Pancreas and islet transplantation in diabetes

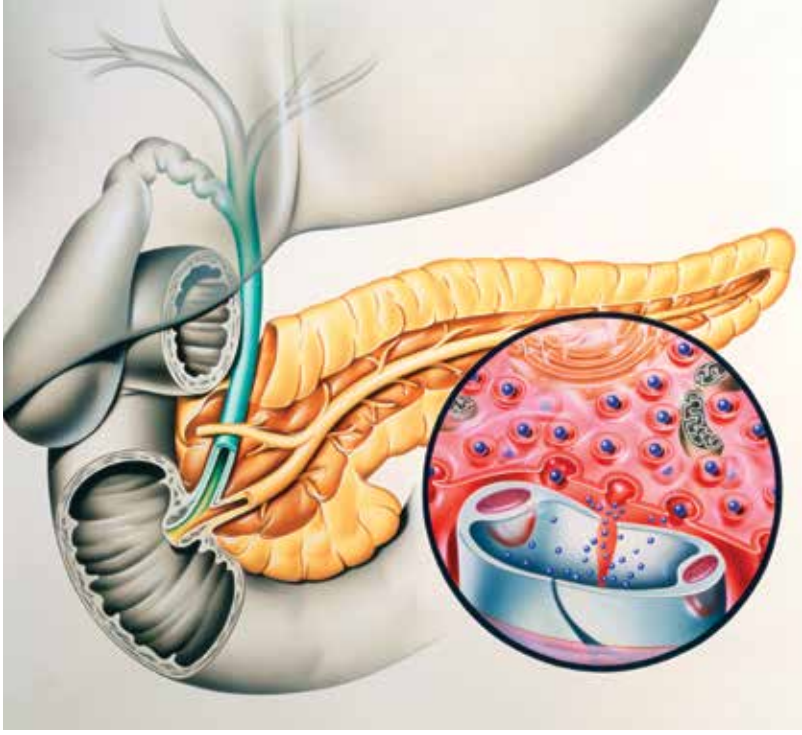
Who is eligible?

HEATHER BURNS BSc; **CHARMAINE CHEUNG** BSc; **JENNY E. GUNTON** MB BS, FRACP, PhD

Pancreas and islet transplantation offer recipients greatly improved quality of life and the possibility of a cure of diabetes. Both are associated with reduced mortality and diabetes-complications risks but they have very different suitability criteria. Suitable patients should be considered for assessment with consideration of the long-term burden of immunosuppression on the patient.

Key points

- **Pancreas and islet transplants offer eligible patients with type 1 diabetes improved quality of life.**
- **Whole pancreas transplantation in Australia is usually performed with a kidney transplant (simultaneous kidney-pancreas transplant; SKPT).**
- **SKPT has a high long-term success rate and improves kidney-transplant outcomes.**
- **Islet transplantation is a less invasive procedure suitable for select people with type 1 diabetes who have good renal function, and is very successful at ameliorating severe, recurrent hypoglycaemia.**
- **Both forms of transplantation require long-term immunosuppression, and the potential side-effects of these must be considered for each patient.**
- **If a patient is interested in having and may be suitable for a transplant, consider referring them for assessment.**



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Type 1 diabetes is a life-long condition that has increased risk of microvascular and macrovascular complications. Pancreas transplantation offers superior long-term control of blood glucose levels (BGL) by replacing the beta-cells lost in type 1 diabetes and is usually performed together with kidney transplantation. This therapy, called simultaneous kidney-pancreas transplantation (SKPT), offers both cure of diabetes and renal replacement therapy, with potential for an insulin- and dialysis-free life for patients. It can result in greatly improved quality of life, decreased acute and chronic complications associated with type 1 diabetes and kidney disease, and better long-term function of transplanted kidneys. In addition, patient life span and kidney-graft survival are extended and diabetes complications usually cease to progress, or may even improve slowly (Table 1).[1-6] Pancreas transplantation has been traditionally offered only to patients with type 1 diabetes; however, SKPT has been performed in highly-selected, insulin-sensitive people with type 2 diabetes, with good outcomes.[7,8]

In Australia and New Zealand, pancreas transplant numbers (99% SKPT) have increased over time.[1-5] Patient survival is excellent; for those transplanted during or after 2010, one-year survival is greater than 97% and five-year survival is 93.2%.[1,2] For comparison, the Australia and New Zealand Dialysis and Transplant Registry reports show people with kidney transplants over the same timeframe had a one-year mortality rate of 3% and five-year mortality of 9 to 11%.[6] These figures, however, are likely underestimated as they include people without diabetes whose outcomes are usually significantly better. People requiring dialysis had mortality rates of 15.5 to 16.2 per 100 person years, which is over seven times higher than seen in transplant recipients.

