REVIEW ARTICLE

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# Islet cell transplantation

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## ABSTRACT

Islet transplantation is considered an interesting and efficient therapeutic alternative for some Type 1 Diabetes Mellitus patients, mainly as it is a much simpler surgical procedure than complete pancreas transplantation. Due to the need for chronic immunosuppressive therapy to avoid rejection, however, both pancreas and islet transplantation are currently considered only for patients presenting with a very labile and problematic diabetes or when combined with a kidney transplant for patients who had developed chronic kidney failure. Although most islet transplant patients present continued graft function and benefit from improved glycaemic control, recent trials have shown insulin independence rates of around 50-70% and less than 10% at 1 and 5-year follow up respectively. The islet transplantation field has made significant and steady improvements over the past years, but further progress is needed to bring the procedure into current and general clinical use. The large number of studies currently underway on both the basic and clinical front will certainly promote a renewed interest in the islet transplantation field over the coming years.

**Key-Words:**
Diabetes Mellitus, Type I; Islets of Langerhans; Transplantation.

## INTRODUCTION AND HISTORY OF ISLET TRANSPLANTATION

Type 1 Diabetes Mellitus (T1DM), also known as Insulin-dependent Diabetes Mellitus (IDDM), is caused by the destruction of the insulin-producing β-cells of the pancreatic islets of Langerhans, either by an autoimmune (Type 1A) or an idiopathic (Type 1B) mechanism[1]. β-cell destruction leads to insulin deficiency and hyperglycaemia, the main characteristic of the disease. Virtually complete insulin deficiency leaves type 1DM patients at risk of developing diabetic ketoacidosis and most of them need exogenous insulin replacement to survive. Autoimmune destruction of β-cells has multiple genetic predisposition and is also related to poorly defined environmental factors.

Worldwide prevalence of Type 1DM is estimated to be around 0.09% with the highest rate (0.25%) in North America, according to 2005 data from the International Diabetes Federation[2]. In the USA the disease affects 300,000 to 500,000 people and the incidence is around 30,000 new cases per year[3].

Type 1DM is associated with the development of several chronic complications in affected individuals which are closely related to patients' long-term blood glucose levels, as demonstrated by The Diabetes Control and Complications Trial (DCCT) study[4]. Retina, kidneys, heart, blood vessels and nerves are the organs most commonly damaged by chronic hyperglycaemia in diabetes[5]. Nearly 30% of people with long-term T1DM develop kidney disease, which requires end-stage treatment with dialysis or even kidney transplantation.

The conclusions of the DCCT study raise an important topic: intensive insulin therapy can delay the onset and slow the progression of chronic diabetic complications[4], shedding light on the importance of effective control of blood glucose levels.

Current insulin replacement therapies for Type 1DM patients involve multiple (3 to 5) daily injections or continuous subcutaneous infusion by means of insulin pumps to improve blood glucose control[6,7]. The DCCT study also noted the adverse events associated with intensive insulin therapy regimens: weight gain and a significant increase in severe hypoglycaemic episodes.

Among the available therapeutic alternatives, pancreas (whole organ) and islet transplantation are the only ones that can reconstitute the physiologic pattern of insulin secretion and free Type 1DM patients from daily insulin injections[8-10].

Pancreas transplantation is being increasingly performed nowadays, in most cases successfully reverting the need for exogenous insulin in Type 1DM patients. Over 14,000 pancreas transplants had been registered by the International Pancreas Transplant Registry (IPTR) by the year 2000. From 1994 to 1998, one-year patient and organ graft survival rates were 94% and 82% respectively[11]. As pancreas transplantation is a major surgery requiring continuous immunosuppressive therapy to avoid organ rejection, it is only usually indicated for diabetic patients with chronic kidney disease who would also benefit from a combined kidney transplant. Current indications for a pancreas-alone transplantation are restricted to patients with a history of frequent and severe metabolic complications, a very labile and problematic diabetes, for whom the risks of insulin therapy are potentially greater than those of surgery and immunosuppressive drugs[8].

More recently, islet transplantation has been seen to be of benefit in the treatment of T1DM patients with very labile diabetes or when combined with a kidney transplant for diabetic patients who had developed chronic kidney failure[12,13]. While it also requires immunosuppressive therapy to prevent graft rejection, islet transplantation may well be an alternative to pancreas transplant as it involves a much simpler surgical procedure, meaning reduced risks for the patient.

