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Combined Kidney-Islet Transplantation

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1. Introduction

The possibility to transplant uniquely the endocrine part of the pancreas, islets of Langerhans, with the aim to recovery the endogenous insulin production in diabetic patients has always aroused attention from researches.
The initial experience of this procedure however was unsatisfying especially for what concerns the long term efficacy of the islet transplantation. The exciting results obtained by the Edmonton group in 2000, 100% of insulin independence in seven diabetic patients after 1 year from the islet transplant, encouraged several centers worldwide to approach this technique. Since then several programs of islet transplantation have been launched, and important multicentric clinical trials including an high number of patients were realized.
The Collaborative Islet Transplant Registry (CITR) collects data from 27 North American, 3 European and 2 Australian islet transplant centers and reported that a total of 412 patients underwent an islet transplantation in the time period between 1999-2009.
The global long-term results of CITR demonstrated an insulin independence after islet transplantation in a low percentage of cases but a partial function of the graft, and consequently important advantages for the patients, in the majority of these.
Actually islet transplantation is considered a valid therapeutic option only for selected patients affected by type 1 diabetes mellitus (DMT1). This limitation is a consequence of the benefit/cost ratio between improvement of the glycemic control and the necessity for transplant recipients to be treated with chronic immunosuppressive therapy which has, as well known, important side effects.
These considerations and the availability of new generation basal insulin and sophisticated micro insulin pumps lead the majority of European centers to perform islet transplantation almost exclusively in combination with kidney transplant in DMT1 patients candidate (simultaneous islets-kidney transplant), or just subjected (islet after kidney transplant), to a kidney transplantation for end-stage diabetic nephropathy. These patients therefore would anyway be treated with immunosuppressive drugs.
Even if the combined kidney-pancreas transplantation showed excellent results in DMT1 patients with end-stage diabetic nephropathy, the combined kidney-islet transplantation is considered a valid option in selected cases for this patient category.

2. History of islet transplantation: Past and current era

The history of the islet transplantation is long. The first transplant of fragments of the pancreatic gland in order to cure diabetes dates back even to the 20th December 1893, 28

years before the discovery of the insulin. Two English medical doctors from the Bristol Royal Infirmary Hospital, Dr. Watson-Williams and Dr. Harsant, harvested a pancreas from a deceased sheep and transplanted three pieces of the gland into the subcuticular tissue of a 15-years-old boy with uncontrollable diabetic ketoacidosis. Obviously, despite a temporary improvement of the clinical situation, the xenotransplant failed after three days for acute rejection.

After that first experiment almost one century passed before Paul Lacy and collegues in 1967 developed the technique of islet isolation in rats. Two important innovations made this procedure possible: the injection of digestion enzyme solution in the pancreatic duct and the centrifugation with different density gradients to separate the islets from the discarding tissue.

After few years the improvement of the glycemic control by intraperitoneal transplantation of islets was demonstred in diabetic rats (Younoszai et al., 1970) and subsequently the liver, using the same experimental model, was selected as preferable implantation site (Kemp et al., 1973). Actually the liver, by islets injection through the portal vein, is still the site preferably used for islet transplantation in the clinical setting.

The first clinical series of islet transplantations was reported in the late seventy using azathioprine and steroids as immunosuppressive therapy (Najarian et al., 1977). Although these first cases did not experience any complications the efficacy of the transplant was very limited. Seven patients over seven failed to reach the insulin independence after intraperitoneal or intraportal islet transplantation even though some of them reduced the need of exogenous insulin for a period.

Interestingly the first real clinical success in the field of islet transplantation was reported in one case of combined islet-kidney transplantation performed on a DMT1 uremic patient in Zurich in 1978. This patient reached the insulin independence and maintained it almost one year after the embolization in the spleen of fragments of donor pancreas (Largiader et al., 1979). In 1990 a series of nine islet transplantations was reported by the University of Pittsburgh. The patients underwent multivisceral resections for tumors and sequentially liver, kidney and small bowel transplantation: islets were injected in the portal vein at the liver reperfusion. More than 50% reached and mantained the insulin-indipendence until their death caused by neoplastic relapse (Tzakis et al., 1990). Subsequently other positive experiences were reported (Ricordi et al., 1992) but the global clinical results obtained by the Islet Transplant Registry from the total amount of islets transplantation performed between 1974 and 1999 were very disappointing with an insulin-indipendence presents in only about 10% of cases at one year from the transplant.

In 2000 the group of the University of Edmonton reported 100% of insulin indipendence at 1 year from islet transplantation in a series of 7 patients (Shapiro et al., 2000). Such extraordinary result was possible thanks to the employment of a protocol subsequently called the "Edmonton protocol". The key elements of this protocol were principally two. Firstly the recourse to two or more islets intrahepatic transplants in the same recipients provided an higher total number of transplanted islets (over 11000 IEQ/Kg of the patient body weight). Secondly the use of an immunosuppressive regimen without steroids and their hyperglycemic effect and consisting in interleukin-2 receptor blocking antibody daclizumab (Zenapax®) for induction therapy and sirolimus (Rapamune®) combined with low doses of tacrolimus (Prograf®) for chronic therapy.

