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Pancreas Transplantation

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<http://dx.doi.org/10.5772/intechopen.76667>

Abstract

Pancreas transplantation is a treatment alternative to patients with type 1 diabetes, particularly to those with associated end-stage renal disease (ESRD). Recently, pancreas transplant centers have widened their criteria for pancreas transplantation to selected type 2 diabetic patients. This chapter reviews the most important topics on pancreas transplantation, including epidemiology and natural history of type I and type II diabetes, indications for pancreas transplantation, different alternatives for pancreas transplant recipients (simultaneous kidney-pancreas transplantation, pancreas after kidney, or pancreas transplant alone—PTA), and their outcomes. This chapter gives a detailed description of the surgical procedure for pancreas procurement and engraftment, as well as the most frequent surgical complications. An approach to the management of the recipient following pancreas transplantation (immunosuppression and infection prophylaxis) is also discussed. Finally, outcomes and complications following the pancreas transplantation are reviewed.

Keywords: pancreas transplantation, surgical complications, acute rejection, diabetes, end-stage renal disease, immunosuppression, kidney transplantation

1. Introduction

Diabetes is a disease characterized by an imbalance in glucose metabolism homeostasis, highly prevalent worldwide, and presents a significant morbidity and mortality due to vascular and neurological complications. It is the single most frequent cause of end-stage renal disease in incident patients on hemodialysis. The clinical presentation and epidemiology of diabetes varies according to the etiology. For selected patients, pancreas transplantation is the best treatment alternative to achieve glycemic control. In this chapter, we describe the most

important topics regarding pancreas transplantation, including indication and patient evaluation, surgical techniques, immunosuppression protocols, and outcomes.

2. Epidemiology and pathophysiology of diabetes

Diabetes is a spectrum of diseases characterized by a disorder in glucose metabolism leading to persistent hyperglycemia, with clinical manifestations varying according to disease etiology (Table 1).

Type 1 diabetes mellitus (DM) is an autoimmune disorder characterized by the generation of autoantibodies against β cells and the development of a localized inflammatory response with consequent islet destruction. Current models suggest that the disease progresses as a relapsing-remitting disease, with a nonlinear β cell mass loss at each relapse as a result of the imbalance between β cell proliferation and destruction, eventually leading to persistent hyperglycemia. At diagnosis, these patients may present with nearly normal serum concentrations of insulin and C-peptide but with a rapid decrease in the following 8–12 weeks.

Several autoantibodies have been described in patients with type 1 diabetes—antibodies to insulin (IAA), glutamic acid decarboxylase (GAD), Zinc transporter 8 antibodies (ZnT8A), and protein tyrosine phosphatase-like protein IA2 (IA2 or ICA512). The risk for overt diabetes better correlates with the number of autoantibodies present rather than the titer of a single antibody [1].

Type 1 diabetes usually presents at a young age (6 months to 25 years old), and there is a geographical variation, with a tendency toward an increased incidence in developed countries—as

Diabetes	Age presentation	Clinical presentation	Etiology	Prevalence (of total diabetes)	Obesity
Type 1	6 months to young adulthood	Most often acute, rapid	Autoimmune (some genetic associations); β cell mass loss; Insulin deficiency	5–10%	Uncommon
Type 2	Adulthood	Variable; from slow, mild (often insidious) to severe	Insulin resistance; β cell exhaustion	80–90%	Common
Monogenic	Often post pubertal except glucokinase and neonatal diabetes	Variable (may be incidental in glucokinase)	Reduced insulin production or secretion; higher glucose sensor threshold	2%	Incidence similar to general population

Table 1. Etiology and clinical presentation of diabetes.

recognized by the World Health Organization (WHO), this may be due to differences in registry data, since few data that exist from sub-Saharan Africa, South America, and Asia [2].

A genetic predisposition has been identified with an increased risk for the disease in siblings and offspring of diabetics. There is an increased incidence in patients with human leukocyte antigen–antigen D related (HLA DR)*03 and DR*04.

Type 2 diabetes is characterized by peripheral cells insulin resistance with a consequent persistent hyperglycemia. Insulin production and secretion is often maintained with normal or high serum insulin and C-peptide. It usually presents in adulthood and is often associated with obesity and a sedentary lifestyle.

