (31 eyes—8 mild NPDR, 7 moderate NPDR, 3 severe NPDR, 13 PDR)	5.5 years (66 months)	Significantly reduced DR progression post-islet transplant (0/51 eyes) versus controls (10/82 eyes), $p < 0.01$ DR progression (controls only) highest in those with more severe DR baseline	Improved
Tekin et al 2016 (S4)	Cohort	9 included, 4/9 completed follow-up (2 no PDR, 2 PDR) 5/9 withdrew early in study	None	7–8 years	No progression in retinopathy in 4 patients who completed study compared with pre-transplant baseline	Stable

Note: The table summarises the main ICT studies examining the impact on diabetic retinopathy. In all studies, HbA1c was reduced following transplantation. Abbreviations: DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative retinopathy.

All such studies have to be interpreted in the context that ICT recipients are on immunosuppression.

3 | Microvascular complications

3.1 | Retinopathy

A meta-analysis suggests that ICT may be more effective than medical therapy in preventing diabetic retinopathy for people with longer durations of diabetes, although only three islet studies were included.⁴⁹ A retrospective analysis of retinal screening records from >100 islet transplant recipients, including our own islet transplant cohort, found retinopathy progression was significantly reduced following islet transplantation compared with a cohort managed with intensive multiple daily injections of insulin.⁵⁰ In a prospective crossover study, rates of retinopathy progression in people awaiting islet transplantation were compared with progression rates following islet transplant (S1). From a total of 44 participants who were receiving intensive medical therapy on the islet transplant waiting list, 27 people received an islet transplant and crossed over to form the treatment group. Progression rates in both eyes pre-transplant for those in the intensive medical group who had not yet received a transplant ($n = 17$) and who had been on the waiting list during the study but were later transplanted ($n = 27$) were compared with retinopathy progression post-transplant ($n = 27$). Mean follow-up time was 36 months in the islet group and 34 months in the intensive medical group. Eyes were excluded if they had vitrectomy pre-study or were blind (six eyes). When compared with retinopathy progression in the islet group (0/51 eyes), retinopathy progression was significantly more likely in the intensively treated medical groups (progression in 10/82 eyes in all waiting list participants, $p < 0.01$ and 6/51 eyes in participants who were later transplanted, $p < 0.02$). Participants in the medical group with more advanced retinopathy at baseline were more likely to progress. At subsequent follow-up, 66 months in islet group, 47 months in medical group no additional patients had developed retinopathy progression.³⁰

Islet cell transplantation significantly improves HbA1c,⁴⁴ and the adverse effects of abrupt tightening of glucose control on retinopathy progression remain a concern (S2, S3). An early report from the Edmonton group showed 4/47 participants receiving islet transplants had a deterioration in retinopathy requiring photocoagulation or vitrectomy within the first 5 months of transplant²⁹; however, this was a high-risk group with proliferative retinopathy present in 46% of people at baseline. Other small studies have shown stable disease in the early post-transplant period (S4, S5). Such studies also concord with whole organ pancreas transplantation studies which demonstrate stabilisation of diabetic retinopathy over 6–60 months of follow-up (S6).

Reduced retinal blood flow may be an early sign of retinopathy. Blood flow velocities to the central retinal artery and vein on colour Doppler were increased in 10 ICT recipients 1 year after transplant versus matched controls on the islet transplant waiting list (S7). This may be consistent with reduced progression of diabetic retinopathy, but the exact clinical impact of this finding remains uncertain.

Overall, the literature suggests ICT improves or stabilises diabetic retinopathy at a cellular and clinical level. It is not known if glycaemic variability predicts retinopathy progression independently from HbA1c (S8). Careful prospective studies examining the independent effect of glycaemic variability and HbA1c as well as their potential additive effects on retinopathy outcomes are required. Studies examining the effects of islet transplantation on diabetic retinopathy are summarised in Table 4.

