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Invited Review

β-Cell and renal transplantation options for diabetes

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Abstract

Despite major advances in structured education, insulin delivery and glucose monitoring, diabetes self-management remains an unremitting challenge. Insulin therapy is inextricably linked to risk of dangerous hypoglycaemia and sustained hyperglycaemia remains a leading cause of renal failure. This review sets out to demystify transplantation for diabetes multidisciplinary teams, facilitating consideration and incorporation within holistic overall person-centred management. Deceased and living donor kidney, whole pancreas and isolated islet transplant procedures, indications and potential benefits are described, in addition to outcomes within the integrated UK transplant programme.

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Introduction

A century after the introduction of insulin therapy, advances in the understanding of insulin action and its biosynthesis have enabled production of increasingly physiological insulin analogues which, coupled with improved methods of insulin delivery including continuous subcutaneous insulin infusion pumps and continuous glucose monitoring, have fostered improved glucose control and overall well-being [1–3]. Nevertheless, diabetes self-management with conventional therapy remains an unremitting life-long burden, with diabetic retinopathy developing in the majority and diabetes remaining a leading cause of blindness and non-traumatic lower limb amputation [4]. Some 20–40% of people with type 1 diabetes develop diabetic nephropathy and diabetes is the most common cause of end-stage renal disease, accounting for up to 30% of all people on dialysis [5]. Type 1 diabetes is associated with an increased absolute risk of major cardiovascular disease events which, over the age of 45 years, are observed at a rate similar to a matched general population 10–15 years older [6]. Proteinuria in both type 1 and type 2 diabetes is associated with a very high incidence of major cardiovascular events. Risk increases with nephropathy progression in type 1 diabetes evidenced by a three- and 18-fold greater all-cause standardized mortality ratio with microalbuminuria and end-stage kidney disease, respectively, when compared with age-matched controls [7].

Glucose variability leading to significant hypoglycaemia remains the limiting factor to straightforward achievement of sufficiently tight control to prevent complications of chronic high glucose. Severe hypoglycaemia is one of the most feared complications of diabetes and its treatment with insulin [8]. Risk increases with diabetes duration, affecting around 50% of people each year with type 1 diabetes for more than 15 years and may also be experienced by people with type 2 diabetes on sulphonylurea treatment or insulin [9].

Here, we review the currently available transplant procedures for those with diabetes, together with the indications and outcomes for renal and β-cell replacement alone and in combination. We reflect on potential approaches for optimal integration within holistic diabetes care pathways.

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Renal transplant procedure and complications

Renal transplantation was first performed during an era predating dialysis. In 1954, Joseph Murray working in Boston performed the first renal transplant between 23-year old monozygotic twins – the world's first living donor transplant of any organ. Good outcomes were observed with recipient survival for 8 years. Murray undertook the first allogeneic living donor renal transplant in 1959 and deceased donor transplant in 1962 [10]. Renal transplantation is now the most commonly performed transplant, with activity in 102 countries [11].

Transplantation is performed under general anaesthetic and takes 2–3 h. Rates of living donation have increased remarkably over the past two decades, as morbidity of donation has been reduced by performing it laparoscopically. A single kidney is sufficient to provide good renal function in healthy individuals. A renal transplant is placed heterotopically in the right or left iliac fossa, with native kidneys left *in situ* unless simultaneous nephrectomy is indicated for

What's new?

- Kidney transplantation for those with diabetes and end-stage renal failure dramatically reduces mortality compared with dialysis.
- Best long-term survival is achieved following simultaneous pancreas kidney transplantation or live donor kidney transplant.
- Islet transplantation can prevent recurrent life-threatening hypoglycaemia and restore optimal overall glucose control in type 1 diabetes.
- This review is targeted at the diabetes multidisciplinary team to instil confidence in supporting early access to transplantation and providing well-informed ongoing care for all suitable recipients.
- The international evidence base is reviewed and comparative UK outcome data for all renal and β-cell replacement modalities are provided.

symptomatic disease (recurrent infection/pain) or to create more space in polycystic kidney disease. Arterial and venous anastomosis of the renal graft is to recipient iliac vessels. Immediate renal perfusion should be evident with subsequent ureteric anastomosis to the bladder. Ureteric stenting at the anastomosis is usually performed to reduce risk of stenosis and secondary infection. Vascular complications including renal arterial and venous thrombosis occur rarely, but often lead to graft loss [12]. Urological complications of obstruction or urine leak may occur (< 5%); fluid collections (haematoma/urinoma/abscess/lymphocele) are more common [12]. Discharge from hospital is usually within 7–10 days depending on whether the kidney starts to function immediately. Delayed graft function following an uncomplicated procedure is more common with non-heart beating donors following circulatory death (DCD), where the kidney is subjected to a greater ischaemic insult compared to a donor after brain stem death (DBD) [13,14].

Pancreas transplant procedure and complications

Successful pancreas transplantation leads to insulin independence and normoglycaemia. Working in Minnesota, Richard Lillehei performed the first pancreas transplant in 1966. Outcomes have improved steadily over time through refinements in surgical technique, donor selection and immunosuppression [15]. Relatively high perioperative risk mandates demonstration of adequate cardiovascular fitness, usually assessed by stress cardiac imaging/cardiopulmonary exercise testing before listing. The pancreas is procured from a DBD/DCD donor and transported on ice in preservation solution to the recipient hospital. A small number of living donor segmental pancreas transplants have also been performed for highly sensitized individuals where the risk of dying on the waiting list is high. The native pancreas, continuing to fulfil its exocrine function, is left *in situ* and the donor pancreas is implanted in the pelvis. Arterial anastomosis is usually to the common iliac artery with venous drainage via the common iliac vein, inferior vena cava or superior mesenteric/portal vein. Portal venous drainage is associated with reduced systemic hyperinsulinaemia and lower circulating free cholesterol, but physiological importance is unclear with systemic venous drainage favoured exclusively for UK transplants. Exocrine drainage of the pancreatic duct may be to the bowel or bladder, which carry respective risks of anastomotic leak/acidosis or recurrent urinary tract infection/reflux pancreatitis [15]. Although bladder drainage allows graft monitoring through urinary amylase, with a fall indicating potential graft rejection, up to 25% require conversion to enteric drainage due to intractable urinary tract symptoms, leading to increasing preference for enteric drainage [15]. Cardiovascular events are the commonest cause of early mortality but can be reduced significantly by meticulous work-up. Other significant complications include portal venous thrombosis, anastomotic leak, graft pancreatitis (higher after DCD transplantation) and infection [15,16]. A period of monitoring in a critical care unit is anticipated with insulin independence routinely achieved and discharge 1–2 weeks after an uncomplicated procedure.