Subsequently, with the aim to assess the applicability and reproducibility of the results obtained from the Edmonton group, a multicentric study started using the Edmonton protocol involving 9 transplant centers, 6 of which were American and 3 European.

The data from this study reported in 2006 did not confirm however the Edmonton results, showing an high variability in the outcome of the transplantation according to the isolation centre (Shapiro et al., 2006).
The critical passage in the procedure of islet transplantation is exactly the phase of organ processing in order to isolate the islets of Langerhans. These considerations lead to the development of several networks in which the isolation procedure is performed by few specialized and experienced centers and the islet transplantations are spread to several different centers even at long distance (Kempf et al., 2005).
In 2008 the Collaborative Islet Transplant Registry reported approximately a 30% of insulin independence by 3 years postoperatively over 325 adult recipients which were treated between 1999 and 2007 with an islet alone or a combined kidney-islet transplantations. However more than 75% of the recipients maintained a residual graft functionality detected by the endogenous secretion of C-peptide at 3 years from the transplantation.
This apparently disappointing outcome, showed anyway an important improvement in the quality of life of the patients reducing the episodes of severe hypoglycemia and the development of complications related to the diabetic disease (Alejandro et al., 2008).
In particular some studies have also focused on comparing the outcome of diabetic patients who underwent combined kidney-islet transplantation versus patient operated with kidney transplantation alone.
The group of Milan showed a decreased risk for micro and macroangiopathy, an improvement in the cardiovascular functionality and a reduced neuropathy also in cases of partial islet function after transplantation (Fiorina et al., 2003; Del Carro et al., 2007). Moreover the same authors showed that the improved glycemic control in patients with combined kidney-islet transplantation significantly increased also the kidney graft survival when compared to DMT1 patients with transplantation of the kidney alone (Fiorina et al., 2005).

3. Islets of Langerhans procurement

3.1 Pancreas harvest

The organs used for the islets isolation generally are pancreas previously proposed and not utilized or excluded for the whole pancreas transplantation. This strategy, adopted in order to decrease the competition between the two types of transplantation, allows in the case of pancreas for islets isolation the use of organs from donors with high BMI or >50 years old. Moreover, with the aim to expand the pool of donors, some authors reported positive experience of islet transplantation using donors after cardiac death (Saito et al., 2010).
The harvesting procedure of the gland is similar to the procedure for the whole pancreas transplantation. However, after perfusion with cold preserving solution, the pancreas is collected paying particular attention not to section the pancreatic capsule, event that may impair the enzymatic digestion while, obviously, the accuracy in the isolation and preservation of pancreatic vessels is not important as in case of the pancreas procurement for the transplantation of the whole gland.
The pancreas is harvested en bloc with a portion of duodenum and the spleen. After the pancreas is procured it is kept in cold preservation solution at 4°C. At the moment the pancreas preservation is obtained thanks to a double-layered system: the organ is placed within a superior layer of preservation solution and an inferior layer of perfluorocarbons (PFC) which are constantly oxygenated and help maintaining an high oxygen solubility

coefficient. This method allows the development of a highly oxygenated environment for the pancreas which is of great importance for the protection of the islets (Hering et al., 2002). The gland can be kept in this solution for several hours although it was reported that the best results were achieved when the cold ischemia time was < 16 hours at the beginning of the isolation procedure (Tsujimura et al., 2004).

3.2 Automated method for islets of Langerhans isolation

Before the beginning of the isolation procedure the spleen and the duodenum are removed from the pancreas and an accurate dissection and discard of the peripancretic fat, lymphonodes and vessels is performed (Fig. 1).

The procedure currently used to extract islets from human pancreas is the so called automated method for isolation of the islets of Langerhans, established in 1987 by Ricordi and collegues**.**

This procedure consists of two phases: digestion and purification phase. The digestion phase includes the digestion of the collagen scaffold of the pancreas releasing the esocrine and endocrine tissues within the gland. It includes a procedure of enzymatic and mechanical digestion. The phase of purification is aimed to obtain only the endocrine part of the gland, islets of Langerhans, separating them from the remain of the gland which is useless (acinar cells, ductal elements, fat tissue, lymph nodes, ganglia, etc).

Digestion phase: after the preparation of the pancreas the gland is devided at the isthmus and the pancreatic duct is cannulated in the proximal part (head and body) and in the distal part (body-tail) with two angiocatheters 18 gauge. The solution containing the digestion enzyme is injected in the Wirsung duct with a pressure of 180 mmHg slowly distending the two parts of the gland. The collagenase at warm temperature (37°C) is activated and starts the enzymatic digestion of the internal scaffold of the pancreas (Fig.2).