3.2 | Neuropathy

Studies of the effects of ICT on neuropathy have emerged over the past few years. A crossover study compared the rate of change of nerve conduction velocities (NCVs) over 6 years post-transplant with changes in participants awaiting transplantation on intensive medical therapy. NCV scores were measured from seven nerves in each participant and a standardised score ('Z score') was calculated to allow the total burden of neuropathy from multiple nerves to be assessed. Diabetic neuropathy was present at baseline in 29/44 (66%) of all study participants though the proportion with baseline neuropathy who were transplanted and crossed over to the ICT group were not specified, and there was significant heterogeneity in the baseline 'Z scores' across participants. ICT recipients trended towards improved NCV scores versus medically treated controls ($p = 0.11$), with significant improvements when participants with baseline neuropathy were evaluated ($p < 0.05$) (S9). This is similar to previous studies showing improvements post-ICT in sensory NCV over 5 years in both IAK and ITA recipients, compared with their pre-transplant baselines. Motor NCV showed no improvement, and a deleterious effect of tacrolimus on motor neuropathy was postulated (S10). To minimise confounding effects of immunosuppression on neuropathy, a study compared T1D transplant recipients receiving IAK with those receiving kidney transplant alone (KTA). They demonstrated significant improvement in NCV Z scores in IAK versus KTA controls at 4 years, although significance was lost at 6 year follow-up when 9/18 IAK participants were assessed (mean IAK follow-up 53.4 months post-transplant). This study showed reductions in advanced glycation products and their receptors in skin biopsies of islet recipients, which are thought to be associated with the pathogenesis of diabetic neuropathy (S11).

TABLE 5 Summary of current evidence for effects of islet transplantation on peripheral neuropathy

Author and year	Study type	Number of ICT subjects included	Control group	Follow-up post-transplant	Main findings	Neuropathy outcomes post-islet transplant
Short-term follow-up						
Lee et al 2005 (S5)	Cohort	8 included (5/8 baseline neuropathy)	None	1–2 years	No significant difference in pre- and post-transplant motor or sensory NCV from baseline	Stable
Long-term follow-up						
Ryan et al 2005 ²⁹	Cohort	65 included 47/65 completed procedure (defined as insulin independence for >4 weeks) and were assessed at follow-up	None	5 years	No significant change from baseline in neurothesiometer scores during follow-up	Stable
Del Carro et al 2007 (S11)	Cohort	18 IAK	9 KTA recipients	6 years	Significant improvement in ICT NCV Z scores at 4 years ($n = 18$, $p = 0.01$) but not at 6-year ($n = 9$) follow-up. No significant NCV change in control group over 6 years Reduction in markers of neuropathy on skin biopsies from islet subjects versus controls	Improved
Vantghem et al 2014 (S10)	Cohort	21 (13 ITA, 8 IAK)	None	5 years	Significant improvement in post-transplant sensory NCV (41.2 m/s) and action potentials (11.8 mV) from baseline NCV (47.5 m/s) and action potential (5.5 mV) ($p < 0.01$ for both)	Improved
Fensom et al 2016 (S9)	Prospective crossover cohort	30	44 medically treated subjects on islet transplant waiting list (45% mild, 16% moderate, 5% severe baseline neuropathy)—30/44 later transplanted, 14/44 not transplanted	6.2 years (74 months)	Improvement in combined NCV scores from seven peripheral nerves in ICT group versus medical group ($p = 0.11$) Improvement significant for those with baseline neuropathy ($p < 0.05$)	Improved
Tekin et al 2016 (S4)	Cohort	9 included, 4/9 completed follow-up (baseline neuropathy in 2/4) 5/9 withdrew early in study	None	7–10 years	Improved neuropathy assessment in two patients with baseline neuropathy, no neuropathy in one patient, mild axonal neuropathy which remained stable after 2 years in one patient	Stable

Note: HbA1c was significantly reduced post-transplant in all studies.

Other centres have demonstrated stable neuropathy post-islet transplantation, although control groups were lacking (29, S4, S5).

ICT appears to stabilise or improve sensory neuropathy but not motor neuropathy post-transplant. Longer term follow-up may elucidate the impact on motor neuropathy. Studies examining the effects of islet transplantation on neuropathy are summarised in Table 5.

