Islet of Langerhans Autotransplantation: Rationale, Results, and New Developments

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Autotransplantation of islets of Langerhans should be offered to patients undergoing extensive pancreatic resection for chronic pancreatitis. Results of clinical trials of islet autotransplantation (in which allorejection and recurrence of autoimmunity do not exist as causes of graft destruction) have been superior to those of allotransplantation, with insulin independence for more than 1 year achieved in 47% of recipients. The number of islets transplanted is a major indicator of outcome, since insulin independence at 1 year increases to 71% in recipients of more than 300,000 islets. Importantly, long-term pain control after extensive pancreatic resection is excellent and reaches 82% to 100%. Even in patients who achieve insulin independence, responses to intravenous glucose challenge are depressed and functional insulin secretory reserve is markedly decreased, indicating that only a reduced mass of islets engrafts. New indications for islet autotransplantation are emerging and include benign pancreatic tumors, blunt trauma, and, more controversially, malignant tumors of the pancreas.

ABBREVIATIONS

CP	Chronic pancreatitis
DIC	Disseminated intravascular coagulation
IEQ	Islet equivalent
ITR	International islet transplant registry
IVGTT	Intravenous glucose tolerance test
PP	Pancreatic polypeptide

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Introduction

Islet of Langerhans transplantation is in the limelight, thanks to remarkable results recently obtained by the Edmonton group after islet allotransplantation in type 1 diabetes mellitus patients.[1] A new surge of interest has been generated and is likely to benefit other domains of islet transplantation, notably autologous transplantation for the prevention of surgical diabetes. This is an interesting role reversal, since autotransplantation was recently viewed from a technical standpoint as a critical model for studying the determinants for successful islet transplantation in the absence of immunological mechanisms of graft loss, and thus as a first step to master before successful islet allotransplantation.[2-4] Indeed, successful results of functional islet autotransplantation after extensive pancreatectomy were frequently obtained, as compared with the dismal outcome of a vast majority of allogeneic transplantation procedures.[4,5] A number of factors doubtless account for the differences observed, including the absence of administration of diabetogenic drugs (steroids and calcineurin inhibitors), allogeneic rejection, and the recurrence of autoimmunity. Other not-as-well-defined mechanisms, such as the result of the interaction between the islet graft and the microenvironment at the site of implantation, might also be involved in islet graft loss.[6]

Surgical diabetes, provoked by extensive pancreatic resection, is a condition comparable in severity to type 1 diabetes. Chronic pancreatitis is the most common indication for extensive pancreatic resection. Such patients are hyperglycemic and at risk of ketosis in the absence of exogenous insulin. They suffer frequent hypoglycemic episodes, resulting from a lack of counterregulatory mechanisms (i.e., absence of glucagon), and of poor compliance in the context of chronic alcohol abuse.[7] On the other hand, extensive pancreatic resection is often required for patients with intractable pain due to chronic pancreatitis, and islet autotransplantation

has emerged as a valuable solution for the prevention of surgical diabetes.

Chronic Pancreatitis: to Resect or Not to Resect?

Patients suffering from chronic pancreatitis (CP) are usually referred to the surgeon for chronic intractable abdominal pain. The type of surgical treatment is a matter of controversy, but it is generally accepted that pancreatic duct drainage should be performed in the presence of a dilated duct, whereas resection should be offered to patients with "small duct disease."[8,9] However, this principle has been challenged by the failure to obtain pain relief by pancreaticojejunostomy in a number of patients with "enlarged duct" CP.[9-11] The notion that the pancreatic head might be the "pacemaker" of the disease in alcohol-induced chronic pancreatitis[12] and the fact that damage to nerves located around and within the pancreatic inflammatory mass plays a significant role in the generation of pain[13] are likely explanations for failed duct drainage procedures. Suspicion of carcinoma or local complications, such as thrombosis, pseudoaneurysms, pseudocysts, and compression of the biliary or digestive tracts, also indicate the performance of a resection procedure.