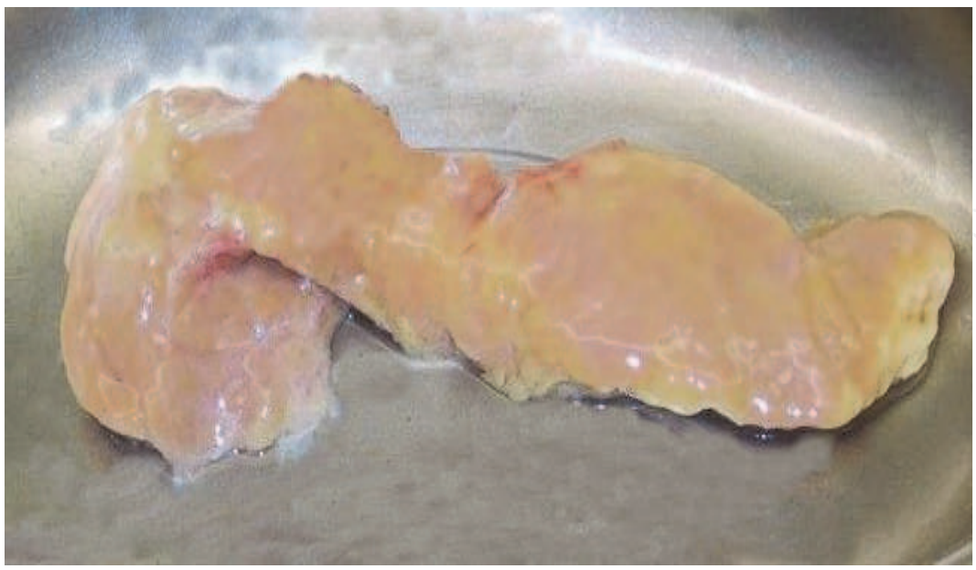


Fig. 1. Pancreas prepared for the isolation procedure.



Fig. 2. Cannulation of the pancreatic duct and injection of the collagenase solution.

After some minutes the two portions of the pancreas are divided in smaller pieces and placed in a digestion chamber named "Ricordi chamber" after its inventor. This chamber is composed of a superior and an inferior part divided by a semi-permeable membrane which has holes of about 300 μm. Seven stainless steel balls together with the fragments of the pancreas are put into the inferior part, which is then filled with the digestion solution and closed together with the superior one. The chamber is connected to a mechanical arm with 10 cm excursion which is activated with a sussultory movement (300 oscillation/min) helping the complete mechanical digestion of the pancreas through the steel balls in the chamber. In the meantime a peristaltic pump connected to the system is activated creating a flow of 40 ml/min. The digestion runs in a closed circuit where warm Hank's solution is pumped in the inferior chamber and the tissue released in the solution passes in the superior chamber through the filter. The solution is collected in a cylinder passing in a refrigerator circuit at 4°C; at this temperature the activity of the enzyme and consequently the digestive process is stopped. Samples of the solution are collected from the circuit through a spigot every 2-3 minutes to monitor the progress of the digestion. When free islets are found in the samples the system is converted from closed to open: the solution is collected from the chamber into containers placed on ice. The procedure is stopped when no more islets are detected at samples (Fig 3).

Phase of purification: this includes the separation of the islets from the waste tissue through centrifugation cycles on different Ficoll density gradients. Islets which have a lower specific weight than the other structures, remain in the supernatant, the less dense part of the solution**.** Nowadays this procedure is generally performed using a COBE® 2991 cell processor system (Fig 4). At the end of the procedure samples of the islets preparation are collected and evaluated through a staining with dithizone (DTZ) which marks zinc in the

insulin granules resulting in a characteristic red stain. Adding few drops of DTZ solution to a sample is possible easily evaluate the morphology and number of the isolated islets through a computerized digital analysis. Specific features of the final volume of islets are required in order to perform the islets transplantation, in particular purity (> 90% of the preparation composed by islets) and adequate number of islets (Fig.5).

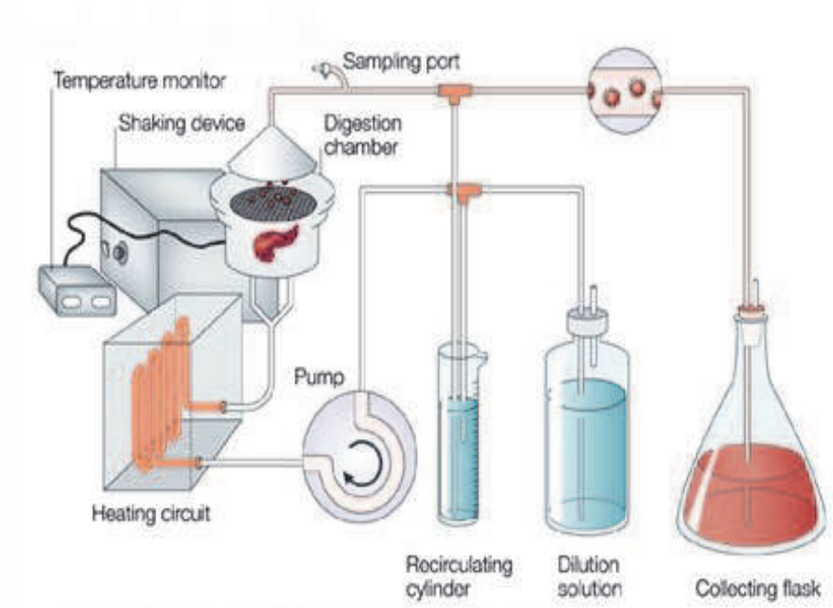


Fig. 3. Schematic representation of the automated method for islets of Langerhans isolation (modified from: Ricordi and Strom, *Nature Reviews Immunology* 2004).

