An unmet need: Pancreatic beta cell replacement

C Adams, MMed (Int Med), Cert Endo Metab (SA); **B Mansfield,** MSc (Edin), Cert Endo Metab (SA);
F Mohamed, MMed (Int Med), Cert Endo Metab (SA)

Division of Endocrinology and Metabolism, Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

***Corresponding author:** C Adams (constance.adams@wits.ac.za)*

Diabetes mellitus (DM) is a growing public health concern in South Africa (SA) and poses a substantial economic burden on healthcare globally. A century has passed since the discovery of insulin, and despite advances in diabetes management, exogenous insulin remains a primary treatment for type 1 DM, posing challenges of hyperglycaemia and hypoglycaemia. Pancreas transplantation should be considered a treatment for insulin-deficient DM, offering sustained euglycaemia and preventing complications associated with the disease. However, there has been a global decrease in the number of transplants performed. In SA, only a few pancreas transplants have been performed, primarily because of surgical risks and the need for immunosuppression. Islet transplantation is an alternative but faces limitations due to donor scarcity and immunosuppression requirements. This review explores recent progress in pancreas and islet transplants for DM, with the aim of providing insights into expanding treatment options for people with insulin-deficient DM.

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Globally, diabetes mellitus (DM) affects 521 million people, with ~4% having type 1 DM (T1DM). In South Africa (SA), the prevalence of DM is estimated to be 3 million, with T1DM accounting for 5% of all people with DM.[1,2] Despite the primary focus on glycaemic control in diabetes care, comprehensive management includes prevention of hypoglycaemia, stabilisation of complications, improvement of quality of life, and restoration of life expectancy.[3] DM requires ongoing clinical care and management, with an estimated medical cost in the SA public health sector in 2018 of ZAR2.7 billion, increasing to ZAR21.8 billion when both diagnosed and undiagnosed people with type 2 DM (T2DM) were considered.[4] The estimated projected cost for 2030 is ZAR35.1 billion, with 51% of the costs attributed to management and 49% to complications.[4]

The diabetes care armamentarium has expanded beyond pharmacological glucose-lowering therapy to revolutionary technological advances. An advanced hybrid closed-loop system essentially functions as an artificial pancreas. The system comprises a dispensing pump containing both insulin and glucagon, a real-time continuous glucose monitoring (CGM) sensor, and a bluetooth-enabled smartphone application for programming.[5-8] These advances in diabetes management help to reduce hypoglycaemia, but may compromise strict glycaemic control.[6-8] Despite T1DM being an immune-mediated disease, few immune therapies have shown promise for its cure.[9] While a number of candidate drugs remain in development, teplizumab, an anti-CD3 monoclonal antibody, is the only therapy registered by the US Food and Drug Administration for the dysglycaemic stage of T1DM. It slows down the T-cell-mediated destruction of beta cells, thereby delaying progression to clinical hyperglycaemia.[9,10] However, finding a cure for the disease has proved challenging, with limited success in immune therapies. Curative biological approaches target restoration of glucose-regulated pancreatic beta cell function that results in normoglycaemia and termination of exogenous glucose-lowering therapy use. The only definitive restoration of glucose control is through the replacement of a functioning endocrine pancreas or islet cells.[11] Pancreatic beta cell replacement therapies are therefore of interest.

Restoring beta cell mass through whole-pancreas or pancreatic islet transplantation is considered the most effective and physiological approach to achieving and maintaining normoglycaemia while reducing hypoglycaemia, particularly in people with diabetic nephropathy. It also aims to stabilise the progression of micro- and macrovascular complications.[12] Most transplants are performed as simultaneous pancreas-kidney transplants (SPKTs) or pancreas-after-kidney (PAK) procedures. Advances in patient and graft survival have been achieved since the inception of pancreas transplantation (PTx) in 1966, demonstrating improved glycaemic control, reduced hypoglycaemic events, and better quality of life.[13]

Islet transplantation (ITx) has made significant advances in the past 20 years and should not be seen as a competing treatment option, but rather a complementary therapy to conventional treatments and PTx. It has its own unique patient population and primary goals and has shown great potential in achieving true euglycaemia.[14] Further research is required in a local context to optimise clinical practice and inform decision-making regarding ITx in our population.[13,15]

Pancreas transplants and global progress

Surgical management of DM is often an overlooked and underutilised treatment option. While solid-organ transplantation has traditionally been reserved for end-stage organ failure, it may hold promise as a potential 'cure' for DM.[13] However, there are challenges to consider, including surgical risks, graft failure, the economic burden, chronic immunosuppression, and limited organ availability.[16]

