

Beta Cell Replacement Therapies

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Abstract

Type 1 diabetes mellitus is a long-term disease, which prevalence is increasing worldwide. It is caused by autoimmune destruction of the β cells in the pancreas and the standard treatment is subcutaneous insulin. However, patients with type 1 diabetes are still at risk of diabetic ketoacidosis (DKA) and severe hypoglycaemia. They can also develop cardiovascular complications related to diabetes mellitus, that increase mortality and morbidity of patients with type 1 diabetes. β cell replacement therapies (pancreas and islet transplantation) are available for the treatment of type one diabetes and they have demonstrated improvement in glucose control and reduction of cardiovascular complications. This review aims to provide an update on β cell therapies; the advantages and drawbacks of each technique and the eligibility criteria.

Keywords: *Type 1 Diabetes Mellitus; Insulin; Hypoglycaemia*

Introduction

The prevalence of type 1 diabetes worldwide has increased by 2 - 5% in the recent years [1] and currently it is estimated that 48 million people will have type 1 diabetes by 2030 worldwide [2].

With the discovery of insulin in 1921 by Banting and Best, the prognosis of type 1 diabetes radically changed, transforming type 1 diabetes in a long-term disease. However, the life expectancy of people with type one diabetes is still estimated to be 11 - 13 years less than general population [3]. The main causes of death in people with type 1 diabetes are diabetic ketoacidosis (DKA) and cardiovascular disease, including, ischaemic heart disease, stroke, peripheral vascular disease and nephropathy [4]. Furthermore, cardiovascular complications and hypoglycaemia can also cause increased morbidity in individuals with type 1 diabetes and they can cost over £ 2.000 per year per patient to health services in inpatient care [5].

For these reasons, it is important to continue to work in more effective treatments for people with type 1 diabetes to avoid complications and to prolong life expectancy in these patients.

Type 1 diabetes is caused by autoimmune destruction of β -cells in the pancreas producing insulin deficiency. Upon diagnosis, patients show an age-dependent loss of, at least, 40% of their β cell mass [6] and they require subcutaneous insulin life-long. Furthermore, the DCCT showed that patients with higher levels of c-peptide, and therefore, bigger functional β cell mass, had reduced incidence of microvascular complications and problematic hypoglycaemia, as they were more likely to achieve intense glucose control targets [7]. Consequently, replacing β cell mass seems a logic approach to treat type 1 diabetes.

β cell replacement therapies include pancreas transplantation and islet transplantation. In the first one, the whole organ is transplanted from a deceased donor to the recipient, whereas, in islet transplantation the recipient will only receive the purified Langerhans islets from the deceased donor. They both could be combined with a kidney transplant from the same donor or different one and both require immunosuppression life-long [8].

Pancreas transplant

Experimental pancreas transplantation started in 1890s, however the first successful pancreas transplant did not happen until 1966 in University of Minnesota Hospital [9]. Nowadays, it is a standardised procedure in many countries in the world.

Currently, pancreas transplantation is the only treatment for type 1 diabetes that provides insulin independence. It can be performed alone (pancreas transplant alone or PTA) or after a previous kidney transplant (pancreas after kidney or PAK) or simultaneously with a kidney transplant from the same deceased donor or different life donor (simultaneous pancreas-kidney or SPK) [8]. The different procedures have different eligibility criteria.

Simultaneous pancreas kidney transplant	Type 1 diabetes (in US also type 2 diabetes and BMI < 30 kg/m ²) with eGFR < 20 ml/min or on dialysis
Pancreas alone transplant	Type 1 diabetes (in US also type 2 diabetes and BMI < 30 kg/m ²) with eGFR > 40 ml/min and persistent severe hypoglycaemia (at least 2/24months) and failure of other approaches to control diabetes
*Based on Dholakia S., <i>et al.</i> Advances in pancreas transplantation. <i>Journal of the Royal Society of Medicine</i> ; 2016, Vol. 109(4) 141-146	

Table 1

Furthermore, the surgical techniques and immunosuppression regimens have improved and the graft survival rate is currently from 87 - 92% one year after the transplant and 78 - 84% five years after the transplant in the UK [10].