Islet transplant procedure and complications

Islet transplantation is a minimally invasive procedure usually performed under local anaesthetic. This was first performed clinically in Minnesota in 1974, with seminal demonstration of the potential for attaining insulin independence with the 'Edmonton protocol' published in 2000 [17,18]. Islets comprise 1–2% of pancreatic mass and are isolated and purified from the exocrine pancreas following enzymatic digestion of a deceased donor organ [17]. In the UK, organs are procured by the National Organ Retrieval Service and transported to the on-call islet isolation facility. Following isolation and 24-h culture, islet preparations are released for clinical transplantation and transported by road to the recipient centre, provided they meet minimum criteria: adequate islet mass; viability > 70%; purity > 50%; and negative endotoxin, Gram stain and microbiological culture results [19,20]. Islet mass is reported as the number of equivalents (IEQs) relative to a mean islet diameter of 150 μm [19]. Islets are infused into recipient portal vein following percutaneous transhepatic cannulation (or in some centres via a mini-laparotomy) and are revascularized over time via collateral blood vessels from the hepatic artery. Activation of coagulation/complement cascades in the instant blood-mediated inflammatory response leads to a considerable loss of islets during the peri-transplant period [21]. With peri-transplant heparin anticoagulation, anti-inflammatory agents and optimal glycaemic control, it is estimated that

75% of transplanted islets successfully engraft [21]. Many recipients require two transplants on different occasions, although some centres transplant pooled islets from two or three donors (accounting for 10% of infusions worldwide) [22]. The main operative risks are portal vein haemorrhage and thrombosis, but both occur in < 5% of cases and have been reduced further by sealing the liver tract on catheter tip withdrawal, reduction in the volume of islet tissue infused, routine portal pressure monitoring and careful post-transplant heparin anticoagulation [21]. A short-lived transaminitis may be observed post procedure [22].

Immunosuppression

All allografts require life-long immunosuppression to prevent graft loss through acute rejection. In addition to suppressing alloimmunity, immunosuppression reduces the risk of recurrent autoimmunity to transplanted islet antigens in pancreas or islet recipients with type 1 diabetes [15]. Induction immunosuppression is usually with a T-cell depleting agent (anti-thymocyte globulin; alemtuzumab) or interleukin-2 receptor antagonist (basiliximab) with or without an anti-inflammatory tumour necrosis factor (TNF)-α inhibitor (etanercept). Maintenance steroids are usually used in kidney transplantation alone (KTA), with most common immunosuppressive regimens for pancreas and islet recipients comprising a calcineurin inhibitor (usually tacrolimus) combined with an anti-metabolite such as mycophenolate mofetil or azathioprine. In some cases, an mTOR inhibitor such as sirolimus is combined with low-dose tacrolimus [22]. Contraindications to immunosuppression include active infection and malignancy. To exclude these, careful screening of donors and recipients is essential. Immunosuppression for renal transplantation is associated with a threefold increased risk of malignancy and malignancy-related mortality in 4% of recipients [16,23]. Non-melanomatous skin cancer is the most common malignancy observed. Post-transplant lymphoproliferative disease is a risk that is increased 20-fold by Epstein–Barr virus mismatch of a sero-positive donor to negative recipient [23]. In addition, immunosuppression increases the risk of (particularly atypical) infection including cytomegalovirus (CMV) and polyomaviruses [23].

UK provision of renal, pancreas and islet transplantation

There are 24 renal transplant centres across the UK receiving deceased organs through the National Kidney Allocation Scheme [14]. DBD and DCD kidneys are allocated to recipients on the waiting list through a points-based allocation scheme that considers waiting time, human leukocyte antigen (HLA) match and age, donor-recipient age difference, location, HLA-DR and HLA-B homozygosity and blood group [14]. High-risk DBD kidneys account for up to 40% of DBD transplanted kidneys and may also be considered for a dual adult kidney transplant to increase the functioning nephron dose [24]. In addition to direct donation by a relative or friend to a named recipient, kidneys for living donor transplantation are allocated through paired, pooled or altruistic donor schemes [13].

There are eight pancreas-transplanting centres and seven islet-transplanting centres in the UK, located geographically to provide access to both procedures for all potential recipients (Fig. 1) [25]. Islets are isolated in one of three isolation centres and transported to the recipient centre. The UK National Pancreas Allocation Scheme was introduced in 2010 and provides a shared national waiting list for vascularized pancreas and islet transplantation with deceased pancreata allocated to the highest ranked ABO-compatible recipient according to a points-based allocation system [26]. Similar to the renal transplant scheme, priority is based on waiting time, HLA match, age, distance between donor and recipient/islet isolation centre and also considers HLA sensitization, dialysis status and donor BMI. Within the points score, a pancreas from a donor with a BMI > 28 kg/m^2 is preferentially offered for islet transplantation to maximize isolated islet yield and a donor with a BMI < 23 kg/m^2 is preferentially offered for vascularized pancreas transplantation. In addition, islet recipients with graft function awaiting a second transplant are given priority for a second islet graft towards transplantation of a total islet mass of over 10 000 IEQ/kg recipient body weight within a median time of 3 months, with the goal of attaining maximal islet engraftment and optimal initial graft function [26].