PTx is particularly complex and carries a higher risk of complications compared with other solid-organ transplants. Recipients already have DM and its associated complications, and the pancreas graft is susceptible to early loss within hours or days after surgery, usually due to technical factors resulting in thrombosis, leaks, bleeding, infection and pancreatitis. In experienced centres, the technical graft failure rate is 5%.[16] Nevertheless, advances in surgical techniques and immunosuppression management protocols have led to improved survival rates.[17] Despite these improvements, there has been a documented global decline in PTx rates, particularly PAK and pancreas transplantation alone (PTA) procedures, while the rate of SPKTs remains stable.[17]

Since the first PTx in 1966, the International Pancreas Transplant Registry (IPTR) has recorded >65 000 PTxs performed worldwide, including >35 000 in the USA up to December 2020. In 2004, the annual number of PTxs in the USA peaked at 1 500, but it has declined to <1 000 per year, a 6% decrease from 2018 to 2021.[16,17] However, data from SA show a significantly lower number of PTxs, with only 70 performed between 2009 and 2017.[18] SA has experienced a 47% reduction in PTx between 2009 - 2013 and 2014 - 2018, with the majority (75%) being SPKT procedures.[18] Limited data are available from other African countries. Fabian *et al.*[19] conducted a retrospective review of solid-organ transplants at Wits Donald Gordon Medical Centre (WDGMC), a private academic teaching hospital in Johannesburg, SA. WDGMC performed 79.1% of all national PTxs over a 10-year period, 2004 - 2013. Of all these 72 PTxs performed at WDGMC, SPKT accounted for 93.1%, while PAK and PTA comprised 5.5% and 1.4%, respectively. All the patients had T1DM, and only 1 procedure was a paediatric SPKT. The median (interquartile range) age at SPKT was 34.6 (28.5 - 40.5) years. One-year survival for the recipient, kidney and pancreas was 97%, 97% and 86.1%, respectively. Ten-year survival for the recipient, kidney and pancreas was 84.7%, 73.1% and 43.2%, respectively. Owing to the retrospective nature of this study, records describing the indications, surgical approach and early complications of these transplants are lacking. This decline in PTx is concerning, as it fails to reflect the progress made in graft survival, patient survival, and transplants in higher-risk patients.[20,21] Furthermore, it raises concerns about maintaining high-volume transplant centres, training fellows, and the preservation of surgical skills and transplant expertise.[20]

Eligibility for beta cell replacement therapy

Pancreatic beta cell replacement therapy is recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes as an effective treatment for well-selected people with T1DM. The ADA criteria for PTA include patients without diabetic nephropathy and with normal renal function who experience severe, life-threatening acute metabolic complications of DM or have clinical and emotional problems with exogenous insulin use.[12] PTA can improve the course of diabetic microvascular complications and reduce atherosclerotic cardiovascular risk in suitable recipients.[21-23] Seventy-five percent of insulin-dependent people with DM and end-stage kidney disease on dialysis do not survive 5 years.[24] The need for a kidney transplant is therefore time sensitive.

Recipient eligibility for beta cell replacement therapy is determined through preoperative assessments, including considerations of surgical fitness based on factors such as age, body mass index (BMI), cardiovascular disease severity, reversibility, presence of other life-limiting illnesses, and psychosocial support.[25] The risks and benefits of the procedure need to be carefully evaluated on an individual basis.[26] While guidance primarily focuses on T1DM, analysis of transplant data has shown comparable outcomes in well-selected people with T2DM who exhibit certain characteristics such as younger age, lower BMI, and a predominant defect in beta cell function rather than peripheral insulin resistance. It is important to note that people initially diagnosed with T2DM may have latent autoimmune diabetes, emphasising that the most significant criteria for eligibility are exogenous insulin dependence and evidence of reduced endogenous insulin production, which is quantified by low C-peptide levels.[25,26] Internationally, the median age at PTx was 42 years and the majority of recipients had T1DM as opposed to T2DM.[16] Indications for beta cell replacement therapy include frequent severe metabolic emergencies such as hypoglycaemia (particularly with impaired awareness), hyperglycaemia and diabetic ketoacidosis, as well as incapacitating clinical and emotional challenges related to exogenous insulin use (e.g. insulin allergy or phobia), or consistent failure of insulin-based management to prevent acute complications.[27-29]