Both distal pancreatectomy and pancreatoduodenectomy have been associated with growing safety—with mortality rates under 1%.[14,15] Good quality of life[16] and satisfactory long-term pain control are achieved by an appropriate resection procedure in about 90% of cases.[17] A significant number of patients have a long-lasting history of pain and undergo multiple surgical procedures before pancreatic resection is decided on, suggesting that resection is often considered and performed too late in the course of disease.[18,19]

In the extreme, total or near-total pancreatectomy is the most effective procedure in relieving pain, but it invariably results in insulin-dependent diabetes. Surgical diabetes is severe and difficult to manage: patients develop hyperglycemia and are at risk of ketoacidosis in the absence of insulin therapy. They may also develop long-term diabetic complications if they live long enough. Moreover, they present frequent hypoglycemic episodes because of poor compliance in a context of continued alcohol abuse, and because of a lack of the counterregulatory mechanisms provided by glucagon.[7,20] Therefore, the possibility of preserving endocrine function through islet autotransplantation would be a significant asset for pancreatectomized patients.

Another important consideration when balancing the metabolic risks and symptomatic benefits of extended pancreatic resection resides in the natural history of chronic pancreatitis. A prospective series of 245 patients reported a 74% incidence of diabetes with a median time of 5.7 years from diagnosis.[21] We have reported a 26% diabetes-free survival at 10 years after pancreatic resection for CP, with no difference regarding type (duodenopancreatectomy vs. distal pancreatectomy) or extent of resection.[18] These findings illustrate the relentless character of the disease with an almost inexorable progression toward total glandular destruction. They might provide a rationale for the performance of earlier and more extensive pancreatic resection and islet autotransplantation in order to provide these patients, who are inexorably headed toward diabetes, with a larger number of healthier islets. Although these considerations remain controversial, islet autotransplantation should nonetheless be offered to any patient with CP undergoing extensive pancreatic resection.[18]

Experimental Islet Autotransplantation

The door to successful clinical islet autotransplantation was opened with the description of new methods for the isolation and transplantation of islets of Langerhans in rodents, and the demonstration of diabetes reversal after the transplantation of syngeneic islets in animals with "chemical pancreatectomy" induced by streptozotocin injection.[22] However, the experiments conducted in inbred rodents did not reflect the technical difficulties that are encountered when applying the method for application in larger mammals, including the human. Studies performed on large animals to demonstrate the feasibility of diabetes reversal by islet autotransplantation have been instrumental in applying the concept to the clinical situation. Reinfusion of islets isolated after total pancreatectomy into the portal system was shown to result in consistent long-term correction of surgical diabetes in subhuman primates (dogs and pigs) and enabled the

quantification of the critical mass of islet tissue necessary to revert diabetes in each species.[23-26]

Much research was conducted in the search for an optimal implantation site for the islets. The liver (by intraportal infusion) and the spleen (by retrograde infusion into the splenic vein) were consistently identified as the most favorable sites for implantation of purified autologous islets in large mammals, as demonstrated by rate of engraftment or posttransplant metabolic studies.[23,27-29] The theoretically more physiological insulin secretion, directly into the portal vein of the splenic location, does not seem to offer significant advantages. Interestingly, free intraperitoneal islet autotransplantation showed better engraftment and long-term endocrine function when unpurified dispersed pancreatic tissue was compared with purified islets in canine models.[28,30] Moreover, long-term autograft function of intraperitoneal unpurified tissue was similar to that of intrahepatic purified islets.[30] Omental pouches were designed in a canine model as ideal transplant sites, combining the advantages of insulin secretion into the portal flow with easy retrievability for biopsy purposes. However, this method required a significantly larger autologous islet mass to reverse diabetes than did the intrasplenic site.[31] The kidney capsule is a highly favored transplantation site in rodents because of the technical simplicity of the procedure and the possibility of demonstrating graft function by observing a return to diabetes after nephrectomy. Analysis of nonimmunologic mechanisms of graft failure can be performed in murine models of transplantation of a marginal mass of syngeneic islets under the kidney capsule.[32,33] However, largely because of lack of engraftment, which is likely due to poor vascularization of the graft site,[25,28,34] poor functional outcome is achieved after transplantation of purified autologous islets under the kidney capsule of large mammals.

With islets isolated from healthy animals, autotransplantation falls short of the situation encountered when dealing with patients with chronic pancreatitis, in which islets must be isolated from a fibrous and scarred pancreas. In an attempt to reproduce the clinical situation, islet isolation and autotransplantation in canine models of chronic pancreatitis induced by duct ligation achieved diabetes reversal in, at best, 50% of recipients, a result of low yields, but demonstrated the feasibility of the method.[35-38]