According to the WHO, diabetes incidence and prevalence is increasing [3] at a particularly alarming rate among children. This has led to a shift in the paradigm of age of presentation of type 2 diabetes with an ever-increasing incidence in young adults, and consequent presentation of diabetes complications at younger ages [4].

The first line of treatment for type 2 diabetes is lifestyle modification, followed by oral anti-diabetic agents. The mechanism of action of oral agents is diverse, from reduction in glucose absorption, to increase in insulin secretion, stimulation of gluconeogenesis, or reduction of tubular reabsorption with an increase in urinary glucose excretion. Despite these alternatives, several patients still need exogenous insulin to achieve glycemic control. Chronic insulin resistance may lead to β cell exhaustion, and insulin and C-peptide levels may decrease below normal range in patients with long-standing type 2 diabetes.

3. Indications for pancreas transplantation

Transplant of β cells is a treatment alternative to insulin-dependent diabetic patients with the objective of reestablishing glucose homeostasis without the need for exogenous insulin.

Both pancreas and islet transplantation are currently used in clinical practice as β cell mass transplant techniques. Islet transplantation is still limited to nearly experimental protocols, though a few centers have introduced them into their clinical practice. According to the Collaborative Islet Transplant Registry (CITR), 1927 procedures have been performed worldwide from 2004 to 2013 [5]. Though conceptually attractive, its high cost of isolation and the sub-optimal insulin-independency results (when compared to whole-organ transplantation) have halted its clinical application.

Pancreas transplantation is indicated in patients with insulin deficiency and end-stage renal disease (ESRD) in those or with brittle diabetes and normal renal function. Indications should take into account disease-related characteristics:

- a. Type of DM: pancreas transplantation is indicated in patients with type 1 DM, selected patients with type 2 DM, as well as to those with diabetes secondary other etiologies (acute

and chronic pancreatitis, cystic fibrosis, and trauma). According to data obtained from the last US Pancreas Transplant Registry (OPTN/SRTR), pancreas transplantation in type 2 diabetes is increasing worldwide [6], representing up to 8% of all transplants performed in the US [7]. The most recent report demonstrates a 3-year graft survival of 83.3%. Indication in these patients is not consensual. At our center, we indicate in patients <50 years, body mass index (BMI) <30, at least 5 years of insulin therapy, C-Peptide <3.0 ng/mL, and daily insulin at <0.5 U/kg/day. Larger cohorts, standardized inclusion criteria, and long-term results are warranted.

- b. Age: an age limit is not established. Though it is usual to accept candidates up to the age of 50 and assessing individually those aged between 50 and 55 years, some groups accept patients who are >60 years old [8].
- c. Diabetic complications: the presence and severity of these complications, at the time the patient is studied for transplantation, is another parameter to assess. Successful pancreas transplantation requires suitable vascular permeability for arterial and venous anastomosis. Presence of severe calcifications in the iliac vessels, where the vascular anastomoses of the organs are usually performed, as well as the existence of a severe peripheral vascular disease, can technically allow the implantation of a graft, but it is inadvisable to implant both organs. In these cases, priority is given to kidney transplantation. Coronary heart disease is also a frequent contraindication for pancreas transplantation. The implantation of two organs requires a major surgery with longer anesthesia time and a greater probability of presenting some type of complication or surgical re-intervention. Other secondary diabetic complications, such as retinopathy and neuropathy, rarely represent by themselves as a contraindication for the transplant, but due consideration should be given to the patient during pre-transplant evaluation.

3.1. Indications according to transplant modality

Pancreas transplantation can be performed individually or simultaneously with kidney transplantation in patients with ESRD. Each type of transplant has certain characteristics that must be highlighted.