Renal transplant indications and outcomes

International perspective

Renal replacement therapy with dialysis improves survival [27]. However, mortality rates on dialysis remain 20-fold greater than in the general population, with risk increasing disproportionately in the presence of other co-morbidities (hypercholesterolaemia, hypertension and higher BMI) [28]. Survival is significantly better after kidney transplantation. US registry data show that the adjusted 5-year survival in people with diabetes who received a kidney from a deceased or living donor in 1995 was 75% and 83%, respectively, far higher than the 29% 5-year survival of those with diabetes who started dialysis in the same year [29].

Although survival in people with diabetes and a kidney graft is worse than in those without diabetes, mainly as a result of a higher prevalence of pre-transplant cardiovascular disease, the gain in life expectancy after renal transplantation is proportionally much higher so that transplantation is the first-choice option, particularly in those with diabetes [27].

Renal transplantation provides survival benefit across all ages transplanted [28] with a 48–82% reduction in long-term mortality rate and estimated 10-year increase in life-

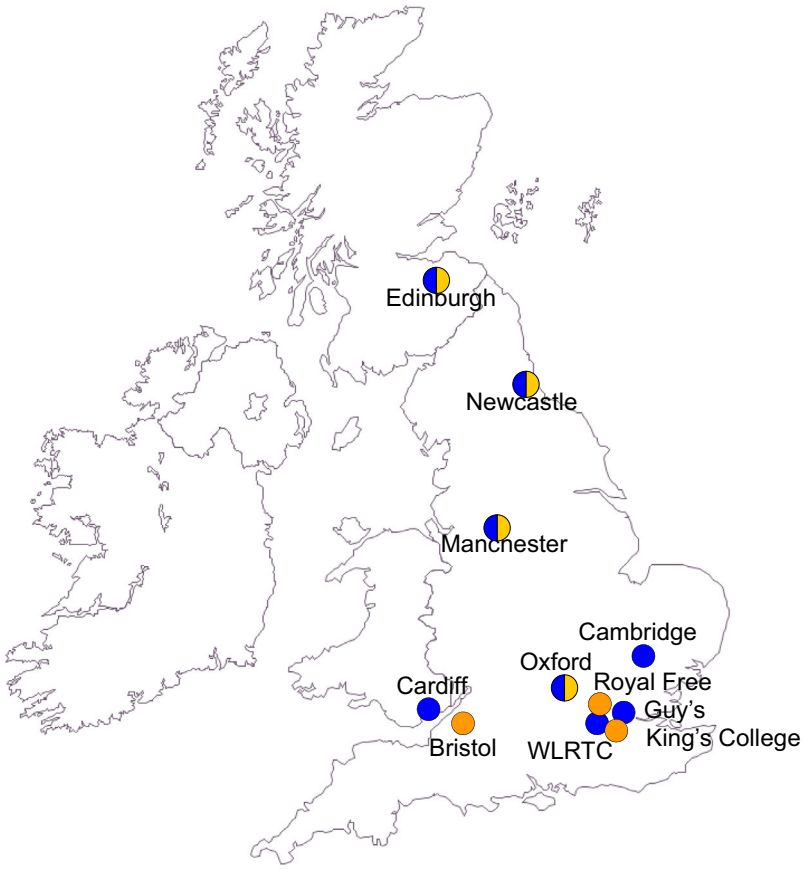

FIGURE 1 UK Pancreas and Islet Transplant Centre map. Yellow, islet transplant centre; blue, pancreas transplant centre (WLRTC – West London Renal and Transplant Centre); islet isolation facilities are co-located with transplant centres in King's College London, Oxford and Edinburgh.

expectancy [27]. A survival benefit over dialysis is observed even with transplantation of marginal kidney grafts with an adjusted annual death rate of 4.7% and estimated life-expectancy of 20 years compared with 6.3% and 15 years for individuals on the transplant waiting list [30]. Renal transplant recipient and graft survival outcomes are maximal with kidneys from living donors [31]. However, despite improved medium- and long-term survival, there is an increased risk of early myocardial infarction and mortality within 6 months of renal transplantation, which in addition to standard risk factors, is worsened by delayed graft function and graft failure [28]. Early cardiovascular events are further increased in renal transplant recipients with diabetes, underlining the importance of pre-transplant cardiovascular risk management including smoking cessation [28].

Any time spent on dialysis prior to KTA or simultaneous pancreas kidney (SPK) transplant is associated with reduced person and graft survival outcomes, with further detrimental impact with increased dialysis duration. Pre-emptive transplantation before dialysis improves outcomes after both KTA and SPK transplantation [32].

Renal transplant improves long-term cardiac function and quality of life (QoL) [28,30]. Correction of uraemia may improve peripheral neuropathy but no improvement in autonomic neuropathy has been confirmed [33].

UK indications

In the UK, renal transplantation is the gold standard for treatment of end-stage renal failure of any cause [34]. Suitable individuals can be listed on the active waiting list within 6 months of their anticipated dialysis start date. Obesity is not an absolute contraindication to renal transplantation as a survival benefit is still observed with a recipient BMI > 30 kg/m^2. However perioperative cardiovascular risk should be considered, with coronary artery disease screening and exclusion of those at highest risk [34].