Types of pancreas transplants

PTx in the management of insulin-deficient diabetes involves three main approaches. SPKT is performed when there is end-stage diabetic nephropathy, with both organs obtained from a single cadaveric donor. Simultaneous cadaver pancreas with a living-donor kidney or a segmental pancreas and kidney from the same live donor are alternative options.[30-32] Segmental PTxs are seldom performed, comprising 0.4% of all PTxs as per the IPTR, owing to the risk of the living related donor developing DM after undergoing hemipancreatectomy.[33] In 2019 and 2020, 90% of PTxs were SPKTs, with PAK and PTA accounting for 5% each.[16] PAK can follow after an initial living-donor kidney transplant for end-stage diabetic nephropathy, and PTA is performed when there is no diabetic nephropathy.[34] Owing to the poor prognosis of end-stage diabetic nephropathy and the challenges of dialysis, the need for a kidney transplant often drives the decision for SPKT. Evidence shows that SPKT has superior outcomes compared with kidney transplant alone (KTA) or PTA, with a mutually beneficial relationship between the kidney and pancreas grafts.[35-37] In PTA, it is challenging to monitor rejection. Serum amylase and lipase are sensitive markers for rejection, but are not specific, as levels are generally elevated owing to the presence of both the graft and the native pancreas. The simultaneous presence of a kidney transplant can be used to anticipate pancreas graft rejection indirectly through appraisal of kidney function. Synergistically, kidney grafts in the context of SPKT and PAK have better outcomes than KTA because the pancreas graft leads to 'cure' of DM. The amelioration of chronic hyperglycaemia reduces microvascular complications in the kidney graft. Studies have shown an improvement in creatinine levels and reduced albuminuria of the kidney graft in the context of a concurrent PTx.[38] In the WDGMC study,[19] 1-year and 10-year kidney graft survival for KTA was 91.7% and 66.8%, respectively. In SPKT, 1-year and 10-year kidney graft survival was increased at 97% and 73%, respectively. The age at transplant is affected by the time taken to progress to end-stage organ failure, which is ~20 years from the diagnosis of T1DM. Moosa[39] reviewed 542 renal transplants over a 23-year period and found age to be an important determinant of outcome. Survival of both patient and graft was inversely related to age, with age >40 years being associated with decreased survival. The superior outcomes of SPKT and PAK compared with PTA necessitate the presence of impending end-stage renal failure to justify a synchronous kidney transplant. Data on SPKT in people without significant chronic kidney disease are insufficient, and outcomes in PTA are poor.

Outcomes of pancreas transplantation

Successful beta cell replacement therapy, as defined by the International Pancreas and Islet Transplantation Association and the European Pancreas and Islet Transplant Association, involves achieving normoglycaemia with evidence of endogenous insulin production and discontinuation of exogenous insulin use. Rejection is the primary cause of pancreas loss after transplantation, and lifelong immunosuppressive therapy is necessary to prevent graft rejection.[16] Rejection can occur shortly after the transplant, or even years later. Early rejection is managed using T-cell-depleting antibodies and high doses of glucocorticoids, which are gradually tapered to near-physiological levels over the following weeks. Chronic immunosuppression involves a combination of a calcineurin inhibitor such as cyclosporine or tacrolimus, and an antimetabolite such as mycophenolate mofetil or azathioprine.[40] During the early years after the transplant, the primary cause of death is often related to atherosclerotic cardiovascular disease.

There were no differences in outcomes of PTx between T1DM and T2DM.[16,26] Before 2009, African American recipients had an increased risk of pancreatic graft failure, but the risks for Hispanic and Asian recipients were both comparable to their Caucasian counterparts. However, the risk of pancreatic graft failure in African American recipients dropped to 1% and was no longer significant after 2009.[41,42] When considering the role of PTA or SPKT, the decision must weigh the risks associated with lifelong immunosuppression against the morbidity of DM and its complications. Monitoring for rejection presents challenges, as amylase and lipase levels are sensitive but not specific indicators, because elevated levels can be due to the presence of two pancreases in the recipient. The ominous appearance of impaired fasting glucose and low C-peptide undoubtedly occurs too late. Survival rates after PTx vary at different time points post-transplantation.