3.1.1. Simultaneous transplantation of pancreas and kidney (SPK)

Simultaneous kidney-pancreas transplantation (SPK) is the most common type of pancreas transplant, representing over 98% of all pancreas transplants performed in the US [7]. It is currently the best treatment alternative to patients with ESRD who are candidates to a kidney transplant. In addition to the demographic and clinical parameters previously described, immunological and waiting-list vintage should be considered when proposing a patient to an SPK. The presence of HLA alloantibodies reduces the probability of finding a suitable donor and increases waiting-list vintage. In moderate (cPRA > 50%) and highly sensitized (cPRA > 90%) patients, an individual approach is advised

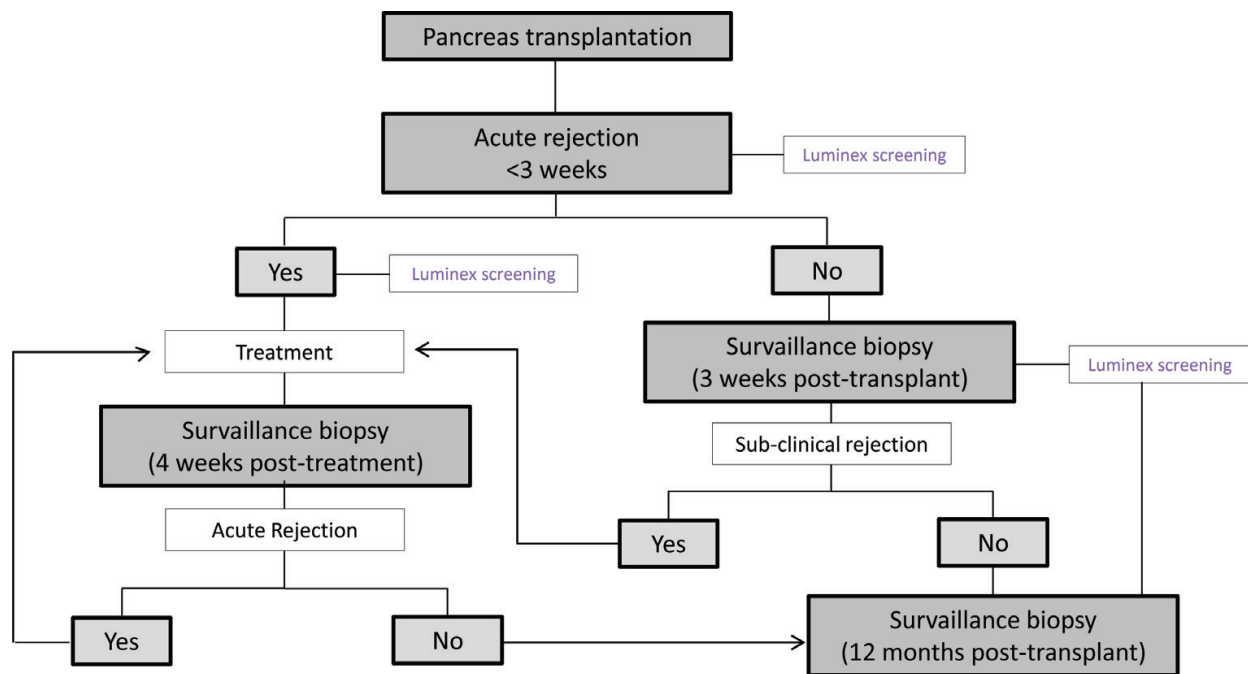


Figure 1. Hospital Clinic's flowchart for performing pancreas graft biopsy. Ultrasound-guided surveillance biopsies are performed at 3 weeks and 12 months post-transplant. Biopsies are also performed if clinically indicated, and are followed by a surveillance biopsy 4 weeks after the treatment of rejection.

and a kidney transplant followed by a pancreas transplant alone should be considered. Similarly, centers with long pancreas waiting lists (>2 years) should evaluate the risk of maintaining the patient on dialysis or use a pancreas after kidney transplantation (PAK) approach, since mortality on the waiting list can be up to 42% at 4 years in this population (**Figure 1**) [9].

3.1.2. Pancreas after kidney transplantation (PAK)

This type of transplant is considered for those patients who are candidates for a kidney and pancreas transplant and who have an available living kidney donor or where waiting-list vintage is significantly shorter to kidney when compared to pancreas transplant. The major benefit of PAK is reducing, or avoiding, time on dialysis while waiting for pancreas transplantation. Restoration of kidney function may reduce uremia-induced anti-coagulation and possibly reduce bleeding during surgical complications. This approach implies, nonetheless, two different surgical procedures. Moreover, up-to-date results are somewhat poorer for patients who have undergone PAK transplant, with an inferior pancreas graft survival and higher acute rejection incidence [10]. The decision to perform a PAK (live donor kidney) or an SPK will depend fundamentally on the characteristics of the living donor (age, HLA compatibility), the possibility of performing a preventive transplant, the expected time on the waiting list, as well as the patient's expectations (**Table 2**).