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Ms Burns and Ms Cheung are Researchers for the Centre for Diabetes, Obesity and Endocrinology, The Westmead Institute for Medical Research, The University of Sydney, Sydney. Professor Gunton is Professor of Medicine at the Westmead Clinical School, The University of Sydney, Sydney; and Centre Director of the Centre for Diabetes, Obesity and Endocrinology, The Westmead Institute for Medical Research, The University of Sydney, Sydney, NSW.

Since 2000, islet-cell transplantation has been an alternative beta-cell replacement therapy available to select patients with type 1 diabetes with good kidney function who are particularly difficult to treat using conventional insulin replacement therapies due to their severe hypoglycaemic unawareness. Because in islet-cell transplantation only the islets of Langerhans are given, they can be infused into the liver, and the procedure is much less invasive than SKPT.

The Collaborative Islet Transplant Registry is a global group that influences clinical islet-cell transplant programs on a global level. The Registry has helped to standardise clinical islet-cell transplant programs, and success rates are improving with time. Selection of suitable donors and improvements in surgical technique and immunosuppression are contributing factors to the increasing success rates. Five-year islet-recipient survival is approaching 100% as there appears to be only one reported death.[9] This contrasts quite markedly with the more than 3% mortality rate in people with severe hypoglycaemic unawareness referred for consideration of islet-cell transplantation, despite their relatively young age.[10] The outcome data are summarised in Table 1.

The current donor and recipient eligibility criteria guidelines in Australia for pancreas and islets are available in the Transplantation Society of Australia and New Zealand clinical guidelines and are summarised in Tables 2 and 3.[11] Careful donor selection for both pancreas and islet-cell transplantation is partly responsible for the improved outcomes over time. However, although donor organ availability is a major limiting factor for both whole pancreas and islet-cell transplantation, it is important to note that a wider range of both donors and recipients are suitable for islet-cell transplantation. Patient suitability to whole pancreas or islet-call transplantation is outlined in the Flowchart.

The growing need for donor organs and established standardised protocols for the use of pancreas transplantation is being increasingly recognised and was addressed in 2019 at the First World Consensus Conference on Pancreas Transplantation in Pisa, Italy. This conference was held to delineate some global guidelines for the use and allocation of organs, pancreas transplantation surgery and patient follow up after surgery.

Table 1. Patient outcomes for whole pancreas and islet-cell transplantation[1-6]

	Pancreas transplantation	Islet transplantation
Number of transplants required	1 (with kidney)	Up to 3 islet-cell preparations (>4000 IEQ/kg recipient body weight per islet transplant)
Type of surgery	Abdominal Major laparotomy	Radiologically guided keyhole surgery
Patient survival 1 year 5 year 10 year	 97.2% 93.2% 83.1%	 100% One death in a patient receiving islet after kidney transplant Unknown
Graft survival 1 year 5 year 10 year	 90.4% 85.8% 82.3%	 80% of initially successful transplants 10% insulin independence, 80% C-peptide+ (most patients who are C-peptide+ have few or no hypoglycaemic episodes) Unknown

Organ allocation

Organ compatibility

There are four main considerations in the allocation of any organ: blood group (ABO) compatibility, crossmatching, presence of donor specific antibodies (which can increase the risk of graft failure) and minimal variation in human leukocyte antigen between the donor and recipient. Currently, most transplant centres require all four considerations to be met for most recipients before an organ is allocated for transplant. Anecdotal evidence from the few ABO incompatible transplants suggests outcomes are similar to ABO compatible transplants. Positive T-cell and/or B-cell complement dependent cytotoxic crossmatch and significant human leukocyte