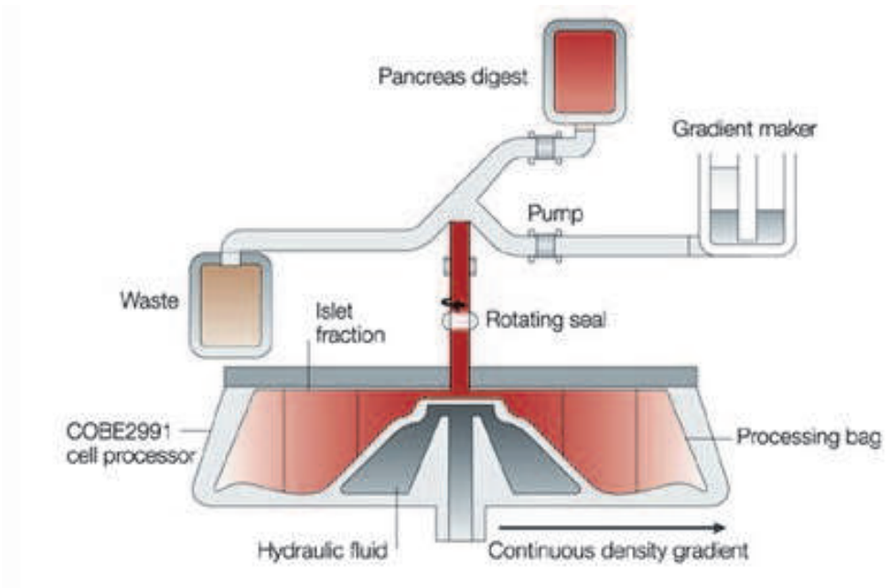


Fig. 4. Islets of Langerhans purification by density gradient separation (modified from: Ricordi and Strom, *Nature Reviews Immunology* 2004).

Although the procedure is quite standardized, only centers with the greatest experience in the field can count on an high percentage of procedures with a satisfactory purity and quantity of islets for the transplantation. Indeed the more the pancreas is manipulated in order to discard the exocrine part, the more islets are lost during this procedure. An additional important variable that reduces the reliability of the isolation process is the different enzyme lot used for the digestion procedure. The adequate amount of islets obtained is calculated with respect to the body weight of the recipient and resuspended immediately before the intrahepatic transplantation in 100 mL of adequate solution (45 mL of HBSS, 0.2 mL od HEPES 1M, 50 mL 20% Human Albumin and 2000 IE of heparin).

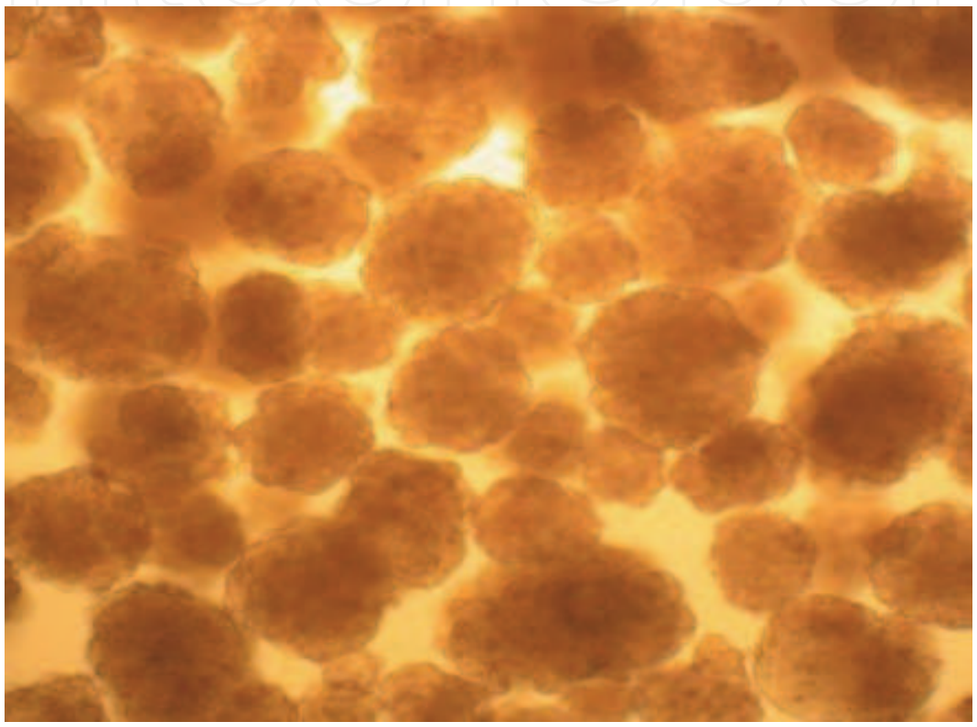


Fig. 5. Highly purified human islets of Langerhans at the end of the isolation procedure.