3.3 | Nephropathy

Assessment of nephropathy post-ICT is complicated by the effects of pre-transplant variability in renal function and the use of different combinations of potentially nephrotoxic medications, particularly immunosuppression. Whether participants are receiving an ITA, SIK or IAK also needs to be considered as the latter two groups may have complications secondary to pre-transplant renal failure and uraemia, and poorer baseline renal function is associated with higher rates of albuminuria post-transplant (S12).

Studies of ITA recipients show decline in renal function post-transplant compared with baseline pre-transplant levels.^{28,29} This concurs with results from CTR assessing 677 individuals with both uraemic and nonuraemic baselines showing eGFR declines with time.²⁵ The Edmonton retrospective analysis of islet transplant recipients up to 10 years post-transplant, the majority of whom were on immunosuppression with tacrolimus and MMF, showed progression of albuminuria and decline in eGFR of up to 30% at 5 year follow-up which then stabilised.²⁴ Conversely, a study comparing renal function in 16 recipients pre- and post-ITA³⁰ demonstrated that the median rate of eGFR decline was significantly reduced from -6.7 ml/min/1.73 m²/year pre-transplant to -1.3 ml/min/1.73 m²/year post-transplant and was not affected by the degree of baseline proteinuria. This study used antithymocyte globulin and basiliximab as induction agents and a combination of tacrolimus and MMF for maintenance immunosuppression.

These studies made comparisons to renal function pre-transplant and lacked a separate nontransplanted control group. Some decline in renal function is expected with time in people with T1D and should be considered when interpreting change in renal function in these studies. In the DCCT, those with normoalbuminuria showed a mean rate of change in eGFR of 1.2% per year, while those with microalbuminuria, or those who developed macroalbuminuria, had a mean rate of change of 1.8% and 5.7% per year respectively.³

While studies have not confirmed benefits of ICT in preventing diabetic nephropathy in native kidneys, evidence suggests that it may be protective for transplanted kidney grafts. (S13, S14). A recent prospective study in 24 IAK

recipients showed relatively stable renal function over 3 years post-transplant, with eGFR of 78 ml/min/1.73 m² from a baseline of 82 ml/min/1.73 m².⁴⁸ IAK recipients ($n = 24$) with C-peptide present versus those with unsuccessful grafts ($n = 12$ IAK) with C-peptide absent had better renal graft survival rates of 83% versus 51% in the respective groups at 7 years follow-up (S13). Glycaemic control (HbA1c) between the groups was not significantly different, but the C-peptide positive group had increased Na/K ATPase activity and a reduction in natriuresis over time. It is not known if C-peptide contributed to kidney graft function, acting via Na/K ATP channels to improve sodium resorption in renal tubular cells (S13). It is also not clear whether IAK recipients with unsuccessful islet grafts may be more immunologically susceptible to rejecting their kidney graft, which makes the data difficult to interpret.

Evaluation of IAK renal outcomes relative to other renal transplant recipients has also proved useful in evaluating the specific benefits from islet transplantation itself. IAK recipients with successful islet grafts previously described ($n = 24$ people) were compared with those with T1D receiving either simultaneous pancreas and kidney transplant (SPK; $n = 166$ people) or KTA ($n = 44$ people) (S14). KTA recipients showed a significant increase in urinary albumin excretion and creatinine levels over 6 years, while successful IAK and SPK recipients showed no significant decline (S14). This is concordant with another study showing comparable outcomes in IAK and SPK recipients, with no significant differences observed in the rate of decline in eGFR over a ten year follow-up period.³²

Changes to renal function in ICT involving both native and transplanted kidneys will also be impacted by the immunosuppression used. CNIs such as tacrolimus are nephrotoxic and changes in immunosuppression from tacrolimus to MMF in people with declining eGFR post-transplant has been shown to stabilise renal function (S12, S15). It is common clinical practise to switch from tacrolimus to the mTOR inhibitor sirolimus when GFRs diminish post-transplantation, and there is evidence that this is protective in the short term (S16). Sirolimus is also associated with post-transplant microalbuminuria (S12) and proteinuria; in some reports, proteinuria resolves following withdrawal of sirolimus (S17).