UK outcomes

Over 3000 adult kidney transplants were performed in the UK in the financial year 2017/2018 (42% DBD; 29% DCD; 29% living donor) [24]. Living donor kidney transplants were almost three times more likely to occur before dialysis commencement, despite pre-emptive listing in half of all cases. Median waiting time for a deceased donor kidney was

755 days, with median of 3.1 years on dialysis, differing between blood groups with blood group O recipients waiting longest. For adults with diabetes as the primary indication for kidney transplantation between 1 April 2008 and 31 March 2018, 1- and 3-year recipient survival following first living donor kidney transplants was 98% and 94%, with comparative outcomes for first deceased donor kidney transplant of 94% and 86%, respectively (Fig. 2a). Graft survival at 1 and 3 years post-living donor kidney are 98% and 97%, compared with 93% and 89%, respectively, following deceased donor transplantation (Fig. 2c). Ten-year patient survival from listing for deceased donor kidney transplant is 75% [24].

Simultaneous pancreas kidney transplant indications and outcomes

International perspective

SPK transplantation is considered for people with insulin-treated diabetes and good cardiovascular fitness eligible for renal transplantation. Between 1966 and 2014, more than 48 000 pancreas transplants were performed world-wide and over 1000 pancreas transplants are performed in the USA each year [16]. Pancreas transplant outcomes have improved steadily due to iterative refinements including careful donor selection, optimized pancreas procurement, minimizing cold preservation shortening overall cold ischaemic time, and modifications to immunosuppression regimens [35]. Outcomes are better in medium- to high-volume transplanting centres [36]. Simultaneous transplantation of a pancreas and kidney retrieved from the same deceased donor accounts for over 90% of pancreas transplant activity [16]. Early mortality has been higher than after KTA because of higher procedural morbidity and complications associated with a dual transplant [32]. The international registry reported 97% 1-year recipient survival between 2010 and 2014, with cardiovascular/cerebrovascular events (31%) and infection (24%) the leading causes of death. Ongoing graft function is the greatest predictor of recipient survival, with relative risk of death increasing 18-fold and threefold with a failed SPK-kidney and failed SPK-pancreas graft, respectively [16]. Pancreas graft failure has classically been defined as return to insulin therapy, requirement for graft pancreatectomy or death. Pancreas graft survival after SPK is better than solitary pancreas transplantation [16]. Successful pancreas transplantation results in insulin independence without hypoglycaemia [37]. Excellent glycaemic control with a mean HbA_{1c} of 34 mmol/mol (5.3%) has been reported for up to 10 years post SPK transplant [38]. The survival benefit of the improved glycaemic control attained with long-term pancreas graft function following SPK transplant is observed after 10 years with a reduced cardiovascular mortality risk observed compared with living donor KTA [32,39, reviewed in 40].

There is some evidence that sustained optimal graft function associated with pancreas transplantation can improve microvascular complications of diabetes [15,41] (reviewed in [40]). Studies have demonstrated improvement/stabilization of neuropathy (peripheral and autonomic function) and retinopathy in SPK recipients, although advanced retinopathy already associated with visual loss clearly cannot be reversed by β-cell replacement and stable retinopathy is preferred at the time of listing to minimize risk of worsening during the early postoperative period [15]. Improved cardiovascular outcomes are also observed with SPK in comparison with KTA [32] (reviewed in [40]). Sustained QoL improvement is observed following both

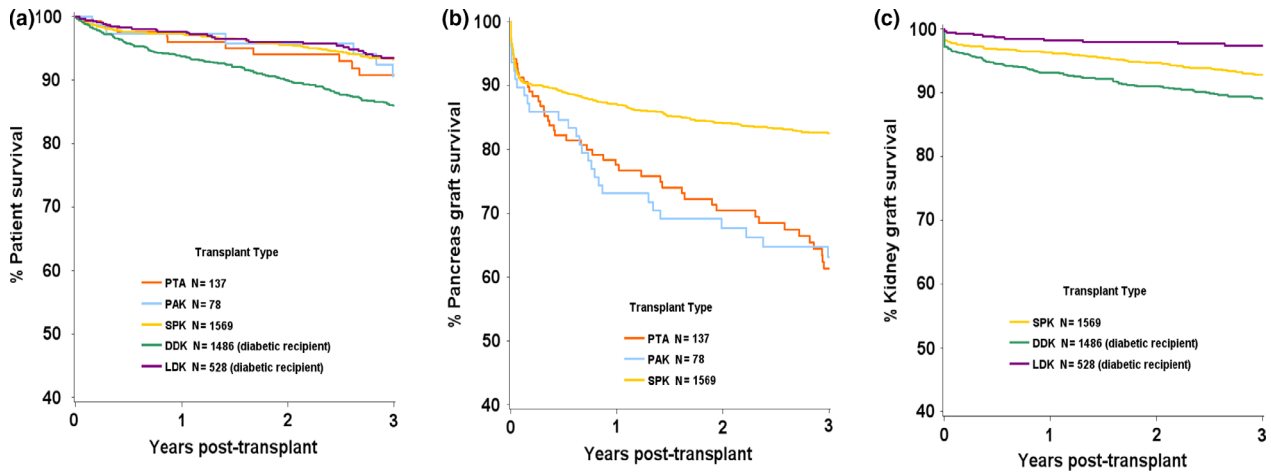

FIGURE 2 UK solid organ transplant outcomes. Three year recipient (a), pancreas (b) and kidney (c) survival after first pancreas or first kidney (recipients with diabetes) transplant from 1 April 2008 to 31 March 2018 (Kaplan–Meier plot). Orange line, pancreas transplant alone (PTA); blue, pancreas after kidney (PAK); yellow, simultaneous pancreas kidney (SPK); green, deceased donor kidney (DDK) recipient with diabetes; purple, live donor kidney recipient with diabetes.