4. Islet transplantation procedure

The islet transplantation can be performed at the same time as the kidney transplantation (simultaneous islet-kidney transplantation) or in diabetic patients who had previously received a kidney transplant alone (islet after kidney transplantation). In both cases AB0 compatibility and a negative serum cross-match between the pancreas donor and the recipient are required. Obviously when a simultaneous kidney-islets transplantation is performed the pancreas which will undergo the isolation procedure is generally harvested from the same donor of the kidney.

As previously reported in recent years networks have developed connecting several islet transplant centers and single centers dedicated to the procedure of isolation.

The GRAGIL, Swiss-French Multicenter Network of Islet Transplantation, was organized as to send the pancreas to the Genève center for the procedure of isolation; and then distribute the islets obtained to different transplant centers in the south-east area of France.

By this network islet transplantations were performed also in centre at long distance provided that it would be done within 72 hours from the end of the isolation procedure (Langer et al., 2004). This organization allowed a cost decrease and an increase in the experience of the isolation center with a positive rebound on the percentage of successful isolations and consequently on the number of the transplants performed (Kempf et al., 2005). Further similar collaborations were created between north european centers (Nordic Network) and between american centers (Porrett et al., 2007).

In the case of simultaneous kidney-islets transplantation while the pancreas undergoes the procedure of isolation, generally the recipient contemporaneously undergoes kidney transplantation. Once the islets are received, they are infused through a surgical or, radiological procedure.

The implantation site is usually the hepatic parenchyma through the portal system of the recipient. Islets are infused by gravity into the portal circulation and flow with the portal blood to lodge in the hepatic sinusoids (Fig 6).

The surgical procedure is performed after the conclusion of the kidney transplant through injection of the islets in the portal system by opening the peritoneum and catheterization of an ileal vein.

The percutaneous approach is done by a minimally invasive procedure requiring interventional radiology technology. The portal vein is reached by a percutaneous catheter placed under ultrasound or angiographic guidance (Fig. 7).

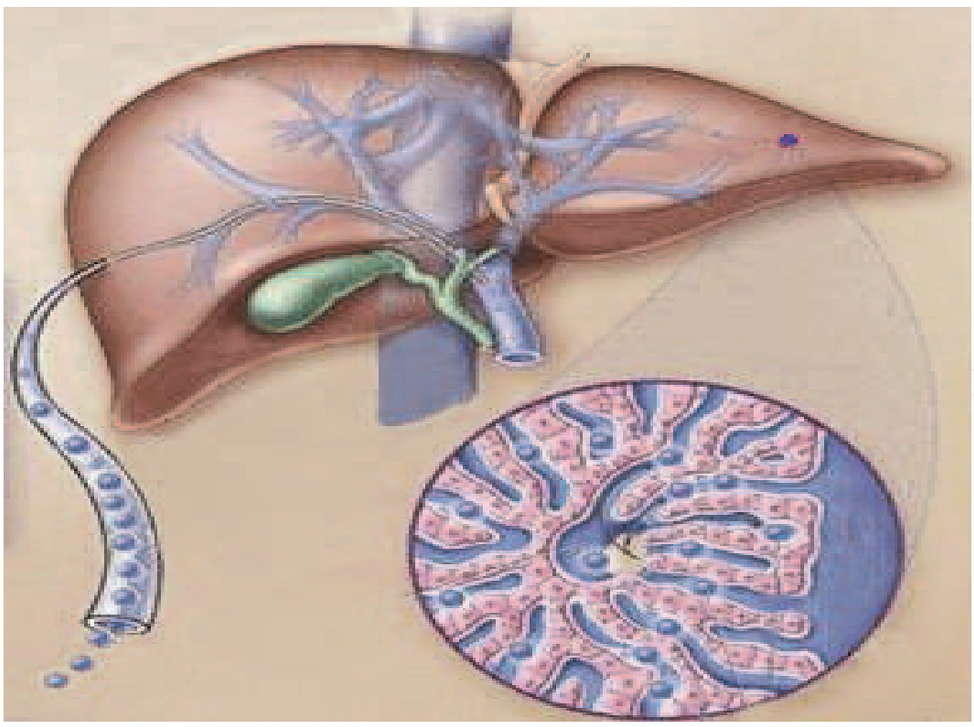


Fig. 6. Islet infusion into the recipient's liver (modified from: Robertson, *New England Journal of Medicine* 2004).

The radiological infusion of the islets can be performed few hours after the end of the kidney transplant or at long time after the operation, as for the islet after kidney transplant or in the case of subsequent islets infusions in patients just transplanted with islets.
Recently other implantation sites have been proposed in the clinical setting , like bone marrow (Cantarelli et al., 2009) or striated muscle (Christoffersson et al., 2010) which probably could show to be valid alternatives in a near future.