Most studies in IAK recipients show a decline in renal function post-transplantation in the initial phase secondary to immunosuppression—mainly tacrolimus. Graft function then stabilises over time, but there is still a valid concern that immunosuppression with tacrolimus increases the risk of worsening renal function, in which case alternative immunosuppression may be used. The field is hindered by a lack of control groups. A summary of the main studies examining the impact of islet transplantation on nephropathy is shown in Table 6.

TABLE 6 Summary of current evidence for effects of islet transplantation on nephropathy

Author and year	Study type	Number of ICT participants included	Control group	Follow-up post-transplant	Main findings	Nephropathy outcomes post-islet transplant
Short-term follow-up						
O'Connell et al 2013 (S29)	Cohort	17 ITA recipients	None ^a	1 year	13% decline in eGFR at 1 year (77 ml/min at baseline vs. 67 ml/min at 1 year)	Worsening
Hering et al 2016 ²⁸	Prospective cohort	48 ITA recipients	None ^a	2 years	12% decline in GFR at 1 year and 20% decline at 2 years (GFR 102 ml/min/1.73 m ² at baseline to 90 ml/min/1.73 m ² at 1 year and 82 ml/min/1.73 m ² at 2 years)	Worsening
Intermediate follow-up						
Markmann et al 2020 ⁴⁸	Prospective cohort	24 IAK	None ^a	3 years	4% change in eGFR at 3 years (eGFR 82 ml/min/1.73 m ² at baseline to 78 ml/min/1.73 m ² at 3 years)	Stable
Long-term follow-up						
Fiorina et al 2003 (S13)	Prospective cohort	24 successful (C-peptide positive) IAK transplant recipients	12 unsuccessful (C-peptide negative) IAK transplants	7 years	Improved renal graft survival rates in successful islet transplant recipients (85%) versus unsuccessful recipients (51%)	Improved
Fiorina et al 2005 (S14)	Prospective cohort	24 successful (C-peptide positive) IAK transplant recipients	166 SPK transplant recipients, 44 KTA recipients	6 years	Significantly increased urinary albumin excretion and creatinine levels in KTA recipients versus those receiving successful IAK or SPK	Improved
Ryan et al 2005 ²⁹	Cohort	65 included 47/65 completed procedure (defined as insulin independence for >4 weeks) and were assessed at follow-up	None ^a	5 years	11% decline in creatinine clearance at 1 year (1.8 ml/s at baseline versus 1.6 ml/s at 1 year)	Worsening
Thompson et al 2011 ³⁰	Prospective crossover cohort	32 ITA recipients, of which 16 had data for paired pre- and post-transplant analysis	45 medically treated participants on islet transplant waiting list—32/45 later transplanted, 13/44 not transplanted	5 years	Significantly lower rate of eGFR decline post-transplant compared with pre-transplant on paired analysis (−1.3 vs. −6.7 ml/min/1.73 m ² /year)	Improved

(Continues)

TABLE 6 (Continued)

Author and year	Study type	Number of ICT participants included	Control group	Follow-up post-transplant	Main findings	Nephropathy outcomes post-islet transplant
Barton et al 2012 ²⁵	Cohort	677 ITA, IAK and SIK recipients	None	5 years	Decline in eGFR compared with pre-transplant baselines (results given in tabular format, exact eGFR values not provided)	Comparison to nontransplanted individuals not available ^b
Lehmann et al 2015 ³²	Prospective cohort	38 SIK/IAK transplant recipients	94 SPK transplant recipients	13 years	No significant difference in rate of decline of renal function in islet transplant recipients compared with pancreas transplant recipients	Stable

Note: HbA1c was significantly reduced post-transplant in all studies.

^aFor studies without a suitable control group, reference has been made to the maximum mean rate of decline seen in eGFR in DCCT (mean rate of change in eGFR of 5.7% per year in those developing macroalbuminuria) to compare nephropathy outcomes post-transplant.; ^bUnable to assess if decline in eGFR higher than what may be predicted in nontransplanted individuals.