Table 1 UK listing criteria for β-cell transplantation

Simultaneous pancreas kidney (SPK)	Simultaneous islet kidney (SIK)
• Type 1 diabetes; or insulin-treated type 2 diabetes with BMI ≤ 30 kg/m^2 • End-stage renal failure with GFR ≤ 20 ml min^{-1} 1.73m^{-2} or on dialysis	• Type 1 diabetes or insulin-treated diabetes secondary to pancreatectomy/pancreatitis • End-stage renal failure with GFR ≤ 20 ml min^{-1} 1.73m^{-2} or on dialysis
Pancreas after kidney (PAK)	Islet after kidney (IAK)
• Type 1 diabetes; or insulin-treated type 2 diabetes with BMI ≤ 30 kg/m^2 • Previous kidney transplant with maintained function on immunosuppression	• Type 1 diabetes or insulin treated diabetes secondary to pancreatectomy / pancreatitis with confirmed C-peptide negativity • Previous kidney transplant with maintained function on immunosuppression • Severe hypoglycemia within the last 24 months or HbA_{1c} ≥ 53 mmol/mol (7.0%)
Pancreas transplant alone (PTA)	Islet transplant alone (ITA)
• Type 1 diabetes; or insulin-treated type 2 diabetes with BMI ≤ 30 kg/m^2 • Disabling hypoglycemia with at least two severe hypoglycemia events within the last 24 months	• Type 1 diabetes or insulin treated diabetes secondary to pancreatectomy/pancreatitis with confirmed C-peptide negativity • Disabling hypoglycemia with at least two severe hypoglycemia events within the last 24 months

KTA and SPK transplantation [35]. Although QoL measures are difficult to compare between KTA and SPK, given the selection bias for baseline cardiovascular fitness and age (SPK recipients are generally younger) [15], there is evidence that maintained insulin independence following SPK-kidney graft failure has been associated with less QoL decline compared with maintained kidney function and pancreas graft failure [35].

Increasingly, pancreas transplants are being performed in individuals with insulin-treated type 2 diabetes with lower BMI, accounting for ~ 9% of SPK procedures performed internationally [16].

UK indications

SPK is indicated for people with insulin-treated diabetes and renal failure (Table 1). Potential recipients are assessed by the multidisciplinary team and can be listed when GFR is ≤ 20 ml min^{-1} 1.73 m^{-2} or on dialysis [42]. Individuals with adequate cardiovascular fitness may be considered, including suitable individuals with insulin-treated type 2 diabetes and BMI < 30 kg/m^2 [42].

UK outcomes

In total,1662 SPK transplants were performed in the UK between 2008 and 2018 [25]. The median waiting time for a pancreas transplant in the UK was 342 days, and 28% of pancreata were from DCD in 2017/2018 [25]. At 1 and 3 years after first SPK transplant, recipient survival is 97% and 93% (Fig. 2a), pancreas graft survival is 87% and 83% (Fig. 2b) and kidney graft survival 96% and 93% (Fig. 2c). One-year pancreas graft survival after SPK is comparable in type 1 (88%; $n = 1452$) and type 2 diabetes (84%; $n = 65$), although numbers in the latter group remain small [NHS Blood and Transplant (NHSBT) data 2007–2017].

\Pancreas after kidney transplant indications and outcomes

Pancreas after kidney (PAK) transplantation is performed to achieve freedom from exogenous insulin, improving recipient QoL while attaining optimal glycaemic control and protecting the renal allograft from diabetic nephropathy. In the USA, early living donor kidney transplant followed by deceased donor PAK is often considered more favourably given long waiting times for SPK [32]. A previous DBD kidney graft has been shown to reduce patient survival following PAK, demonstrating the association between organ quality and outcome [16]. Some recipients may see a small decline in renal function after PAK but this is not detrimental to overall survival.

UK indications

In the UK, PAK transplantation is considered for recipients with insulin-dependent diabetes following a living or deceased donor renal transplant with good renal function and sufficient cardiorespiratory fitness (Table 1). Potential candidates with type 2 diabetes must be insulin-treated with BMI < 30 kg/m^2 [42].

UK outcomes

The number of PAK transplants is small compared with SPK. One- and 3-year patient survival is 97% and 91% (Fig. 2a) and pancreas graft survival 73% and 63%, respectively (Fig. 2b) [25].

Pancreas transplant alone indications and outcomes

Pancreas transplant alone (PTA) is performed internationally to stabilize control and achieve insulin independence in people with highly unstable glucose leading to life-threatening severe hypoglycaemia and/or ketoacidosis, or with progressive microvascular complications. There is evidence of improved diabetic nephropathy following PTA with sustained graft function, as demonstrated by regression and reversal of histological changes (reduced glomerular and tubular basement membrane thickness) on serial kidney biopsies at 10-years post transplant [35,43]. Stabilization of diabetic retinopathy has been demonstrated [35,40]. A decline in renal function secondary to calcineurin inhibitor use may be seen, which supports consideration of SPK in those with marginal GFR. This is a difficult area because, in the UK, people can only be listed for SPK once GFR is < 20 ml min^{-1} 1.73 m^{-2} and in those with GFR < 60 ml min^{-1} 1.73 m^{-2} a renal transplant will often ultimately become necessary after PTA [15]. Reduced progression of neuropathy, improved neuropsychological function and regression of atherosclerosis following pancreas transplantation have been described [15,35,40,44]. PTA can improve diabetes-specific QoL and fear of hypoglycaemia despite short-term procedure-related pain and immunosuppression side-effects [45]. US PTA outcomes between 2010 and 2014 show 97% patient survival and 86% graft function at 1-year post transplant, with risk of technical failure similar to SPK [16]. PTA graft survival of > 70% at 5 years has been reported in a single Italian centre [46].

UK indications

In the UK, PTA is indicated solely for recurrent severe hypoglycaemia complicating insulin-treated diabetes (Table 1) [42]. Diabetic ketoacidosis alone is not an indication due to concerns over the likelihood of underlying incomplete adherence to insulin/optimal self-management. Evidence-based management of progressive microvascular complications requires multimodality interventions, without sufficient evidence at present to justify the additional mortality and morbidity of pancreas transplantation accompanied by life-long systemic immunosuppression. PTA is justified as a life-saving intervention for those with the most severe hypoglycaemia, however. At least two events requiring assistance within the last 2 years are required for listing. Renal function must be adequate [42]. Individuals with type 2 diabetes may be considered if BMI is < 30 kg/m^2.