The islets of Langerhans form what is known as the "endocrine pancreas" and are made up of $\alpha$, $\beta$, $\delta$ and PP cells, producers of the hormones glucagon, insulin, somatostatin and pancreatic polypeptide respectively. These hormones are the main contributors to the maintenance of glucose homeostasis[14]. There are about one million islets in an adult human pancreas, representing 1-2% of its mass.

The idea of using islet transplantation as treatment for T1DM was first envisioned in 1972, when Ballinger and Lacy demonstrated that experimental diabetes in rodents could be successfully reverted with transplanted islets[15].

During the 70s and 80s, several clinical transplants were carried out using foetal allogeneic or xenogeneic islets, owing to the inefficiency of the isolation techniques for application in adult human pancreases. The available information is scarce on most of these cases, but there is no evidence of confirmed cases of insulin independence[16].

In 1988 Ricordi *et al.* described an automated technique which allowed the isolation of a large number of viable islets from a human donor pancreas[17]. In 1990 Scharp *et al.* reported for the first time insulin-independence after islet transplantation in a T1DM patient, although for only a short period of time; less than a month[18]. At that time, insulin independence after islet transplantation was also obtained for prolonged periods of time (up to five years) after the transplant of allogeneic islets in patients who had the entire pancreas and liver surgically removed due to abdominal cancer[19]. In a different approach, successful results also came from patients with chronic pancreatitis submitted to total pancreatectomy and subsequent islet auto transplantation[20].

Disappointingly, success rate after islet transplantation remained extremely low in most T1DM patients, however. Data presented by the International Islet Transplant Registry (ITR) in 2001 for 355 transplants performed between 1990-1999 showed that only 11% of the cases reached insulin independence for a period of one year after the transplant[21].

One of the most significant breakthroughs in the islet transplant field came in 2000 in a landmark study published by the group from the University of Alberta in Edmonton, Canada[13]. After introducing modifications to the islet transplant and immunosuppressive protocol, this group reported seven consecutive patients treated under the "Edmonton Protocol", all of who maintained insulin independence after one year.

The main characteristics of the Edmonton Protocol were the use of a new, steroid-free immunosuppressive strategy consisting of daclizumab (anti-CD25 monoclonal antibody) induction, sirolimus (rapamycin) and

low dose tacrolimus (calcineurin inhibitor) maintenance; an islet alone transplantation for selected T1DM patients suffering from hypoglycaemia unawareness or a very labile diabetes; transplantation of a large mass of islets to each patient, often administered as two or even three infusions from sequential donors and the isolated islets were prepared for transplant in the absence of xenogeneic proteins such as bovine albumin[22].

The transplant procedure used in the Edmonton Protocol was also extremely simple and considerably non-invasive, posing a much reduced surgical risk. The isolated islets are grafted to the liver through a percutaneous trans-hepatic ultrasound (US) guided approach of the portal vein with local anaesthesia. After embolising small portal capillaries and undergoing neovascularisation, the transplanted islets start producing and secreting insulin.

The results reported by the Edmonton group led to the creation of several other islet transplant centres around the world. Today there are probably over 60 groups, half of which are in the United States, and an estimated 500 islet transplants have been made based on the original Edmonton Protocol or its variations and improvements since 2000[22]. Our group at the Pontifícia Católica Universidade do Paraná, in Curitiba, Brazil, after preparing the islet laboratory and undergoing training periods with the Edmonton and Miami groups, started human islet isolation work in 2004[23] and in 2005 we successfully performed the first islet transplant in a T1DM patient.

## HOW ISLETS ARE ISOLATED AND TRANSPLANTED

Pancreases for islet isolation are generally obtained from multiorgan brain-dead donors. Some donor and organ characteristics seem to affect islet isolation yield and viability, emphasising the need to establish selection criteria for organ acceptance and rejection[24].

The organ is procured through a conventional technique[25]; pancreas is perfused with cold University of Wisconsin (UW) solution, harvested *en bloc* with duodenum-spleen and rapidly sent to the laboratory immersed in cold UW solution (cold ischemia time should be under 8 hours to maintain cell viability). Alternatively, to prolong transportation time, the organ can be sent to the islet lab using the "two-layer" method. This technique consists of immersing the pancreas between a lower layer of perfluorocarbon (PFC) and an upper layer of UW solution[26]. The PFC is an extremely dense solution with a high oxygen affinity. Its high density means both solutions will not mix, the pancreas will be kept in its interface and the oxygen will be continuously liberated from the PFC to the pancreas, oxygenating the organ.