According to data from 2004 to 2015, patient survival rates ranged from 96% to 99% at 1 year, from 89% to 91% at 5 years, and from 70% to 80% at 10 years.[16] In people with end-stage kidney disease on dialysis, SPKT provides better survival benefits compared with KTA.[23] If SPK is not immediately available, an initial KTA from a living donor followed by a subsequent PAK is necessary to improve life expectancy. Pancreatic graft survival rates at 5 years are 80% for SPK, 67% for PAK, and 62% for PTA recipients.[16] Long-term data also show that PAK improves patient and kidney graft survival rates and provides higher glomerular filtration rates compared with KTA.[35-37]

SA outcome data from the WDGMC showed 10-year recipient and graft survival rates of 80.4% and 66.8%, respectively, for KTA. For SKPT, the 10-year recipient survival rate was 84.7%, while kidney and pancreatic graft survival rates were 73.1% and 43.2%, respectively.[19] Recipient and graft survival rates were lower in black Africans, potentially because of socioeconomic factors affecting healthcare access and affordability of immunosuppressive medication, lower rates of living related donors, and genetic factors influencing graft function. Genetic susceptibility to hypertension in the kidney graft and mutations in the *APOL1* gene may also adversely affect graft function in recipients of black African descent.[39] PTx is effective in restoring insulin independence, but is associated with a major surgical risk in comparison with ITx, which is a less invasive procedure typically used for individuals with labile T1DM and severe hypoglycaemia.

Islet transplantation and eligibility

ITx, first performed in 1990, led to a short period of insulin independence.[43] However, it was not until the report by the Edmonton group in 2000 that ITx became a realistic treatment modality for difficult-to-control T1DM.[44] Between 1999 and 2020, at least 1 399 recipients of allogeneic islet transplants were reported to the Collaborative Islet Transplantation Registry (CITR).[45] Insulin independence was found to diminish with time, and the initial hope of a cure was replaced by a different goal – diabetes control and the mitigation of severe hypoglycaemic episodes.[46]

Candidates for ITx are people with T1DM (low C-peptide) who have hypoglycaemic unawareness, a history of severe hypoglycaemic episodes, and/or glycaemic variability.[47,48] Furthermore, individuals should be aged >18 years to avoid the risks of chronic immunosuppression in childhood and adolescence.[48] Those with obesity (BMI >30 kg/m^2) or high insulin requirements (>1 U/kg/d) should not be considered.[47,48] Patients should have passed through an intensive diabetes education programme and have been trialled on a basal bolus regimen of multiple daily injections or continuous subcutaneous insulin infusion with or without CGM before being considered for beta cell replacement therapy.[46]

Less stringent criteria can be considered for ITx following kidney transplantation, as patients are already on chronic immunosuppressive therapy. However, good graft function and exclusion of opportunistic infections are prerequisites.[46]

Procuring islet cells and the process of transplantation

The isolation and culture of islet cells in the laboratory is a rigorous process. The primary source of pancreatic islet cells is cadaveric donors, and most transplantation programmes aim to infuse at least 10 000 islet equivalents per kilogram of body weight.[49] The utmost care should be taken to ensure capsular integrity of the pancreas, which is removed *en bloc*. As little handling as possible is required while maximising oxygen supply to the pancreas prior to cross-clamping of the aorta.[50] Donors aged 20 - 50 years with a BMI >30 kg/m^2 and normal glucose levels yield higher quantities of pancreatic islets, leading to improved outcomes.[51,52] Donors with a glycated haemoglobin (HbA1c) level ≥6.5% should be avoided.[53] Automated methods utilising a Ricordi chamber are currently preferred for islet cell isolation. The pancreas is infused with collagenases and proteases through the pancreatic duct, facilitating enzymatic digestion. Density-gradient centrifugation is then performed, significantly improving islet isolation and yield. Isolated islets are subsequently cultured for 24 - 72 hours and the final islet cell preparation is infused intravenously after cannulation of the portal vein, which is accessed by a sonographic and fluoroscopic percutaneous transhepatic approach.[46] Infusion occurs at the time when the recipient receives the induction phase of immunosuppressive therapy.[46]

During the induction phase of immunosuppression, T-cell depletion with antithymocyte globulin (ATG) and etanercept leads to longer-term insulin independence.[54] The Edmonton protocol favoured T-cell depletion with the anti-CD52 monoclonal antibody alemtuzumab, owing to its lower incidence of side-effects compared with ATG.[44] Tumour necrosis factor alpha (TNFα) inhibitors are also sometimes used during induction.[45,46] The choice of long-term maintenance immunosuppressive therapy remains controversial, and the Edmonton protocol aimed to minimise the risk of DM by using an immunosuppressive regimen without glucocorticoids, comprising low-dose tacrolimus, high-dose sirolimus and daclizumab.[44] Tacrolimus, although diabetogenic, has shown success in achieving insulin independence in >50% of patients at 5 years.[54] Sirolimus, an mTOR inhibitor, is no longer included in recent regimens owing to improved efficacy with calcineurin inhibitors and mycophenolate mofetil.[54]