UK outcomes

At 1 and 3 years after PTA, UK patient survival was 96% and 91% (Fig. 2a), with pancreas graft survival 78% and 61% (Fig. 2b), respectively [25]. Graft survival is defined as insulin independence which is associated with resolution of severe hypoglycaemia in virtually all cases.

Islet transplantation indications and outcomes

International perspective

Islet transplantation is performed to reduce glycaemic variability and protect against severe hypoglycaemia. A number of centres transplant with insulin independence as a primary goal, often necessitating repeated infusions from several donors, although this is infrequently achieved following a single transplant procedure [18,20–22]. The level of stimulated C-peptide in a mixed-meal tolerance test challenge following islet transplantation is intrinsically associated with reduced glycaemic variability, improved time in a normoglycaemic range and less hypoglycaemia exposure [47]. Even low-level islet function is sufficient to prevent severe hypoglycaemia, although optimal graft function is necessary to normalize time in range and deliver insulin independence [48]. Where centres have good access to high-quality donor organs enabling rapid repeated transplantation until insulin independence is achieved, long-term outcomes have been particularly good [49,50]. In the Lille programme, delivering two or three transplants within 67 days led to optimal primary graft function in 64% associated with maintained insulin independence and $HbA_{1c} \leq 48$ mmol/mol (6.5%) in 57% of recipients at 3.3 years post transplantation [50]. The Collaborative Islet Transplant Registry, collating activity from many international centres, reported a 44% rate of insulin independence and 83% graft survival at 3 years following islet transplantation [22]. The primary goal of islet transplant in a recent multicentre US trial, undertaken towards Food and Drug Administration (FDA) approval, was attainment of $HbA_{1c} < 53$ mmol/mol (7.0%) without severe hypoglycaemia. This end-point was met in 88% and 71% recipients at 1 and 2 years, respectively [51]. The TRIMECO multicentre randomized controlled trial evaluating metabolic outcomes of islet transplantation vs. medical therapy achieved $HbA_{1c} < 53$ mmol/mol (7.0%) / absence of severe hypoglycaemia in 84% of islet recipients compared with none on conventional therapy [52].

Islet after kidney (IAK) transplantation is performed primarily to improve glycaemic control in renal transplant recipients, particularly if hypoglycaemia continues to be

problematic post KTA. Numbers are lower than islet transplant alone (ITA) but comparable outcomes have been reported [22].

A crossover study by Thompson *et al*. [53] demonstrated reduced progression of microvascular complications (nephropathy and retinopathy) with a trend to improved nerve conduction velocity post islet transplant in comparison with follow-up with intensive medical treatment alone. Improved cardiovascular disease status through a reduction in carotid intimal thickness has also been reported [54]. Improved diabetes-specific QoL and reduced fear of hypoglycaemia has been confirmed post islet transplantation [55].

UK indications

The NHS islet transplant service was commissioned in 2008. ITA is indicated for type 1 diabetes or diabetes secondary to pancreatectomy/pancreatitis complicated by recurrent severe hypoglycaemia (Table 1) [42]. Individuals being considered for IAK transplantation should have good renal graft function and severe hypoglycaemia; or labile glucose levels with HbA_{1c} > 53 mmol/l [42]. C-peptide negativity should be confirmed as a requirement for ITA/IAK listing. Suitable recipients are relatively insulin sensitive (total daily insulin dose < 0.7 units/kg) with good renal function and without macroalbuminuria. Assessment includes liver ultrasound to assess liver steatosis/fibrosis/cirrhosis and exclude haemangiomata because this would necessitate a planned needle-track approach to percutaneous transhepatic portal vein cannulation or consideration of a mini-laparotomy approach.

UK outcomes

In total, 243 islet transplants in 144 recipients have been performed in the UK between 1 April 2008 and 31 March 2018, 85% as ITA [25], with 37% of the recipients receiving a single transplant and 63% receiving at least two. Initial data confirmed successful prevention of recurrent severe hypoglycaemia and comparable outcomes with islets isolated locally or transported to the transplant centre, important for programmes developing an equitable hub-and-spoke infrastructure [20]. Since introduction of the national Pancreas Allocation Scheme in 2010 [26], median waiting time on the active islet transplant waiting list is around 14 months. One- and 3-year patient survival after ITA/IAK in 2008–2018 was 100% and 99% (Fig. 3a) with graft survival, defined as restoration of C-peptide positivity (> 50 pmol/l) after a routine followed by priority graft 96% and 79% (Fig. 3b), respectively. Graft failure rate was higher in those receiving only a single graft, underlining the importance of delivering two consecutive transplants in the majority of recipients. At 12 months post transplant, the median annual severe hypoglycaemic event rate (in all recipients of one or more islet transplants) was reduced to zero with HbA_{1c} of 51 mmol/mol (6.8%) [25]. Median daily insulin dose was reduced by 31%, although the majority remained on exogenous insulin, maintaining optimal glucose stability without dangerous hypoglycaemia [25,56].

Simultaneous islet kidney transplantation

For a simultaneous islet kidney (SIK) transplant, kidney and pancreas are retrieved from the same donor with renal transplantation on the day of retrieval followed by islet transplantation after isolation and culture. SIK is associated with reduced complications including (re)laparotomy rate compared with SPK. In one prospective cohort, mean HbA_{1c} reduced from 64 mmol/mol (8.0%) pre-transplant to 48 mmol/mol (6.5%), remaining significantly reduced until Year 7 post transplant [57].