In the lab, islet isolation is performed following the automated technique described by Ricordi *et al.*[17], with some modifications introduced by the Edmonton Protocol (Fig. 1)[27]. Initially the pancreas is cleaned to remove all non-pancreatic tissue, then the pancreatic duct is canulated in order to permit intraductal perfusion of the organ with an enzymatic collagenase (Liberase™ HI) solution. Liberase is a highly purified, low endotoxin content collagenase blend used at the pancreas digestion step that has shown to improve viability of the isolated cells[28]. Intraductal collagenase perfusion of the pancreas is performed under controlled temperature (4°C) and pressure in a specially designed perfusion chamber developed at the University of Alberta (Fig. 2)[29]. After collagenase loading, the pancreas is cut into smaller pieces and then transferred to the Ricordi's chamber (Fig. 3), where tissue dissociation will occur under enzymatic and mechanical digestion during approximately 20-30 minutes at 37°C, in a continuous flow system with recirculation[17]. To monitor the digestion process, samples are taken from the effluent solution containing the dissociated tissue, stained with dithizone (diphenylthiocarbazone) - a zinc-binding molecule - and

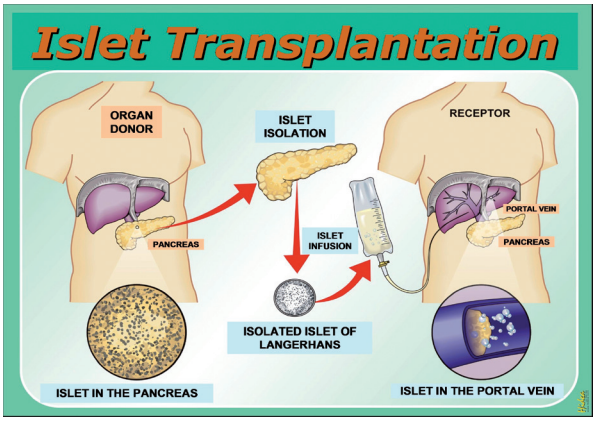


**Figure 1**

Islet transplantation: from donor to infusion

**Figure 2**

Collagenase pancreas perfusion with the Perfusion Chamber

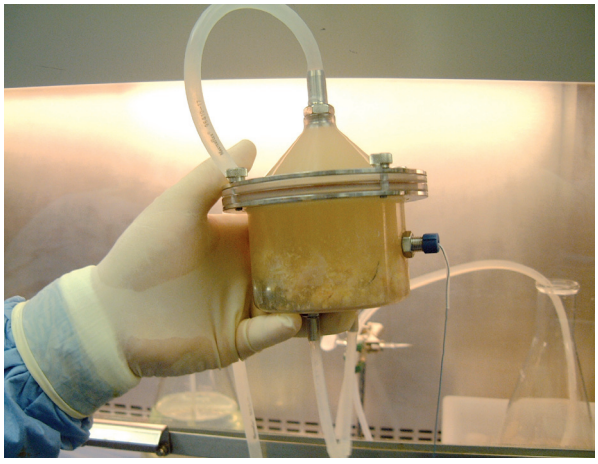

**Figure 3**

Pancreas digestion in the Ricordi's chamber

examined microscopically. Dithizone binds to the zinc complexed with the insulin molecules and stain islets in red. Then, when most islets are separated from the acinar tissue, the solution containing the dissociated tissue is diluted, cooled to 4°C and human albumin is added to stop digestion. All the digested tissue is collected, washed and concentrated by centrifugation to proceed to the purification step.

Islets are purified from non-endocrine tissue by a continuous Ficoll or Iodixanol density gradient centrifugation in a special centrifuge, the COBE 2991 cell processor. Gradient fractions are collected separately, stained with dithizone and examined under the microscope. Fractions containing islets with more than 30% purity are washed, concentrated by centrifugation and resuspended in culture media. Samples of the final product are taken to evaluate yield, purity, viability, cellular composition, volume of the cell pellet, endotoxin and microbiological contamination. Islets are counted as Islet Equivalents (IE), where 1 IE corresponds to an islet with a diameter of 150 μm[30]. Isolated islets (Fig. 4) can then be immediately transplanted or maintained in culture for a 48 hour period. Islets are cultured in media supplemented with human albumin and additional growth factors shown to improve the viability of cultured cells[31,32]. This culture period before the transplant is logistically very useful. It can be used to perform the islets' quality control and pre-transplant compatibility tests, to call the transplant team, to prepare the patient for the transplant, start the immunosuppression induction drugs, and even to send the islets to a distant transplant centre, as has been successfully done by several groups[33-35].