	SPK	PAK
Advantages	<ul style="list-style-type: none">a. Single surgical procedureb. Single cycle of induction immunosuppressionc. Better graft survival	<ul style="list-style-type: none">a. Minimizes or avoids the need for dialysis (in LDKT)b. Shorter surgical procedurec. Avoids uremia-asociated complicationsd. Time to pancreas transplantation usually shorter than for SPK
Disadvantages	<ul style="list-style-type: none">a. Longer waiting-list timeb. Lower probability of receiving kidney transplant preemptively	<ul style="list-style-type: none">a. Two surgical proceduresb. Two cycles of induction immunosuppressionc. Higher incidence of acute rejectiond. Inferior pancreas graft survival

Table 2. Pancreas after kidney transplantation: pros and cons compared to SPK.

This alternative has been gaining increasing interest in recent years due to the current shortage of cadaveric organs from young donors and the consequent increase in waiting-list time for kidney-pancreas transplantation. In some centers, PAK represents up to 50% of pancreas transplants, most of them having received a kidney transplant from a previously living donor.

The indications regarding age, type of DM, and vascular status of the recipient would be the same as in the case of SPK. However, a functioning kidney graft with good and stable renal function (glomerular filtration rate—GFR > 40 ml/min) is recommended prior to inclusion on the waiting list, due to the risk of acute kidney injury following the pancreas transplantation surgery and the increase in doses of immunosuppressors.

One of the issues raised in this type of transplant has been on when to perform pancreas transplantation after the kidney transplantation. There is no established time limit, and it depends on the progression of each patient following the kidney transplant. However, it seems that a better survival of the pancreatic graft has been observed when the interval between both transplants is less than 12 months. For some authors, the optimal interval between both procedures should be less than 4 months.

3.1.3. *Pancreas transplant alone*

Isolated pancreas transplantation in diabetics without documented kidney disease, and with little or no other secondary complication, would theoretically be the ideal transplant. These would be the ones who could benefit the most from the positive effects of this transplant, by being able to prevent the appearance of secondary complications, thanks to an early metabolic control. However, it is considered that the risk of the intervention, as well as the risk of

immunosuppression to which the patient must be subjected for life does not always justify the hypothetical advantages of the transplant.

The results obtained with the PTA are somewhat worse than those of the PAK and SPK. The incidence of technical complications (mainly graft thrombosis) and acute rejection is somewhat higher to the other types of transplant.

It is performed to patients with brittle diabetes and normal renal function, who require repeated hospital admissions due to metabolic decompensation and/or severe hypoglycemic unawareness. These should be confirmed during a hospital stay following treatment optimization using insulin pump and/or continuous glycemic control monitors. It may also be performed to patients with the brittle diabetes and incipient diabetic complications, in order to reduce progression of secondary complications.

The main indications, as well as the absolute and relative contraindications for pancreas transplantation, are presented in **Table 3**.

Indications

SPK: diabetes mellitus and end-stage renal disease (GFR <20 ml/min or dialysis)

PAK: diabetes mellitus and functioning kidney transplant

PTA: Type 1 diabetes with normal renal function (GFR >60 ml/min; proteinuria <1 g/day), and:

- Not aware of severe hypoglycemia (life threatening)
- Frequent hospital admission due to metabolic complications
- Failure to achieve glycemic control using other alternatives—such as insulin pump and/or continuous glycaemic control monitors—during a hospital admission

Absolute contraindications

Severe untreatable coronary heart disease; severe left ventricular dysfunction

Chronic liver or pulmonary disease

Active infection

Active or past cancer without adequate remission period (excluded in situ and skin epitheliums)

Severe psychologic or psychiatric disease; drug and alcohol abuse

Morbid obesity (BMI >35 kg/m²)

Active gastrointestinal bleeding

Relative contraindications

Age: <18 and >55 years old

Obesity (BMI < 30 kg/m²)

Recent acute coronary heart disease

Recent retinal hemorrhage

Symptomatic cerebrovascular or peripheral vascular diseases

Severe autonomic neuropathy or diabetic gastropathy

Active smoking

Table 3. Indications and contraindications to pancreas transplantation.