3.4 | Macrovascular complications

The DCCT showed that intensive glycaemic control improves long-term cardiovascular outcomes⁶; therefore, we might expect that the improved glycaemic markers associated with ICT would be beneficial in slowing atherosclerosis progression. However, immunosuppressive drugs have been implicated in increasing cardiovascular risk, particularly through adverse effects on blood pressure and lipids.^{12,23} In addition, cardiovascular disease following whole organ transplantation remains one of the leading causes of morbidity and mortality.¹² No prospective studies have assessed cardiovascular morbidity and mortality in nonuraemic, nonkidney transplanted islet transplant recipients.

Islet transplant recipients receiving a kidney graft have been studied. In one study, cardiovascular death rates were lower in IAK recipients with islet graft function (5%) versus T1D uraemic controls without a transplant (16%) and people who had received KTA (19%) and comparable with cardiovascular death rates in SPK recipients (8%). However, when islet transplanted participants with successful ($n = 24$) and unsuccessful ($n = 13$) islet graft function were considered together, cardiovascular death rates were not reduced (18%) (S18).

Surrogate markers of cardiovascular disease and atherosclerosis have also been studied. A prospective follow-up study of carotid intima media thickness (CIMT) in 15 people receiving ICT demonstrated that the CIMT was significantly reduced at 12 months compared with pre-transplant baselines (S19). In parallel, there were improvements in glycaemic markers but no significant changes in blood pressure or lipids at follow-up versus pre-transplant. While most participants did have some progression of CIMT thickness after the initial large reduction in the first 12 months, the CIMT thickness remained significantly lower at 50 months follow-up ($n = 7$) for combined common and internal CIMT when compared with baseline values. Post-transplant C-peptide levels were not reported, but mean HbA1c at 50 months was 42 mmol/mol (6%); there were no severe hypoglycaemic episodes reported during follow-up, and all 15 participants achieved insulin independence during the study. Of these, 11 participants remained insulin free at last follow-up, and a further three had >50% reduction in insulin requirements. Graft loss was reported at 19 months in one participant. Further studies of CIMT in 17 people receiving IAK showed stable CIMT over 3 years compared with worsening CIMT in 25 people receiving KTA. Ejection fraction and peak filling rate in end-diastolic volume on echocardiogram were also improved in IAK versus KTA recipients (S20). The clinical significance of these markers remains uncertain. CIMT is a relatively well-established marker in clinical studies, but its use as a clinical predictor of cardiovascular disease is thought to be

TABLE 7 Summary of current evidence for effects of islet transplantation on macrovascular diabetes complications

Author and year	Study type	No. of islet transplanted subjects	Controls	Follow-up post-transplant	Main findings	Proposed effects of islet transplant on macrovascular complications
Short-term follow-up						
D'Addio et al 2014 ⁴⁶		12	10 medically treated subjects on islet transplant waiting list and 10 healthy controls	1.3 years (15 months)	Reduction in prothrombotic factors, platelet size and platelet aggregation in islet transplant recipients versus medically treated diabetic controls, with post-transplant results comparable with non-diabetic healthy subjects	Improved
Intermediate follow-up						
Fiorina et al 2005 (S14)	Cohort	17 IAK transplant recipients	25 KTA recipients	3 years	Stable CIMT, increased ejection fraction and increased peak filling rate in end-diastolic volume on echocardiogram in islet group compared with controls	Improved
Danielson et al 2013 (S19)	Cohort	15	None	4.2 years (50 months)	Significant reduction in CIMT thickness for combined common and internal CIMT when compared with baseline values	Improved
Long-term follow-up						
Fiorina et al 2003 (S13)	Cohort	37 IAK transplant recipients—24 successful IAK (C-peptide positive) and 13 unsuccessful IAK (C-peptide negative)	162 SPK transplant recipients, 42 KTA recipients and 196 people with T1D and ESRD on haemodialysis	7 years	Lower cardiovascular death rate in those with successful islet transplant (5%) compared with KTA recipients (19%) and T1D patients on haemodialysis (16%) Higher survival in all islet transplant recipients (comparable with SPK transplant recipients) compared with KTA recipients (non-significant) and T1DM with ESRD on haemodialysis (significant)	Improved

less clear for individuals with other known cardiovascular risk factors (S21).