Surgical procedure and immunosuppression

The pancreas graft is normally located in right lower abdomen. From this position the endocrine pancreas drainage can be positioned in the portal vein. However, the exocrine pancreas drainage could be either into the bladder or in the small intestine (enteric). Both techniques have similar survival rates, however, enteric drainage avoids the frequently encountered problems of cystitis, urinary tract infection, reflux pancreatitis, metabolic acidosis, haematuria, and dehydration associated with bladder drainage. On the other hand, with bladder drainage amylase in urine could be use as marker of graft status [8].

The immunosuppression consists on induction agents that can be depleting antibodies, such as ATG or alemtuzumab or non-depleting antibodies, such as daclizumab or basiliximab [20]. This is followed by maintenance regime that is adjusted and sustained long-term and normally consists on MMF (mofetil mycophenolate), tacrolimus and, in some cases, steroids [9].

Complications from pancreas transplant

Pancreas transplantation is a major surgical procedure and it is not exempt from surgical complications. The most common cause of non-immunologic graft failure is thrombosis and its frequency has been reported by 10 - 15%. Bleeding can happen in 5% of cases and other complications such as, enteric anastomotic leak, graft pancreatitis, pancreatico-enteric fistula and intraabdominal sepsis, happen in similar frequency as in other major abdominal surgeries [9,12]. Because of major surgical complications 40% patient require re-laparotomy [20].

Furthermore, as any other transplant, to ensure pancreas graft survival long-term immunosuppression is required. This is well known to increase the risk of malignancy and infection [13] and potential risk of nephrotoxicity [22].

Benefits from pancreas transplant

After receiving a pancreas transplant, patients with type 1 diabetes, can achieve intense glucose control (HbA1c below 48 mmol/mol or 6.5%) without insulin. Furthermore, this has demonstrated to improve the quality of life of patients [14].

Moreover, pancreas transplantation has demonstrated reduction in cardiovascular risk. In 2001, La Rocca published a study where they compared cardiovascular mortality in patients with type 1 diabetes and kidney transplant alone vs SPK which showed reduced cardiovascular mortality in the SPK group [15]. This has also been seen by other transplant groups [16].

Additionally, there is evidence of improvement of retinopathy [17], glomerulosclerosis [18], neuropathy [27] and peripheral vascular disease [19] in patients with pancreas transplant.

Islet cell transplantation

The first islet cell transplant was reported in 1893, when a minced sheep pancreas was transplanted in the thigh of a boy with type 1 diabetes. Unfortunately, this experiment did not succeed but produced reduction of glycosuria in the patient. It was not until 1980s, with the improvements in immunosuppression, the development of a semi-automated method for islet isolation and the development of intraportal islet cell infusion, that islet cell transplantation became a reality [21-23].

Islet transplantation has proven protection from hypoglycaemia, improvement in HbA1c levels and, in many cases, sustained insulin independence [22]. However, in most of the cases, there is a gradual decreased of insulin production that lasts from 3 - 5 years [24]. The rates of insulin independence achieved currently vary widely, with experienced centres achieving insulin independence in over 80% of recipients while those with less experience achieving insulin independence in 0 - 63% at short-term follow-up [24]. Nevertheless, the protecting effect from hypoglycaemia and reduced glucose lability are sustainable effects of islet transplantation, comparable to SPK [21].

Consequently, the goal of islet transplantation is substantial or complete remission of severe hypoglycaemia events rather than insulin independence. Graft survival is defined as c-peptide positivity [20,21]. Furthermore, islet transplant can also be done in conjunction with kidney transplant either simultaneously (simultaneous islet kidney or SIK) or afterwards (islet after kidney or IAK).

The eligibility criteria for islet transplantation is type 1 diabetes patients with impaired hypoglycaemia awareness and persistent severe hypoglycaemia (at least 2 episodes in the last 2 years) despite optimised medical therapy (including structured diabetes education and sensor augmented insulin pump) [20]. The combination with kidney transplant is reserved to patients with indication for SPK or PAK but not fit enough for the surgery [20].

Islet transplant	Type 1 diabetes patients with impaired hypoglycaemia awareness and persistent severe hypoglycaemia (at least 2 episodes in the last 2 years) despite optimised medical therapy (including structured diabetes education and sensor augmented insulin pump)
Islet kidney transplant (SIK or IAK)	Type 1 diabetes with indication for SPK or PAK but not fit enough for abdominal surgery
*Based on UK guidelines on pancreas an islet transplantation. July 2019. British Transplantation Society.	