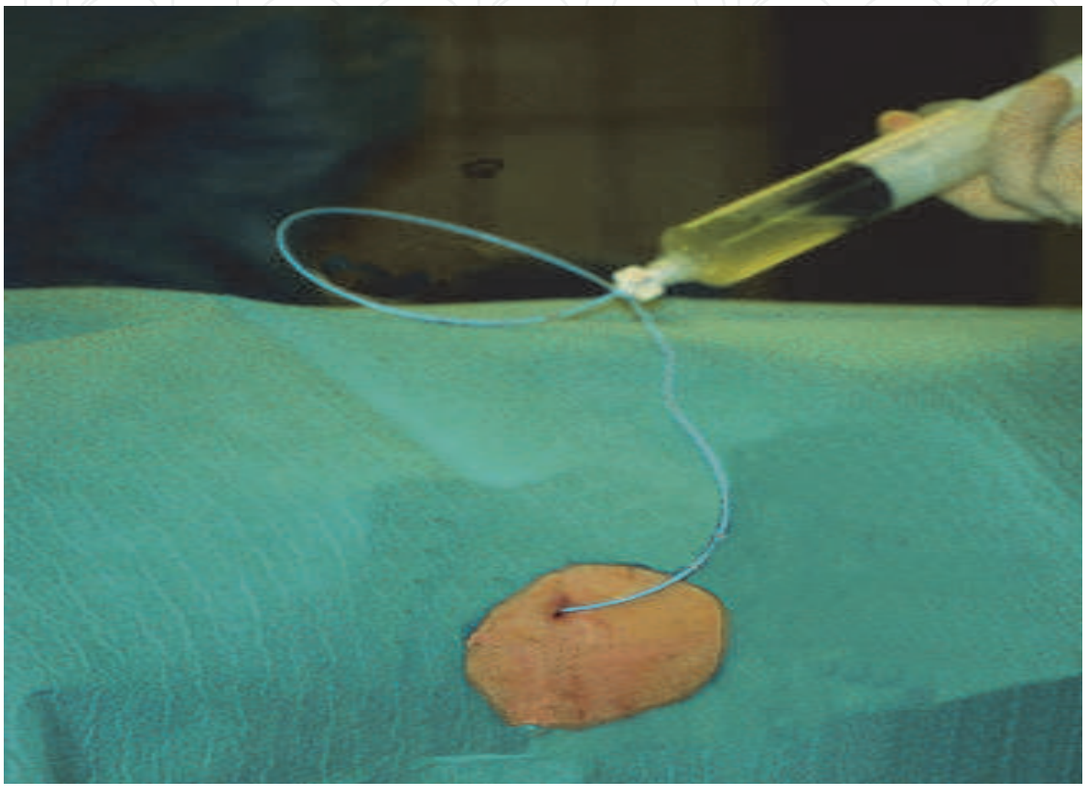


Fig. 7. Islet transplantation through a percutaneous catheter.

5. Complications related to islet transplantation

The procedure of islet transplantation proved to be very safe, especially when compared with the transplant of the whole pancreas. Data from CITR obtained from the analysis of more than 300 recipients showed that no complications occurred in case of injection by surgical approach and less than 10% of complications occurred in case of radiological infusion. Ower and collegues in 2003 showed that the most severe complications occurred in this case were intraperitoneal haemorrhages; anyway these were generally treated conservatively. The exact cause of bleeding in each case is often difficult to determine; however the peri-operative use of heparin to prevent portal thrombosis likely plays a role. The use of fibrin tissue sealant and embolization coils in the hepatic catheter tract seems to be effective in minimizing the bleeding risk.
Another complication related to the intrahepatic islet transplantation procedure is the insurgence of portal hypertension that can occur acutely during the islet infusion especially

in the case of subsequent infusions (Casey et al., 2002). The portal pressure however generally normalizes after the acute phase of the procedure.
Branch portal vein thrombosis was also frequently reported in the past; anyway this complication is generally limited and controlled with appropriate anticoagulation therapy. Actually the use of purer islet preparations, greater expertise in portal vein catheterization and new radiologic devices (catheters medicated for anticoagulation) will constantly reduce the risk of portal vein thrombosis although it will never be completely removed. A complication frequently reported is even the post-transplant elevation of liver enzymes but this is usually temporary and heals without further intervention.
In the past the appearance on magnetic resonance imaging (MRI) of intrahepatic periportal steatosis, occurring in a minority of islet recipients, has raised cautions. This finding is supposed to be due to the local effect of insulin produced by the transplanted islets on the hepatocyte metabolism and is reversible, since the complete resolution of MRI changes was reported in a patient after the graft function failed completely (Markmann et al., 2003). Successively the onset of focal steatosis in patient after islets transplantation was studied by sonogram (Maffi et al., 2005). These authors reported that signs of steatosis were often observed in patients after islet transplantation with total or partial function of the graft and normal liver function anyway was maintained in all of these. It was even proposed to consider the disappearance of this signs as a early marker of graft dysfunction.