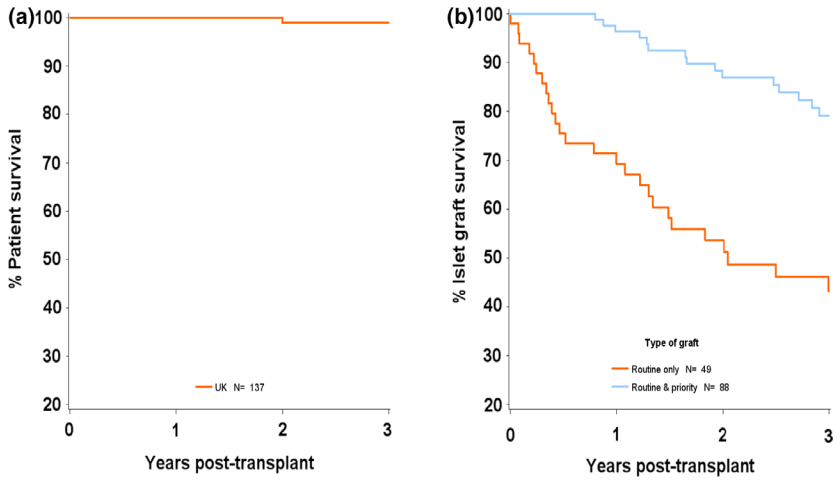

FIGURE 3 UK islet transplant outcomes. Three-year recipient (a) and islet (b) survival after first islet transplant alone (ITA) or islet after kidney (IAK) transplant from 1 April 2008 to 31 March 2018 (Kaplan–Meier plot). (b) Orange line, single islet transplant; blue line, two consecutive islet transplants.

UK indications

SIK transplantation has recently been made available in the UK for individuals with type 1 or post-pancreatectomy diabetes having a GFR < 20 ml min^{-1} 1.73m^{-2} who are unfit for SPK transplant (Table 1). Severe hypoglycaemia is not a requirement for listing; however, potential recipients should have suboptimal glycaemic control to attain an added glycaemic benefit from the transplanted islets [42]. Although total SIK transplant numbers are currently small, numbers listed are increasing and an NHSBT Pancreas Advisory Group (PAG) working group is being established to further consider best practice and optimal follow-up of this group.

Integration of transplantation into holistic type 1 diabetes management

Renal failure

While it is clearly imperative that assessment and planning for renal transplantation is undertaken by the multidisciplinary specialist renal team, the diabetes team have an important role in facilitating early referral, given the benefits of pre-emptive transplantation prior to the need for dialysis [27,34]. In view of the very high risk of major vascular events and overall mortality, early referral is critical to militate against insufficient cardiovascular fitness for transplantation [15,28]. The diabetologist should understand the potential benefits of early living donor kidney transplantation leading to improvement in overall well-being, which may also help stabilize glycaemic control through improved renal function in addition to reduced nausea, gastric stasis and fatigue [15,33].

Equally an understanding that pancreas graft survival may be best following SPK, in comparison with PAK [15,32] from a separate donor, may lead to support for this combined approach, particularly when potential liberation from the unremitting burden of exogenous insulin therapy with intensive blood glucose monitoring is of primary importance to the person with diabetes; and/or when the recipient and diabetes multidisciplinary team consider that achieving good control post transplantation will continue to be unattainable despite improved well-being [34]. Given the greater need for cardiopulmonary fitness in the SPK group, early referral (ideally before the age of 50 years) becomes even more critical, supported by the potential for SPK listing with significant remaining renal function (GFR < 20 ml min^{-1} 1.73 m^{-2} in the UK) [15,42] in order to gain maximum benefit with lowest risk. If recurrent severe hypoglycaemia is truly life-threatening despite optimal medical therapy, listing for SPK with an even higher GFR can be considered in those rapidly progressing towards end-stage renal failure, although this is highly exceptional and requires agreement from the national clinical governance group (NHSBT PAG). Nevertheless, specialist teams and, in our experience, people with diabetes welcome an opportunity to properly understand and discuss all possibilities at an early stage, even if transplantation turns out not to be the best option.

Although evidence for long-term islet function and improved recipient or renal graft survival following SIK is still awaited, we believe that SIK should be considered only for those with severe hypoglycaemia, impaired awareness of hypoglycaemia or at least highly labile glucose levels – again underlining the role of the diabetologist in ensuring that all conventional glucose management options [1,58] have been fully explored and gauging the need for urgent β-cell replacement in those being assessed for renal transplantation.

Individuals with type 2 diabetes are rarely suitable for pancreas transplantation, even if insulin independence can initially be attained [59]. When diabetes is associated with significant insulin resistance, associated metabolic risk factors including hypertension and hyperlipidaemia, and non-alcoholic fatty liver disease (which can deteriorate further after islet transplantation) may remain uncontrolled following β-cell replacement therapy, recurrent high HbA_{1c} may recur despite good graft function and ultimately other diabetologist-led options including bariatric surgery should also be considered.

Following pancreas transplantation, ongoing coordination of care by the recipient's core diabetes team remains essential even for those off insulin. HbA_{1c}, glucose and C-peptide should be monitored regularly within the transplant or diabetes services to detect early changes in graft function necessitating full assessment for potential underlying graft rejection. Active screening for/follow-up of diabetic retinopathy and diabetic foot disease remain imperative even when recipients may consider themselves as no longer having diabetes.

Severe hypoglycaemia

It is now clear that severe hypoglycaemia is not confined to those with intensively controlled glucose levels, being equally prevalent across the range of HbA_{1c} [8]. The need for careful assessment for impaired awareness of hypoglycaemia by validated questionnaire (Gold or Clarke scores) at least annually with record of severe hypoglycaemia events has been advocated by the National Institute of Health and Care Excellence (NICE) and is now widely recognized within specialist diabetes care pathways [60]. Sensitive and informed discussion around hypoglycaemia is critical as it has been reported that up to 82% of people with type 1 diabetes rarely/never report non-severe hypoglycaemia to their healthcare team [61].