Table 2

Procedure and immunosuppression

Before transplantation the islet cells have to be retrieved and isolated. The first step is to infuse and preserve the pancreas in University of Wisconsin solution and transport it to the islet isolation laboratory in ice. Once in the isolation lab, the pancreas is cannulated and infused with collagenase which will separate islets from exocrine and ductal tissues and the remnant tissue is afterwards, centrifugated. Finally, the islets cells are cultured and then sent to the transplantation centre [21].

The transplant procedure takes place in the radiology suit. The isolated and cultured islet cells are infused into the liver parenchyma of the recipient through portal vein cannulation with 4FG catheter under local anaesthetics [21]. Patients normally require 1 - 3 days of hospital stay after the procedure. This involves overall less risk than laparotomic surgery required in pancreas transplantation.

The immunosuppression regime changed dramatically since Edmonton protocol in 2000. In this study, Shapiro tried steroid-free immunosuppression regime with daclizumab as induction agent and sirolimus and tacrolimus achieving improved outcomes in islet transplantation [24]. Since then, steroid-free immunosuppression regime is used in islet transplantation process. The most frequently used regime is alemtuzumab or ATG combined with etanercept as induction agent and MMF (mofetil mycophenolate) and tacrolimus for maintenance. This regime has shown higher incidence of insulin independence and better long-term graft outcomes [20,26].

Complications from islet transplantation

Islet transplantation is performed by percutaneous transhepatic catheterisation of the portal vein under direct fluoroscopic or ultrasound guidance which involves less surgical risk than laparotomy required for pancreas transplant. However, it is not exempt of risks. The main procedural risks are haemorrhage, portal vein thrombosis (4% of cases), and biliary tract damage. Therefore, pre-transplant screening for coagulopathy, ultrasound assessment for hepatic pathology, suspension of anti-coagulants pre-procedure, and routine ablation of the catheter tract are required to reduce the risk. After the procedure is also frequent the presence of short-term liver enzymes derangement with self-resolution in 90% of cases within a month [20].

In islet transplantation is also required long-term immunosuppression, which has been described to increase the risk of infection and malignancy [13]. Furthermore, sirolimus and tacrolimus are used as immunosuppressive maintenance regime, which have showed nephrotoxic effect [20].

Benefits from islet transplantation

After receiving an islet transplant, patients show improvement in hypoglycaemia awareness and protection from severe hypoglycaemia [22]. Furthermore, glucose lability is improved, even when insulin is restarted [21].

Islet cell transplantation has shown positive impact in microvascular complications. It has been reported reduced rate of renal function decline [28,29], stabilization of retinopathy [29] and neuropathy and also improvement in nerve conduction studies velocities [30]. The effect of islet transplantation in macrovascular complications has been less studied [20].

Additionally, the process of islet transplantation is less invasive than pancreas transplantation, which makes it possible in patients who are not fit enough for laparotomy and general anaesthesia.

New criteria to define graft function

In 2017, during EPITA/IPITA conference, the new criteria to define the graft functionality of β cell replacement therapies were discussed and agreed. This proposed that outcomes for all types of beta-cell replacement should be defined through a composite of glycaemic control (HbA1c), severe hypoglycaemia events, insulin requirements, and C-peptide levels [20,31].

Beta-cell graft functional status	HbA1c, % (mmol/mol)	Severe hypoglycaemia, events per year	Insulin requirements, U/kg/day	C-peptide
Optimal	< 6.5 (48)	None	None	> Baseline
Good	< 7.0 (53)	None	< 50% baseline	> Baseline
Marginal	Baseline	< Baseline	≥ 50% baseline	> Baseline
Failure	Baseline	Baseline	Baseline	Baseline

Table 3

Conclusion

β cell replacement therapies are available for the treatment of patients with type 1 diabetes with persistent severe hypoglycaemia or impaired kidney function. They have shown improvement in glucose control and reduction in hypoglycaemia events and also improvement or stabilization of microvascular complications. However, they require long-term immunosuppression and there is still needed improvement in graft survival rates.

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