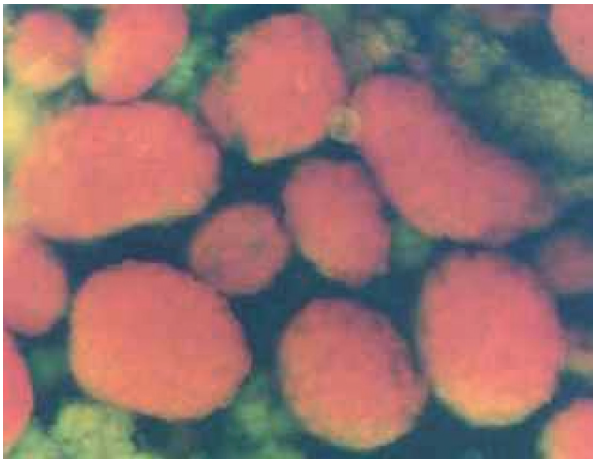

**Figure 4**

A sample of isolated human islets, stained with dithizone (80x)

Acceptable islet preparations for transplant should contain at least 4,000 IE per Kg body weight of the receptor, in order to reach a total dose of 12,000 IE/Kg with a maximum of 3 transplants/infusions per patient. The Edmonton Protocol established a total number of 12,000 IE/Kg as the minimum dose required to obtain

insulin independence with islet transplantation, often administered as two or three infusions from sequential donors. The packed cell volume of the preparation to be infused should not exceed 10 mL, to avoid the risks of thrombosis, portal hypertension and bleeding. This packed cell volume to be infused is diluted into approximately 150-300 mL of transplant media supplemented with human albumin and heparin. Transplant media containing the islets is then placed in a transfer bag and transported to the hospital.

Receptors for the islet transplant are selected on an ABO blood group compatibility basis and after a negative pre transplant donor-recipient lymphocyte cross match test.

The islets are implanted into the liver through a percutaneous trans-hepatic infusion in the portal vein (Fig. 5). The approach to the portal vein is made through cannulation with a Chiba needle guided by ultrasound or fluoroscopy under local anaesthesia[36]. To avoid bleeding due to the infusion, the portal pressure should be monitored sequentially through a 3 way stopcock. The catheter is connected to an infusion line which is connected to the islet bag and the islets are then transferred to the portal system by gravity. The infusion generally lasts 20-30 minutes. At the end, to avoid bleeding, the tract is sealed with coils before removing the catheter. An alternative approach to access the portal vasculature can be made by cannulation of a tributary branch of the mesenteric vein during a surgical laparotomy, a technique that can potentially reduce the risk of bleeding during the infusion[37].

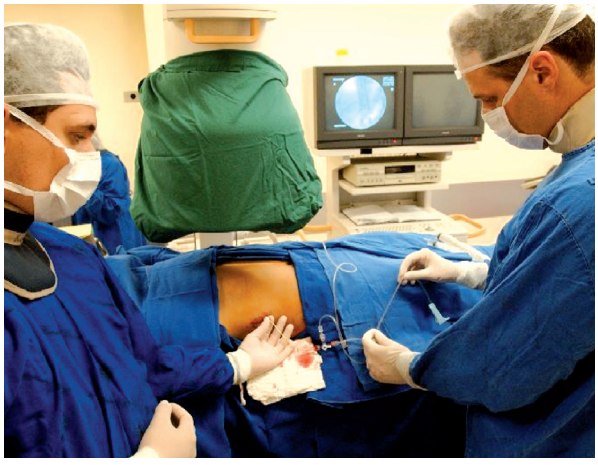

**Figure 5**

Percutaneous intraportal vein placement of catheter for islet infusion.

Glycaemic monitoring should be intensive during the immediate post-transplant period and insulin therapy is used to maintain adequate blood glucose levels. Experimental data supports the benefits of euglycaemia for islet engraftment[38].