6. Combined kidney-islet transplantation: Indications

The American Diabetes Association guidelines (http://www.diabetes.org/) remember that a combined kidney-pancreas transplantation should be always considered in case of uremic patient with DMT1 candidate to kidney transplantation. This recommendation is the result of the beneficial effects observed in terms of quality of life and survival after kidney-pancreas transplantation into patients suffering for DMT1 (Reddy et al., 2003). However since the procedure of pancreas transplantation has an high incidence of mortality and morbidity (Gruessner et al., 2004) it can be proposed only to selected population of patients candidate to kidney transplantation for diabetic nephropathy. In this the European Trial of Immunosuppression in Simultaneous Pancreas Kidney Transplantation (EUROSPK) study group reported that repeated laparotomies in the first 3 months after transplantation were performed in 35% of all the patients. Considering the much lower incidence of complication after islets transplantation several kidney-pancreas centers have also started programs of kidney-islets transplantation basing on the fact that these two procedures are complementary and suitable for patients with different features. Although the success of pancreas transplantation in term of graft survival is higher than islet transplantation with 80% of insulin-independency after 3 years (http://www.iptr.umn.edu/IPTR), some patients can be preferably directed towards a kidney-islet transplantation.
Actually the patient selection for either two therapeutic options is performed after a careful evaluation of possible advantages and disadvantages, with special regard to age and comorbidities. Patients at high risk of intraoperative complications are preferentially assigned to the less invasive procedure of islet transplantation, while younger and healthier patients are generally addressed to pancreas transplantation (Gerber et al., 2008).
In particular kidney-islets transplantation is preferred to kidney-pancreas for patients over 50 years of age or with severe macroangiopathy. Islet transplantation should also be

considered for all the patients who underwent kidney-pancreas tranplantation and have functioning pancreatic graft removed for complications as recidivant anastomotic leackage. In this case the possibility to use the removed pancreas for the islets isolation procedure has to be considered. The obtained islets could be then eventually transplanted in the same patient. The esecution of a combined kidney-islet transplantation is also a possibility for uremic patients with DMT1 and a good compliance to insulin therapy with lack motivation to undergo a combined kidney-pancreas transplant. These patients indeed may not accept the elevated peri-operative morbidity associated with kidney-pancreas transplant, which is much higher than with kidney alone transplant. The recipient's weight is also a key factor in the choice between pancreas or islet transplantation. Considering that the volume of islets necessary to obtain success after transplant is calculated with respect to the body weight of the recipient, patients with high weight are generally excluded from the procedure of islets transplantation and treated with a combined kidney-pancreas transplant.

The islet after kidney transplantation should be considered instead of the pancreas after kidney transplantation in patients over 45 years of age or with severe macroangiopathy if the creatinine blood levels are stable below 2 mg/dl at least six months after kidney transplantation and steroids discontinuation (Vantyghem et al., 2009).

Contraindications to the islets transplantion are severe heart diseases (as untreatable coronary artery diseases, severe dilated cardiomyopathy, previous stroke or recurrent transient ischemic attacks) and hepatic diseases as severe steatosis if the recipient liver is used as transplantation site.

In recent years positive experiences have been reported in the field of kidney-pancreas transplant in insulin-dependent patients with type 2 diabetes mellitus (Light et al., 2005). Nath and collegues in 2005 showed that these patients, as well as DMT1 patients, had an higher beneficial effect from a combined kidney-pancreas transplantation than a kidney transplantation alone. On the basis of the high percentage of DMT2 patients with end-stage renal disease and their characteristics, related to macrovascular degeneration, they are generally patients older and in worse clinical conditions than DMT1 patients likely the combined kidney-islet transplantation could be a valid therapeutical option to combined kidney-pancreas transplantation for these patients if they are lean and with low insulin-resistance.

7. Combined kidney-islet transplantation: Aims and results

As previously reported, the global results of the islet transplantations performed in the last decade showed a progressive decline in graft function in the months following the procedure which allows a long-term insulin-independence in a limited number of patients but a residual partial graft function in the majority of them.

In order to extend the period of insulin-independence after transplant several centers have adopted the strategy to perform two or more islet infusions in the same recipient using different pancreas donors. However it was observed that this strategy could increase the risk of sensitization of the patients and therefore jeopardize the possibility of an eventually kidney retransplantation (Campbell et al., 2007). On the basis of these considerations, nowadays the goal of islet in combination with kidney transplantation is not necessarily to arrive at the insulin-indipendence but the achievement of a good glycemic control by a single islet transplantation (Lehmann et al., 2008). A single infusion of functioning islets can reduce long term levels of HbA1c and consequently prevent the occurrence of severe

asymptomatic episodes of hypoglycaemia and delay diabetes-related complications (Alejandro et al., 2008; Cure et al., 2008).

The group of Zurich (Gerber et al., 2008) reported their own experience in the field of combined kidney-islet and kidney-pancreas transplantation. They compared the long-term outcomes of diabetic patients subjected to kidney-islets transplantation and treated with immunosuppression carried out according with the Edmonton protocol versus patients subjected to kidney-pancreas transplant treated with conventional immunosuppression. In particular in the kidney-islet group induction therapy was performed with daclizumab and long-term therapy was carried out through levels of sirolimus and tacrolimus respectively of 7-10 μg/l and 3-6μg/l. In the kidney-pancreas group the induction therapy was performed with basiliximab and chronic immunosuppression was based on tacrolimus, mycophenolate mofetil and prednisone. The study demonstrated a similar kidney function and survival and an improvement of the blood glucose control in both groups.