Other studies have demonstrated that ICT reduces prothrombotic markers. Platelet size and aggregation, resting Ca^{2+} and levels of protein S and protein C were almost normalised to levels of healthy controls in 12 participants at 15 months post-islet transplant, in contrast to a control T1D group where markers were consistent with a prothrombotic state (increased platelet size and aggregation, increased resting Ca^{2+} , reduced protein S and protein C).⁴⁶ The authors postulate that the improved haemostatic indices in people with T1D post-transplant may reduce atherosclerosis risk by minimising a prothrombotic state. Individuals who had received kidney transplants on similar immunosuppression did not show any change to haemostatic markers, suggesting the effects were not influenced by immunosuppression.

Clearly further evidence is needed to establish the risks and benefits for macrovascular outcomes following ICT and prospective studies in this field are urgently required. We summarise the current evidence for the effects of islet transplantation on macrovascular diabetes complications in Table 7.

4 | FUTURE INNOVATIONS IN ISLET TRANSPLANTATION

Islet transplant alone presents ongoing challenges that limit the widespread use for people with T1D. SIK transplantation deserves particular mention as people with T1D with labile glycaemic control who require a kidney transplant benefit from this combined procedure with no additional immunological risks associated with receiving islets from the same donor (S22). Most pancreases cannot be used for islet transplantation because of prolonged ischaemic times, and patients usually require islets from at least two donors to impact on their insulin requirements, and in the United Kingdom, they may wait over 12 months to receive their first transplant. Furthermore, attrition in graft function is seen, due to nonimmunologic mechanisms of metabolic exhaustion of a marginal islet β -cell mass,¹⁹ and autoimmune and alloimmune mechanisms may contribute. The United Kingdom has expanded its donor criteria and uses islets from donors after cardiac death as well as after brain death. Many investigators are now researching how best to preserve pancreases including with oxygen persufflation (S23) so as to use pancreases with marginally longer ischaemic times.

The cotransplantation of immunomodulatory cells including mesenchymal stromal cells (MSCs) (S24) and T regulatory cells holds promise (S25). Such therapies may mean that people with T1D would only require islets from one donor

pancreas therefore enabling the use of more donor organs to treat more people.

The need for long-term immunosuppression is a major concern. The use of encapsulated islets is in very early Phase 1 studies, and if this approach is successful, it could potentially make immunosuppression obsolete and justify this treatment for many more people with T1D (S26). However, fibrotic reactions around the device site are a major problem, and deviceless alternatives may hold more promise (S27) but still may not be immunosuppression free.

Islets derived from human embryonic stem cells and xenotransplantation, whereby transplantation of islets from a non-human animal source into a human recipient, offer a potentially unlimited supply of islets and is an area of active research (S28).

Finally, technological advances with hybrid closed-loop AID systems which automate basal insulin delivery but are not advanced enough to cover mealtime insulin requirements are now available but require significant user input; anticipated trials comparing ITA versus sensor augmented pump therapy are awaited.

Follow-on studies will be important to ascertain the impact these therapies have on both overall glycaemic control particularly hypoglycaemia and awareness of hypoglycaemia, glycaemic stability, QoL measures and the impact on microvascular and macrovascular disease in the longer term.

5 | CONCLUSION

Islet transplantation alone is indicated in people with T1D with SH and IAH where insulin therapy has been intensified and where there are no contraindications to immunosuppression. Metabolic outcomes show improved glycaemic control, reduced hypoglycaemia with improved awareness of hypoglycaemia, diminished glycaemic variability with less dependence on insulin and improved QoL. Evidence suggests that islet transplantation confers benefits on microvascular endpoints including retinopathy and neuropathy. Effects on renal function indicate a nephrotoxic impact of immunosuppressive medication in the short term, but in the longer term, renal function appears to stabilise. For those with coexisting renal transplants, nephropathy outcomes and macrovascular benefits have been shown to be comparable with those receiving SPK. Long-term macrovascular outcomes are an area where prospective studies are needed, but surrogate markers of cardiovascular disease are available and show improvements post-islet transplantation. In the future, as both adjuvant cell therapies as well as insulin pump and sensor technologies advance, there will be opportunities to consider these alternatives in suitable individuals.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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