## CURRENT STATUS OF ISLET TRANSPLANTATION

Latest islet transplantation follow up results were recently published by several groups, and have not been so optimistic. In the report by the Collaborative Islet Transplant Registry (CITR), representing the North American groups, insulin independence was 58% at twelve months post-transplant[39]. These results are also available online at the CITR web site (http://spitfire.emmes.com/study/isl/reports/reports.htm). The results of the international trial of the Edmonton protocol for islet transplantation, a multicentre study conducted by the Immune Tolerance Network (ITN) to explore the feasibility and reproducibility of the Edmonton Protocol, showed a 44% success rate at one-year follow up[40]. The Edmonton group has also published their 5-year follow up results, presenting 10% insulin independence at the end of this period[41]. Despite the lower rates of insulin independence seen in this series, most patients have shown continued production of C-peptide and a drastic reduction of hypoglycaemia episodes, in addition to improved long-term blood glucose levels, stressing the effectiveness of the technique in improving the glycaemic control and the quality of life for diabetic patients.

As clinical indications for islet transplantation are very restricted, a careful patient selection is paramount to guarantee the best risk/benefit ratio and consequently the success of the procedure. A study aiming to more objectively define the criteria for islet transplant candidate selection has recently been reported[42].

Islet transplantation is considered a very safe procedure, although it still carries potential risks such as bleeding, thrombosis of the portal vein, and allosensitisation. Hepatic steatosis has also been reported but it was not associated with clinical sequelae. Adverse events related to the immunosuppressive regimen are

common and include mouth ulceration, anaemia, leukopenia, dyslipidaemia, diarrhoea, hypertension, tumour, pneumonia, pyelonephritis, nephrotoxicity, among others[22,40].

Problems related to allograft rejection, recurrence of autoimmunity, primary non-function of the infused islets, due to both apoptosis and immediate destruction consequent to an "instant blood-mediated inflammatory response" (IBMIR)[43], remain the most important causes of islet graft destruction[22], requiring an increased β-cell mass to achieve insulin independence.

The effects of islet transplantation on long-term complications of diabetes are still not clearly determined, but preliminary reports have shown protective benefits. Studies headed by Fiorina *et al.* have shown improved survival, cardiovascular and endothelial function[44,45] and also an enhanced kidney graft survival and function[46,47] in successful islet-kidney T1DM transplant recipients. Another two studies, however, have shown worsening of the native kidney function in T1DM patients recipients of an islet-alone transplant with a previous baseline decrease of kidney function[48,49]. The impairment of renal function after an islet-alone or an islet-after-kidney transplant using a sirolimus/tacrolimus-based immunosuppressive regimen was also reported by Andres *et al.*[50]. These two latter reports cast serious doubts on the safety (for the kidney function) of the most commonly used islet transplant immunosuppressive regimen.

Another important effect observed is that while intrahepatic islet transplantation may reconstitute a regulated insulin secretion, it generally fails to restore the hormonal counter-regulation in response to hypoglycaemia[51].

Although significant advancements have been achieved with the Edmonton Protocol and the modifications to its original technique[52], all of these latest reports reinforce the view that there is still a long way to go to get better results with islet transplantation and also until it can be considered for most T1DM patients.

## FUTURE PERSPECTIVES

Several lines of research have been developed over recent years to deal with the current difficulties of islet transplantation.

The main obstacle to be surpassed is the need for the chronic use of immunosuppressive agents to avoid graft rejection. Thus, when this type of transplant is considered today, its possible benefits (metabolic stability, reduced chronic complications and insulin shot independence) must be compared to its potential side effects (proneness to infections and cancer occurrence, and toxicity in organs such as the kidneys). Studies focusing on the islet immune protection, the transplant tolerance induction and the development of new immunosuppressive agents are crucial in this area[53].

As to the availability of islets for transplantation, many aspects of the isolation technique have recently been dealt with in order to enhance its efficiency, considering that 2-3 organ donors are still necessary to obtain enough islets to treat a single patient[27,54]. Nowadays, hope comes from the possibility of generating insulin secreting tissue from a renewable source, such as embryonic and adult stem cells[55], or even from β-cell regeneration[56]. Additionally, research on xenotransplant has made great strides, making it a potentially good alternative[57,58].

Finally, the discovery of new, more physiologic implant sites are also required, as some studies have shown that the liver is probably not an adequate home for the islets, due to the exposure to a hyperglycaemic environment arising from the portal circulation and to the high concentrations of immunosuppressive drugs[59].

Considering the great number of studies currently underway on both the basic and clinical fronts of islet transplantation, it is not impossible to imagine the renaissance of this promising technology within the next few years.

***Conflict of interest statement.*** None declared.

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