Islet procurement has improved, resulting in better outcomes. Approximately 50% of recipients remained insulin independent at 5 years, while at 10 years 73% achieved partial control, defined as an HbA1c level <6.5%, detectable C-peptide levels and lower risk of severe hypoglycaemic episodes (hypoglycaemia requiring assistance of another person), leading to lower insulin requirements compared with intensive insulin therapy.[55-57] Data from the National Institutes of Health Clinical Islet Transplantation Consortium revealed that 87.5% of participants with T1DM who received an allogenic stem cell transplant achieved an HbA1c level <7% and experienced no severe hypoglycaemic events during the 1-year follow-up period.[58] Additionally, more than half of the patients were able to discontinue insulin use after 1 year. Factors associated with favourable outcomes include age >35 years, a greater volume of islets transfused (total ≥325 000 islet equivalents), induction immunosuppression with T-cell depletion and/or TNFα inhibition, and maintenance immunosuppressive therapy with a calcineurin inhibitor and an mTOR inhibitor.[58,59] In recipients meeting these four criteria, 95% protection from severe hypoglycaemic episodes was seen at 5 years.[59] The 28-day post-transplant BETA-2 score, which predicts graft survival at 5 years, is a measure of islet graft function and incorporates fasting plasma glucose, C-peptide, HbA1c and the transplant recipient's insulin dosage.[60] The BETA-2 score was effective in predicting graft failure, inadequate glycaemic control (HbA1c >7%) and the need for exogenous insulin therapy.[61,62] Individuals with suboptimal BETA-2 scores could be considered for retransplantation. Over a 20-year period, deaths reported to the CITR were primarily due to cardiovascular causes, and the predictors of mortality were older recipients with a longer duration of DM. Infections and malignancies were also observed as causes of death, although to a lesser extent. Overall, ITx shows promising outcomes in achieving glycaemic control, reducing hypoglycaemic episodes, stabilising diabetic vascular complications and improving the quality of life of individuals with T1DM compared with intensive insulin therapy.[63]

Pancreas v. islet transplant

PTx demonstrated a comparable efficacy and outcome to ITx in one non-randomised study.[64] However, owing to the absence of head-to-head studies and standardised definitions of success, it is challenging to directly compare these two strategies.[65] While a whole-pancreas transplant is more invasive and carries a greater risk of morbidity, ITx is less invasive and avoids the complications associated with major surgery. The less invasive approach of ITx is therefore often preferred.[65] However, it is important to note that the isolation and culture of islet cells in a laboratory setting requires skilled personnel and specialised equipment.

Challenges for beta cell replacement transplant therapy

Despite PTx and ITx proving to be effective treatment options for people with DM, there is a shortage of available organs for transplantation. Advancements in xenotransplantation (porcine beta cell therapies) and pluripotent stem cell-derived islet cells offer promising avenues for the future of islet transplantation.[66,67] Donation after circulatory death (DCD) has the potential to increase the donor pool for PTx. Despite concerns about graft pancreatitis and thrombosis, efforts are being made to assess organ viability and optimise procurement techniques in DCD donation. In addition, regional perfusion techniques such as *in situ* normothermic regional perfusion (NRP) have shown promising results in improving outcomes in liver transplantation and may have a similar benefit for other abdominal organs, including the pancreas. Machine perfusion of the pancreas itself has also demonstrated positive results in experimental models.[49,52] The collective experience with PTx from DCD donors suggests that expanding the use of these grafts is feasible with careful donor and recipient selection, along with the implementation of resuscitation techniques such as NRP and machine perfusion. Developing criteria to evaluate organ viability will be crucial in further expanding the utilisation of DCD donors for PTx in the future.