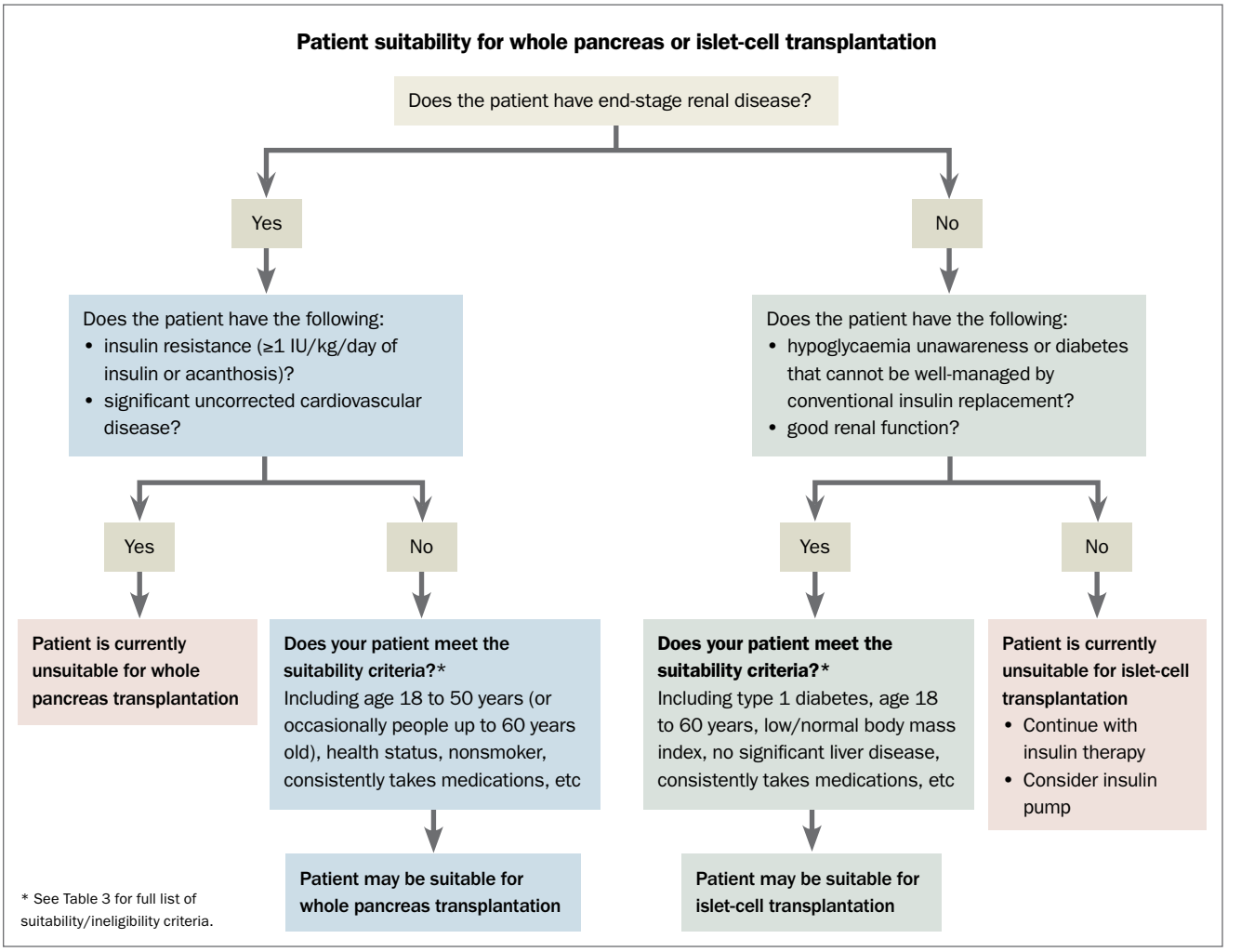
Table 2. Donor suitability criteria for whole pancreas and islet isolation[11]

	Whole pancreas	Islets
Body weight	>25kg and <100kg	>20kg and <150kg
Age	3 to 45 years	3 to 65 years (extended age used if other organs accepted for donation)
Pancreas	No pancreatitis No pancreatic trauma No/minor fat infiltration	Pancreas with some trauma may be considered for islets Fatty pancreas acceptable
Medication use	Insulin requirement before final illness is an exclusion criterion	Insulin requirement before final illness is an exclusion criterion
Medical history	No known diabetes mellitus No history of alcoholism or chronic pancreatitis	No known diabetes mellitus No history of alcoholism or chronic pancreatitis
Other		Deceased brain dead only Hypoxia – 'down time' should be considered

Table 3. Recipient suitability criteria for whole pancreas and islet cell transplantation[11]