Animal models have allowed extensive studies of the metabolic function of the autotransplanted islets. Such studies pointed out that, in spite of a euglycemic status, autotransplanted animals had impaired glucose responses to glucose tolerance tests[39] and markedly reduced insulin responses to glucose and arginine, the latter parameter being a direct measure of the islet secretory capacity, that is, the engrafted islet mass.[29,40] The defective glucagon response to hypoglycemia, observed after human intrahepatic islet autotransplantation,[41] could be reproduced in a canine model but was restored when islets were transplanted intraperitoneally.[42] This finding suggested that the defective glucagon response may not solely be the result of an isolation-induced destruction of α-cells or a lack of autonomous innervation, and was tentatively explained by the lack of a proper hypoglycemic stimulus in the hepatic site because of high glucose concentrations in the microenvironment.[42,43] Interestingly, basal pancreatic polypeptide (PP) levels were consistently low, suggesting a loss of the vagally mediated PP response to hypoglycemic stimuli.[39,42]

Technical Considerations for Human Islet Autotransplantation

When autologous islet transplantation is considered, the surgeon must preserve the vascularization of the pancreas until its final removal to minimize the ischemic injury to the gland. The pancreas is immediately transported to the isolation laboratory, and the islets are isolated with a collagenase digestion method. Liberated by enzymatic digestion, the islets are traditionally not purified from the dispersed ductal and exocrine tissue, mainly to maximize yield.[44] This also reduces the processing time of the pancreatic tissue, which can be ready to infuse in less than 2 h, during which pancreatic surgery can be completed.[45] Transplantation of unpurified dispersed pancreatic islet tissue was introduced by the Minneapolis group after they had shown that it could successfully reverse diabetes in pancreatectomized dogs.[46,47] However, the extra volume of tissue to be transplanted, and the potential presence of activated pancreatic enzymes in the absence of purification, carries an increased

risk of portal hypertension and/or thrombosis and intravascular coagulation.[48-51] For these reasons, certain groups prefer to purify the pancreatic digest on density gradients prior to transplantation.[51,52] The automated method for islet isolation,[53] in which the pancreas is fully immersed in a chamber with a 400 to 500 µm screen filtering the outlet where it undergoes continuous enzymatic digestion by a 37 °C collagenase solution circulating in a closed circuit, can be used effectively to separate islets from glands with CP. It also offers the advantage of a partial purification because the fibrous components of the pancreas are retained in the chamber.[54]

The dispersed islet tissue is brought back to the operating room for intraportal infusion. Islets are infused via a catheter inserted inside a branch of the mesenteric vein after systemic heparinization.[45,51,55] Since the volume of the unpurified digest can be as high as 35 to 45 ml, the infusion is performed slowly and under constant monitoring of the portal vein pressure. Peak portal pressures, as high as 70 cmH_2O (50 mmHg), have been recorded during islet infusion.[45,55] The upper safety limit at which infusion should stop is not well defined and obviously depends on the pretransplantation value. The Minneapolis group has opted to inject the remaining tissue freely into the peritoneal cavity when portal vein pressure reaches 40 cmH_2O (30 mmHg).[45] In this regard, it was shown in canine models that unpurified pancreatic tissue survived better than purified islets in the peritoneal cavity.[28,30]

The spleen has been explored as an alternate site for islet autotransplantation.[51] It has the theoretical advantage of a more physiological location upstream from the liver and is able to sustain islet function in canine models.[29] The islets are transplanted by retrograde venous infusion, generally into a short gastric vein. However, even if this solution is feasible and can lead to insulin independence, it has been associated with an increased rate of thrombotic complications, which implies that the performance of spleen preservation during pancreatic resection in an inflammatory terrain may be difficult.[51]

Interestingly, the lack of an in-house islet isolation facility is not an obstacle for the performance of islet autotransplantation after pancreatectomy. A group in Portland, Oregon, has reported on 5 patients, for whom resected pancreata were shipped in cold preservation solution to Minneapolis for processing and the dispersed tissue was shipped back for infusion. Islet transplantation was performed after a 16- to 24-h delay via a percutaneous mesenteric vein catheter positioned during surgery and continuously flushed with low-volume dilute heparin solution. Satisfactory long-term results in terms of insulin requirements demonstrate that distant processing of islet tissue for autotransplantation is a feasible and reasonable option.[56]

Results of Clinical Islet Autotransplantation

The latest newsletter of the International Islet Transplant Registry (ITR) reports 240 autologous islet transplant procedures performed through December 2000 in 15 institutions worldwide.[5] Early experience in the 1970s and early 1980s, under the pioneering leadership of the Minneapolis group, demonstrated the feasibility of islet autotransplantation after near total or total pancreatectomy, with some success in preserving metabolic function.[7,20,35,57-60] Results of these small series of selected cases are difficult to interpret, but an exhaustive analysis of the published early experience showed that, overall, 32% to 57% of patients achieved at least transient insulin independence, depending on the extent of pancreatectomy.[61]