Even though PTx has proven positive outcomes, it is still perceived as a high-risk procedure, based on outdated notions of risk. Regionalisation of pancreas transplant services and the development of consensus guidelines for considering SPKT for people with DM and chronic kidney disease could help improve access and outcomes. Factors such as age, BMI, insulin requirements, functional status, health literacy and caregiver support should be considered independently of access or awareness issues.[50]

The economic impact of severe hypoglycaemia goes beyond its physical consequences, as it requires frequent hospital admissions, with subsequent direct and indirect economic effects.[68,69] Recent economic analyses in Portugal, the Netherlands and Switzerland have shown varying costs of severe hypoglycaemic episodes in different health systems, ranging from ZAR3 261 to ZAR53 327.[70-72] Unfortunately there is a lack of cost analyses for hypoglycaemia in developing countries, including SA.[69] An SA study analysing medical scheme claims data from two healthcare providers in the public sector from 2015 and 2016 included 2 363 patients with diabetes and examined both direct and indirect costs associated with diabetes care.[73] The findings revealed that hospitalisation and medication were the main contributors to total direct costs, with the average cost per patient being ZAR2 452 in 2015 and ZAR2 486 in 2016. Insulin was substantially more expensive than oral hypoglycaemic drugs when considering the total direct costs.[73] Indirect costs, which accounted for disability-adjusted life-years, were ZAR17 223 per patient in 2015 and ZAR18 711 in 2016. When combining direct and indirect costs, the total cost of diabetes care amounted to ZAR27.9 billion in 2015 and ZAR29.9 billion in 2016, representing 0.688% and 0.689% of the country's gross domestic product, respectively. These findings emphasise the significant impacts of DM and its associated costs on the healthcare sector and the overall economy of SA. Moreover, the actual costs of diabetes may be even higher, considering the large number of undiagnosed individuals.[73] Beta cell replacement therapies such as ITx are expensive interventions with costs similar to PTx and comparable outcomes.[64] Cost-effectiveness studies in high-income countries have demonstrated cost savings after 9 - 10 years following an ITx, but different 'willingness to pay' thresholds for quality-adjusted life-years may apply in low- and middle-income countries.[68] The use of pluripotent stem cell-derived islet cells can significantly reduce costs and improve access to beta cell replacement therapies.[74] Cost-effectiveness models and analyses are needed in SA for all strategies aimed at reducing severe hypoglycaemic episodes, including ITx.

Possibilities for SA

Incorporating PTx or ITx into current transplantation programmes in SA centres should be considered, as they offer promising outcomes in terms of patient survival and improvement in complications associated with DM. The presence of kidney and liver transplantation programmes in specific centres in the country suggests that SA may be well positioned to administer an ITx programme. However, the ongoing decline in PTx rates may lead to a decrease in training opportunities and a decline in surgical skill.

The establishment of an ITx or PTx programme would have to take place in the context of a complex SA healthcare system, in which significant health disparities exist between private and public healthcare. Limited resources already sometimes limit access to basic care for people using the public healthcare system. Most of the population lacks access to other effective diabetes technologies, such as CGM and advanced closed-loop systems. Proceeding to ITx or PTx could then be seen as omitting a necessary step. In ~10% of people with T1DM the disease is difficult to control, resulting in recurrent hypoglycaemic episodes, and these modalities may not always be effective in achieving metabolic control. It is therefore imperative to conduct cost-effectiveness analyses for all modalities aimed at mitigating hypoglycaemia, and to assess the impact of infections associated with immunosuppressive therapy, especially in a country with a high burden of HIV and tuberculosis. It is crucial to emphasise the importance of considering beta cell replacement therapy as an accessible and appropriate option for selected people with DM, as improved transplant expertise has resulted in excellent outcomes.

Conclusion

ITx holds great promise as a potential treatment for a subset of people with T1DM prone to recurrent episodes of hypoglycaemia, particularly those with hypoglycaemic unawareness. Despite challenges such as organ scarcity, lifelong immunosuppressive therapy, surgical risks and the need for long-term specialised transplant care, the development of an ITx programme in SA should be considered. Ongoing research provides hope for overcoming these limitations by focusing on improving success rates, expanding the donor organ pool, optimising immunosuppressive regimens and minimising long-term risks. Addressing the unmet need for beta cell replacement therapy in SA requires increased awareness, research funding, and collaboration between the private and state health sectors and academic institutions. ITx offers a safer alternative to whole-pancreas transplantation, effectively eliminating severe hypoglycaemic episodes and improving quality of life. PTx is not a first-line treatment and is typically considered after a 20 - 25-year period of consistent failure of insulin-based therapy, severe recurrent hypoglycaemia, and the development of significant complications, such as renal failure. The notion of replacing one chronic illness, DM, with another, immunosuppression, may act as a deterrent to the uptake of PTx, particularly PTA. Further research is needed in the local setting to evaluate the role of beta cell replacement transplant therapy and its economic feasibility, considering access to alternative treatments and risks associated with immunosuppressive therapy in a country with a high disease burden.

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