Investigations of possible reversible causes of hypoglycaemia, including coeliac disease, Addison's disease and autoimmune thyroid disease, must be considered as part of routine screening even if diabetes is long-standing [1,60], as demonstrated by the new diagnosis of autoimmune coeliac and thyroid disease in 11 (9%) of new referrals with problematic hypoglycaemia to one islet transplant clinic [62].

NICE guidelines recommend regional hypoglycaemia services [60]. Given the growing convincing evidence that recurrent severe hypoglycaemia can be prevented in the majority by optimized structured education, insulin delivery and informed blood glucose monitoring [2], it is imperative that all affected by impaired awareness of hypoglycaemia and severe hypoglycaemia are able to access specialized services experienced in the management and support of complex type 1 and insulin-deficient type 2 diabetes [1]. Experience with and access to pump therapy and continuous glucose monitoring, including hybrid closed loop systems, is essential. Despite this, a minority continue to experience severe events, particularly if unable to use truly uninterrupted continuous glucose monitoring as this often provides 'technological' rather than physiological hypoglycaemia awareness with real risk of dangerous events whenever off sensor [58]. Indeed, we strongly recommend mandatory temporary basal insulin rate reductions during any time without sensor. To date, those with recurrent severe hypoglycaemia have largely been excluded from closed-loop trials. Moreover, with increased age and frailty (including visual loss, memory impairment, poor dexterity) insulin pump/continuous glucose monitoring/sensor-aug mented pump therapy may no longer be feasible. In addition, the subgroup of people with type 1 diabetes having low concern about but high risk of severe hypoglycaemia should be actively identified through careful assessment given the potential benefits from psycho-behavioural interventions [58].

It appears that there may be another subgroup with irreversible impaired awareness of hypoglycaemia and ongoing severe hypoglycaemia despite multimodality optimized conventional therapy. In the HypoCOMPaSS trial, continued episodes of severe hypoglycaemia were associated with established neuropathy [63]. Identification of those at highest risk allows early referral for a discussion with the transplant team, even though further exploration of medical options may be advocated initially. The need to avoid late referral is evidenced by three deaths due to hypoglycaemia on the islet transplant waiting list in the early years of the UK programme [20].

PTA offers the real potential of insulin independence but is associated with an unavoidable mortality risk and a 3-year graft survival of only 61% in the UK [25]. Sustained insulin independence should not be expected following ITA but, rather, prevention of recurrent severe hypoglycaemia without any significant mortality [25]. Ideally, individuals should consider both procedures in parallel and typically reach a firm decision to favour a whole organ transplant, cell transplant or continuation of conventional therapy. In those choosing to further pursue islet transplantation, all UK centres provide a formal psychologist assessment to ensure psychological fitness to proceed and that expectations are not unrealistic [42,58].

Renal transplant recipients

It is particularly important that recipients are actively reviewed by their diabetes team post renal transplant to discuss re-galvanization of overall self-management towards truly optimal glycaemic control without problematic hypoglycaemia. Strong motivation to maximize renal graft survival can be harnessed at this critical time-point towards stabilization/improvement/prevention of all micro- and macrovascular complications and maximal overall well-being. New treatment modalities including structured education, continuous subcutaneous insulin infusion and continuous glucose monitoring may be more actively considered [1,60]. PAK/IAK may have been planned by the transplant team, particularly after living donor kidney. If not, a relatively low threshold for referral to discuss the risks and potential benefits of these options should be considered in those with good renal function already on full immunosuppression [42].

Unified assessment of function following β-cell replacement

A fully reimbursed truly integrated pancreas and islet transplant programme providing equity of access to the best therapeutic option for all potential recipients is a key strength of national services in the UK and in other countries including Switzerland.

Until recently, definitions of graft function have, however, been very different for solid organ pancreas and isolated islet recipients, with failure defined as a return to exogenous insulin in the former group and complete loss of endogenous C-peptide in the latter. Nevertheless, it has become clear that goals for both procedures are in truth much better aligned – attainment of optimal glycaemic control without significant hypoglycaemia with or without insulin independence. When graft failure is not early and absolute in pancreas transplant

Table 2 Igls classification for β-cell replacement therapy [64]

β-Cell graft functional status	HbA_{1c} (mmol/mol) (%)	Severe hypoglycaemia events per year	Insulin requirement (unit/kg/day)	C-peptide	Treatment success
Optimal	≤ 48 (6.5)	None	None	> Baseline	Yes
Good	< 53 (7.0)	None	< 50% baseline and/or use of other glucose-lowering agents	> Baseline	Yes
Marginal	Baseline	<Baseline	≥ 50% baseline	> Baseline	No
Failure	Baseline	Baseline	Baseline	Baseline	No

recipients (through graft thrombosis or explant), it is now evident that many continue to maintain significant C-peptide and achieve excellent metabolic control despite a return to exogenous insulin [64].

In 2018, an international consensus group agreed unified definitions allowing true comparability of all forms of β-cell replacement – the Igls classification (Table 2) [64]. Optimal function is defined as remission of diabetes; good function as freedom from severe hypoglycaemia with HbA_{1c} < 53 mmol/mol (7.0%); and marginal function as maintained graft C-peptide with incomplete clinical benefit. These criteria provide a framework for an increasingly integrated approach to β-cell replacement with common goals [64].

Concluding comments

Renal replacement in end-stage renal disease is life-saving. β-Cell replacement may be transformative. However, until the advent of immunosuppression-free β-cell replacement, pancreas and islet transplantation will not be for all, but should be considered as part of integrated multidisciplinary team-led care providing stepwise management of diabetes complicated by recurrent hypoglycaemia and metabolic instability despite optimized medical approaches, or for those committed to immunosuppression through renal transplantation.

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Competing interests

None declared.

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