	Whole pancreas transplantation	Islet transplantation
Inclusion criteria		
Diabetes	Type 1 diabetes Occasionally type 2 diabetes with BMI <28 kg/m^2	Type 1 diabetes for >5 years with severe hypoglycaemia unawareness (i.e. hypoglycaemic episodes cause frequent loss of consciousness or need for outside assistance)
Renal function	Usually with a kidney transplant: eGFR <30 mL/min/1.73 m^2	Creatinine clearance >75 mL/min/1.73 m^2 Serum creatinine <130 mcrmol/L 24hr urine protein <300 mg/day
Cardiac status	Adequately treated or no significant cardiovascular disease (surgical risk)	Adequately treated or no significant cardiovascular disease (surgical risk)
Vascular status	Patent iliac vessels bilaterally	
Weight/BMI	BMI <35 kg/m^2	Ideally <80 kg
Age	18 to 50 years (or very medically fit)	>18 years, usually <60 years
Smoking status	Nonsmoker or permanently ceased smoking (>3 months)	Nonsmoker or permanently ceased smoking (>3 months)
Exclusion criteria		
Diabetes	Marked insulin resistance – SKPT requires corticosteroid-containing immunosuppression. Usually total insulin requirement <1 IU/kg/day	Insulin requirement >0.7 IU/kg/day High C-peptide response to arginine (not type 1) Current HbA_{1c} >108 mmol/mol (12%) Chronic pancreatitis
Renal	Kidney-only transplantation deemed more suitable Renal function not relevant for SKPT If for PAKT, needs to have adequate renal function (e.g. eGFR >60 mL/min/1.73 m^2)	Creatinine clearance <75 mL/min/1.73 m^2 Serum creatinine >130 mcrmol/L 24 hour urine protein >300 mg/day
Cardiac status	Inadequately treated CV disease Antiplatelet therapy that cannot be safely ceased for surgery	Inadequately treated CV disease Antiplatelet therapy that cannot be safely ceased for surgery
Pathology testing	Uncorrected anaemia	Baseline anaemia (identify cause and correct) Significant liver disease (islets are infused into the liver)
Psychiatric status	Inability to consent or to comply with long-term immunosuppression	Inability to consent or to comply with long-term immunosuppression
Smoking status	Ongoing cigarette smoking (cardiovascular and cancer risk with immunosuppression)	Ongoing cigarette smoking (cardiovascular and cancer risk with immunosuppression)
Drug usage	Addiction to nonprescription illicit drugs	Systemic corticosteroids (worsen islet-cell transplant outcomes) Terfenadine, cisapride, astemizole, pimozide or ketoconazole that is not ceased before sirolimus administration
Other	Pregnancy Malignant disease, not cured Any chronic infection indicating increased mortality risk Allergy to immunosuppressive drugs	Pregnancy Malignant disease, not cured Any chronic infection indicating increased mortality risk Allergy to immunosuppressive drugs

Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycated haemoglobin; PAKT = pancreas after kidney transplant; SKPT = simultaneous kidney-pancreas transplant.



antigen mismatching result in worse outcomes with more acute cellular rejection and/or antibody mediated rejection.[12,13]

Recipient factors

Recipient eligibility is critical to the undertaking of any organ transplant. Increasing age, obesity and number of comorbidities increase the risks for potential transplant recipients. The recipient eligibility and exclusion criteria for whole pancreas and islet-cell transplantation are summarised in Table 3. SKPT is a major abdominal surgical procedure and patient eligibility should be assessed accordingly. It is important to note that some of the exclusion criteria are treatable, and the patient may be reconsidered after treatment, for example, after correction of cardiovascular disease or after smoking cessation.

Surgery

Although pancreas surgery has improved significantly in recent years, pancreas transplantation is major surgery with a moderate surgical complication rate compared with other transplants.[14] Consequently, there is a significant increase in mortality in the first few months after SKPT, but by one year, transplant recipients have lower overall mortality, which continues to improve.

Pancreas transplant after kidney transplant (or PAKT) is not commonly performed in Australia. Retrospective SKPT and PAKT data suggest that PAKT is associated with better kidney function compared with that in people who receive only a kidney.[15] Worldwide, preference is given to performing an SKPT over PAKT because PAKT requires two separate surgical procedures and there is increased risk associated with rejection of kidney and pancreas allografts from two separate donors.[16]

Islet-cell transplantation continues to show improvements in long-term outcomes for patients, with a five-year insulin independence approaching 70% in some transplant centres. Islets are currently transplanted into the recipient's liver via the portal vein. Surgical and radiological advances in recent years have seen a shift from performing minor abdominal surgery to using radiologically guided keyhole surgery for this transplant, reducing the risk of surgical complications and decreasing recovery time for the patient.[17]

Immunology and immunosuppression

Pancreas transplantation is highly immunogenic, which is likely enhanced by the heightened immune response of the