Between 1990 and 1999, the ITR reports that 64% of patients were insulin independent for more than 1 week and 47% for more than 1 year. If more than 300,000 islet equivalents (IEQ: number of islets if all had an idealized diameter of 150 µm) were transplanted, this proportion rose to 71%,[5] with a longest insulin independence follow-up of more than 13 years (Fig. 1).[62] The most active centers in the past decade have been Minneapolis, MN; Leicester, UK; Geneva, Switzerland; and Indianapolis, IN.[45,51,52,55,63] Recently published results by these institutions are summarized in Table 1 and show a marked improvement in the achievement of sustained insulin independence. In the Minneapolis series, islet yields and probability of insulin independence after islet autotransplantation were significantly increased after the introduction of the automated method for islet isolation in 1991.[45] Unsurprisingly, the major determinant of success (i.e., insulin independence) for islet autotransplantation is the number of islets infused, either calculated as the number

Table 1 | **Functional Results of Islet Autotransplantation in the 4 Most Active Institutions Between 1990 and 1999 According to the International Transplant Register**

Institution[a]	Year[b]	N[c]	IEQ total[d]	IEQ/kg[e]	Insulin Independence >1 Month	Insulin Independence >1 Year[f]	Sustained Insulin Independence[g]	Longest Insulin Independence
Minneapolis (44,62)	1995	48[h]	238,010[j] (400-1,076,000)	n/a[i]	20 (51%)	14 (45%[k])	15 (38%)	13 years
Indianapolis (51)	1998	6	223,667 (83,000-415,000)	3,702 (1,630-6,290)	6 (100%)	1/1 (100%)	6 (100%)	12 months
Geneva (54)	2000	13	163,383 (23,904-450,000)	2,599 (386-6,716)	11 (85%)	7/11 (64%)	7 (54%)	4.5 years
Leicester (64)	2001	24[l]	140,419[m]	2,604 (320-9,240)	8 (33%)	4 (n/a)	4 (17%)	3 years
Pooled results		91	n/a[i]	2,940	45 (49%)	n/a[i]	32 (35%)	13 years

[a]References are indicated in parentheses; [b]year of publication; [c]number of transplanted patients in each series; [d]total number of islet equivalents (IEQ) isolated and available for transplantation (mean). IEQ are number of islets normalized to a diameter of 150 μm; [e]number of IEQ transplanted per kilogram body weight (mean); [f]several patients have less than 1-year follow-up; [g]number of insulin-independent patients at latest follow-up or death; [h]only 39 patients were included for long-term analysis; [j]total number of islets transplanted (number of IEQ not available); [i]n/a: data not available; [k]actuarial value; [l]5 patients underwent intrasplenic islet infusion; and [m]median value (mean not available).

of islets transplanted, with an optimal number above 200,000 to 300,000 islets,[41,45,64,65] or as the number of IEQ per kilogram of body weight, with an apparent cutoff value of 2500 to 3000 IEQ/kg.[55,57,66]

Even if insulin independence was not achieved, nearly all patients in the Geneva and Leicester experiences had functioning grafts as measured by basal C-peptide production, and HbA1c levels and 24-h insulin requirements were significantly lower than in patients who underwent total pancreatectomy without islet autotransplantation.[55,66]

"Burn-out" of a functional islet graft can occur after prolonged insulin independence, but patients in whom the size of the graft is sufficient to function for more than 2 years apparently do not fail beyond that point,[65] although this view has been challenged by occasional observations of later graft failure.[51,55,66]

The islet yield of the isolation procedure greatly depends on the extent of fibrosis in the resected pancreas, as demonstrated by a negative correlation between number of islets recovered and the degree of pancreatric fibrosis.[45] For example, at the University of Geneva the mean islet yield after isolation was 3494 IEQ per gram of resected pancreas and was significantly lower in patients with chronic pancreatitis than in patients with normal pancreatic tissue (2044 IEQ/g vs. 5184 IEQ/g).[55]

A history of previous pancreatic resections will also influence the islet yield, since less pancreatic tissue will be available for islet isolation with a completed pancreatectomy.