Actually different protocols of immunosuppression are applied by different transplantation centers to patients trated with a combined kidney-islet transplantation. All of these protocols are steroid free and schedule different combinations beetween daclizumab or etanercept during the induction period plus mycophenolate mofetil or sirolimus and low-dose of tacrolimus or cyclosporine A. Since the number of the islets transplantation performed worldwide is low, a long period of time will be necessary in order to define which immunosuppressive protocol is the most favourable. Nowadays they seem all equally effective as long as steroids free (Alejandro et al., 2008).

As expected the Zurich group study reported a long-term insulin independence much lower in the group transplanted with kidney-islet than in the group transplanted with kidney-pancreas with a global result in line with the findings of the Edmonton trial group and a residual islet graft function sufficient to maintain glycemic control at a near-normal level. Interestingly it was showed that there was only a marginal benefit in terms of glucose control in those patients who received multiple islet infusions compared to patients who received only a single islet infusion. This finding and the not significant difference in glucose control between kidney-islet and kidney-pancreas patients despite much higher C- peptide levels and insulin independence in the latter group showed that even a minor residual beta cell function can significantly improve glycemic control, provided that patients are intensively treated with insulin. This consideration associate to the shortage of organs and the high risk of patient sensitization after multiple islet infusions reinforce the opinion that it preferable to undergo islet transplantation from a single pancreas donor. Moreover the cost is an additional important point in the context of repetitive islet transplantations. The same study reported that the cost of a combined kidney-islet transplantation is lower than the cost for a combined kidney-pancreas transplantation by about 10%, but exceeds in case two or more islet infusions have to be performed (Gerber et al., 2008).

8. Conclusions

The procedure of islet transplantation has made important progresses in the last decade, but the benefit/cost ratio between the improvement of glycemic control and the necessary chronic immunosuppressive therapy makes this option valid only for a restricted category of patients suffering from DMT1.

Actually the most frequent indication to islets transplantation is in combination with the kidney transplant in patients with end-stage diabetic nephropathy; patients therefore who will anyway undergo chronic immunosuppressive therapy.
The islet transplantation allows a long-term insulin independence in a limited number of patients. A residual partial graft function anyway leads to an improvement of the glycemic control, and consequently important advantages, in the majority of treated patients. In consideration of the low incidence of complications and the excellent kidney graft function results using immunosuppressive regimen avoiding steroids the combined kidney-islet transplantation procedure should be considered a valid alternative to kidney-pancreas transplantation for some patients categories.
Patient selection for either one of the two therapeutic options needs to be performed after a careful evaluation of possible advantages and disadvantages, with special regard to age and comorbidities. Patients older than 50 years or considered at higher risk of intraoperative complications were preferentially assigned to the less invasive procedure of kidney-islet transplantation, while younger and healthier patients could be preferentially assigned to kidney-pancreas transplantation.
Endogenous insulin production by transplanted islets combined with optimal insulin therapy is sufficient for maintenance of near-normal glucose levels that allows a delay of all diabetes-related complications and a strong reduction of the episodes of severe hypoglycemic episodes. Actually this should be considered the primary objective of the islet transplantation while the opportunity of increasing the periods of insulin-independence through multiple islets infusions is not commonly acceptable because of the high risk of sensitization to impair the possibility of a kidney retransplant.
In the face of organ shortage and cost procedure-related, these findings may lead to a new paradigm in islet transplantation, where the primary aim is not necessarily to achieve the same insulin-indipendence as in whole-organ transplantation but to improve the glycemic control of the patient through a much less invasive procedure.
Promising fields of research are nowadays focused on increasing the engraftment and survival of the islets after transplantation. If these studies will give positive results it will be possible in future to extend the actual indications of the combined kidney-islet transplantation procedure.

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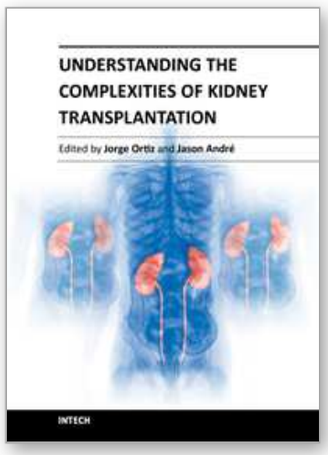
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Kidney transplantation is a complex field that incorporates several different specialties to manage the transplant patient. This book was created because of the importance of kidney transplantation. This volume focuses on the complexities of the transplant patient. In particular, there is a focus on the comorbidities and special considerations for a transplant patient and how they affect kidney transplant outcomes. Contributors to this book are from all over the world and are experts in their individual fields. They were all individually approached to add a chapter to this book and with their efforts this book was formed. Understanding the Complexities of Kidney Transplantation gives the reader an excellent foundation to build upon to truly understand kidney transplantation.

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