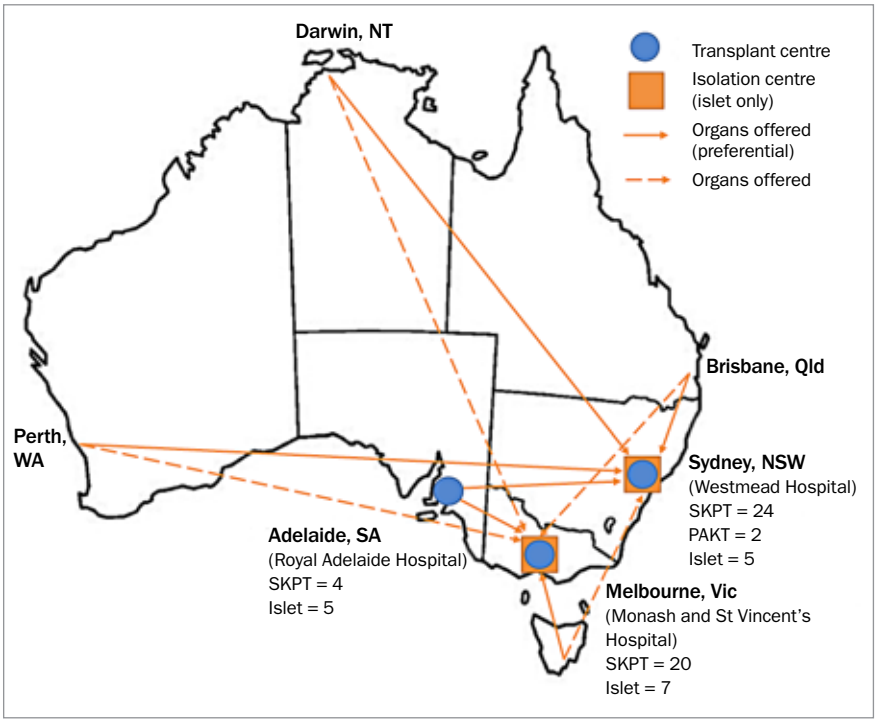


Figure. 2018 data of simultaneous kidney-pancreas and islet transplant across Australia. The map shows pancreas and islet transplant centres (orange box and blue circle, respectively). Unbroken orange arrows indicate preferential organ allocation from states or territories to transplant centres. Broken orange arrows indicate second offer organ allocation if preferred centre cannot receive the organ. In 2018, 50 people in Australia received a pancreas transplant: 26 at Westmead Hospital, 20 at Monash Hospital and four at Royal Adelaide Hospital. In the same period, five islet-cell transplants were performed at Westmead Hospital, seven at St Vincent's Hospital Melbourne and two at Royal Adelaide Hospital.

Abbreviations: PAKT = pancreas after kidney transplant; SKPT = simultaneous kidney-pancreas transplant.

recipient due to their diabetic autoimmunity.[18] It is not safe to monitor grafts by repeat biopsy. However, because kidney grafts are monitored by biopsy and less invasively by blood tests and urinalysis, having an SKPT allows easier monitoring of immune rejection, which in most recipients appears consistent for two organs from the same donor.

In addition, advances in and refinement of immunosuppressive regimens have been tailored to support the pancreas, with the preference towards the use of the non-nephrotoxic and nondiabetogenic induction drugs thymoglobulin, alemtuzumab or basiliximab followed by a combination of tacrolimus and mycophenolate for maintenance.[19] This has also improved graft survival for islet-cell transplantation and the side-effect profiles for recipients.[16,20] Together, the development of surgical techniques and the improvements in the use of immunosuppressant agents correlates to better patient outcomes.

Islet-cell transplant recipients receive steroid-free immunosuppression, and a number of current trials are running worldwide to test new regimens for improved outcomes and side-effect profiles. As with all transplantation therapies, the burden of immunosuppression on the patient must be considered before acceptance for transplantation.

Australia and New Zealand transplant centres

Whole pancreas transplants are performed at Westmead Hospital, New South Wales; Monash Hospital, Victoria, The Royal Adelaide Hospital, South Australia, and in New Zealand. Islets are isolated and transplanted at Westmead Hospital and as part of the Tom Mandel Islet Transplant Program at St Vincent's Hospital Melbourne, Victoria, and are also transplanted at the Royal Adelaide Hospital. These Australian centres each accept out-of-area referrals, including from interstate where the state or territory does not have that particular transplant service, as illustrated in the Figure. If potentially suitable patients with diabetes are interested in pancreas or islet-cell transplantation and are capable of providing informed consent and of taking regular immunosuppression to maintain the transplant (Flowchart), we recommend referring them to the relevant centre for assessment.

Conclusion

The number of pancreas and islet-cell transplants in Australia and New Zealand have increased over the past decade with excellent patient survival rates, and quality of life after successful pancreas or islet-cell transplantation is markedly improved for recipients. Suitability criteria for each transplant differ and these, along with long-term immunosuppression side effects, should be taken into consideration in patients who may be considering or suitable for such surgery. **ET**

References

A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

COMPETING INTERESTS: None.

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