The extent of pancreatic resection does not seem to affect the rate of insulin independence achieved, that is, insulin secretion by the pancreas remnant is unlikely to play a significant role in the posttransplantation metabolic status.[45,55] This is unsurprising given the poor mid- to long-term endocrine function of CP pancreata regardless of therapeutic option.[18,21]

Importantly, long-term pain control results have been excellent, with resolution or improvement of pain in 82% to 100% of patients,[19,45,63] and far better than those achieved in CP patients who underwent duct drainage procedures or minor pancreatic resection.[19]

Complications

Morbidity related to pancreatic resection for CP is significant and has been reported and discussed elsewhere,[15,18,68] but complications directly attributable to islet infusion are much rarer. However, it

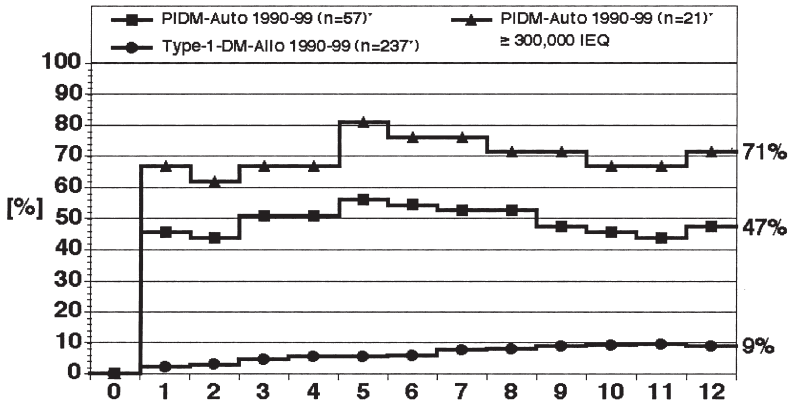

Figure 1. Insulin independence in recipients of islet autografts (squares) for the prevention of pancreatectomy-induced diabetes mellitus (PIDM) transplanted between 1990 and 1999 compared with that observed in recipients of islet allografts (circles) as a treatment of type 1 diabetes mellitus transplanted over the same period. When only autograft recipients transplanted with more than 300,000 IEQ are considered (triangles), sustained insulin independence is markedly increased. Only well-documented cases were included in this figure. (Reproduced from Newsletter No. 9 from the International Islet Transplant Registry.[5])

should be remembered that the early days of islet autotransplantation were marked by reports of serious, and often fatal, complications, seemingly involving a chain of events that began with acute portal hypertension and led to disseminated intravascular coagulation (DIC), and occasionally was accompanied by portal vein thrombosis and hepatic infarction.[48,49,69,70] Pancreatic enzymes, trypsin in particular, have long been known for their thrombogenic properties and ability to lead to DIC if released into the bloodstream, an effect that can be blocked by heparinization.[71] In addition, commercial crude collagenase preparations were shown to activate proteolytic pancreatic enzymes during the digestion process.[72] These factors may well explain the development of DIC after infusion of unpurified pancreatic digest into the portal system. Indeed, since the advent of the automated method of islet isolation, in which partial purification of the pancreatic tissue is achieved,[54] and with the availability of a new generation of gentler enzyme blends[73] and the routine administration of heparin,[45,48] DIC has no longer been reported after infusion of autologous islets into the portal vein.

The only significant complications of islet autotransplantation recently reported have been 2 cases of partial portal vein thrombosis and 1 wedge splenic infarct (all 3 without functional consequence), 1 case of splenic vein thrombosis after intrasplenic infusion, and 2 cases of splenic hilar bleeding after intraportal infusion (all 3 leading to splenectomy).[45,51,66] One case of fatal DIC also occurred after intrasplenic islet infusion, secondary to microembolization into the lungs of pancreatic tissue fragments that migrated through portosystemic collaterals.[50]

The invariable elevation of intraportal pressure that occurs during islet infusion may understandably lead to a marked decrease of the portal blood velocity, with ensuing thrombosis. However, there may be more to these thrombotic events than the sheer effect of a large mass of tissue carrying activated proteolytic enzymes. Interestingly, it was recently shown in allogeneic and xenogeneic in vitro models that isolated islets infused into the bloodstream could activate the coagulation and complement cascades, thus leading to clot formation and platelet consumption.[74,75] This phenomenon is likely of significance in an autologous situation as well.[76] Finally, for reasons that mostly remain unclear, intraportal infusion has been associated with fewer complications than intrasplenic infusion and should therefore be the preferred site for autologous islet infusion.[50,51,66]

Metabolic Studies in Recipients of Autologous Islet Transplants

Preoperative assessment of the pancreatic endocrine function should be obtained by oral and/or

intravenous glucose tolerance tests (IVGTT) and intravenous glucagon challenge[55,66] because it is easy to foresee that a patient with impaired metabolic tests, let alone established diabetes, is unlikely to become euglycemic after islet autotransplantation. Indeed, in the Minneapolis series, almost all patients had normal or near-normal pretransplant glucose tolerance tests.[44]

Normal IVGTTs, defined by a K value (glucose disposal rate) greater than 1% per minute, are often observed when insulin independence is achieved after islet autotransplantation and correlate significantly with the number of islets infused. However, K values are usually higher before isolation, although they have occasionally improved after transplant.[3,41,44,61,62] Similarly, acute insulin responses to intravenous glucose or to arginine are consistently lower in euglycemic islet autograft recipients with normal HbA1c, as compared with healthy controls or pretransplant values.[66,67]

Functional insulin secretory reserve, measured by glucose-potentiated, arginine-induced insulin secretion 3 years after pancreatectomy and autotransplantation in 8 patients with sustained insulin independence, correlated highly to the mass of islets transplanted. Despite insulin independence and normoglycemia, the response was markedly decreased in all patients when compared with matched controls, indicating that only a reduced mass of islets had engrafted.[67]

In further metabolic studies, this group of patients had no glucagon response to insulin-induced hypoglycemia, and a depressed but positive glucagon response to arginine.[41] Similar observations were made in autografted patients after 2.5 years of insulin independence and normoglycemia during hypoglycemic hyperinsulinemic clamp studies.[77] The fact that a glucagon response is obtained after arginine stimulation indicates that loss of α-cells is not responsible for this observation. These findings have been verified in animal models and are discussed above.[42] The defective glucagon response was not observed in recipients of whole organ pancreatic allografts after pancreatectomy.[41]

PP responses to insulin-induced hypoglycemia or to the high-protein meal are completely absent, whereas recipients of pancreatic allografts had a PP response only to the high-protein meal, but not to insulin. No definite explanation has been offered for this observation.[41]

New Indications

The increasing success of islet autotransplantation after pancreatectomy for CP has prompted the Geneva group to expand the indications for the procedure.[78] We have transplanted islets isolated from 6 pancreata resected for other benign pathologies (3 cystadenomas, 2 insulinomas, 1 blunt trauma to the pancreas). Median percentage of resected tissue was 80%. Five of these 6 patients have sustained insulin independence after a median follow-up of 35 months.[55] Caution must be applied when transplanting islets isolated from supposedly benign tumors, and a diagnosis of malignancy must be unequivocally ruled out before making the decision to perform the transplant, especially if the decision for tumor removal arises from preoperative diagnostic uncertainty. However, this approach can be useful for benign lesions whose size and/or location (neck and body of the pancreas) require the performance of an extended pancreatic resection to achieve complete extirpation.

More controversially, total pancreatectomy, combined with islet autotransplantation, was recently proposed as an option for the treatment of pancreatic adenocarcinoma. This was reported in one patient who underwent completion of a proximal pancreatoduodenectomy for a life-threatening anastomotic leakage, and who is alive with a functional islet graft 1 year after the procedure.[79] Obviously, a curative pancreatic resection and the infusion of islets uncontaminated by tumoral cells are prerequisites for the performance of such a procedure. Detection of the K-ras mutation by PCR in the islet preparation might be a useful technique to prevent infusion of contaminated islets.[77]

Conclusions

Numerous advances in understanding mechanisms of islet graft loss at the cellular and molecular levels, in the development of new reagents for islet isolation and purification, and in the clinical management of islet graft recipients, have led to significant improvement and success in the functional results of islet of Langerhans transplantation. As a result, an increasing number of centers are

launching islet transplantation programs. This is likely to lead to an increase in the number of autotransplant procedures after pancreatic resection for chronic pancreatitis or other indications. The islet transplant community will have to take advantage of this ideal situation for the implementation of multicenter, prospective randomized trials, aimed at validating the concept of pancreatic resection/islet autotransplantation. Regarding long-term metabolic results, such studies should focus on determining the optimal timing for, and extent of, pancreatic resection, as well as identifying selection criteria and providing guidelines for pancreatic resection and islet autotransplantation, in comparison to more conservative approaches.

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