4. Waiting list for pancreas transplantation

4.1. Evaluation of candidates

Evaluation of the candidates for pancreas transplantation should be performed as early as possible, in order to identify those who would benefit the most from the procedure. In patients with chronic kidney disease, we recommend referral to a pancreas transplant center as soon as glomerular filtration rate (GFR) falls below 25–30 ml/min. This early referral offers precious time for patient evaluation and possible inclusion on the waiting-list pre-dialysis. Additionally, and depending on transplant center policies, this allows the study of a possible living kidney donor and a preemptive kidney transplant.

Patient evaluation and clinical workup is similar to that performed for kidney transplantation, such as complete medical history, immunological study, uremic state, liver disease, cancer and infection screening, with some additional particularities related to diabetic disease: hormonal study, β cell autoantibodies, as well as study of the main diabetic complications.

- Hormonal assessment: the main purpose is to determine whether or not the patient has endogenous insulin secretion. For this, it is sufficient to determine the fasting plasma levels of C-Peptide. Its negativity indicates the absence of insulin secretion.
- Autoantibodies: the main objective of pre-transplant quantification of β cell autoantibodies (IAA, GAD, ZnT8A, IA2) is to establish a baseline. These tend to be negative after years of evolution of DM, and therefore negative at the time of transplantation. Their presence does not represent a contraindication for pancreas transplantation. During follow-up, nonetheless, its reappearance is associated with an increased risk for disease relapse.
- Diabetic retinopathy is present in up to 90% of all transplant candidates, with varying degrees of severity. It is not considered an exclusion criteria for transplantation.
- Diabetic polyneuropathy is also present in majority of patients but rarely contraindicates the transplant. However, it is advisable to take into account the severe dysfunction of the autonomic nervous system, due to post-transplant complications and the negative impact on patient survival. Diabetic neuropathy can often affect the urinary bladder leading to incontinence or incomplete bladder emptying. If urinary exocrine drainage is used, a urinary urethrocytography is recommended to rule out pathology of the bladder and urethra, as well as a cystomanometry to study and evaluate bladder function.
- Cardiovascular evaluation is the most important due to the impact of cardiovascular disease on post-transplant mortality and morbidity. Previous history of myocardial infarction, angioplasty, or coronary bypass should not necessarily be a contraindication to transplantation. Workup should be exhaustive before including the patient on the waiting list. It is advisable to perform an electrocardiogram (EKG) and a pharmacological stress test with MIBI-dipyridamole, as well as an echocardiography to evaluate ventricular ejection fraction and exclude motility disorders. If any of these tests are pathological, coronary angiography should be performed to identify more accurately the existing lesions and

perform the appropriate treatment prior to transplantation (either angioplasty or coronary artery bypass graft—CABG). A recent acute myocardial infarction, untreatable significant coronary angiography lesions, or severe ventricular dysfunction are contraindications to transplantation (**Table 3**).

- Vascular evaluation: an angio-computed tomography (CT) should be performed to rule out vascular lesions, mainly at the level of the iliac vessels and the celiac trunk that could hinder the implantation of the grafts. In pre-dialysis patients, a magnetic resonance imaging (MRI) with no or low dose of low-risk gadolinium contrast can be used.
- Assessment by the transplant team: once the study of potential candidates has been completed, and before being included on the waiting list, it is advisable to carry out a joint assessment by all the members of the transplant team (nephrologist, endocrinologist, anesthesiologist, and surgeons).

4.2. Inclusion on the waiting list

At the time of inclusion on the waiting list, a checklist should be performed to ensure all pre-transplant studies have been completed, and revised by the medical team. It is important to ensure that the patient has received a clear and comprehensible information regarding the advantages, as well as of the possible complications of the transplant, so that he can decide to freely choose this form of treatment.

Logistical issues should also be discussed in advance with the patient, in order to minimize the time from patient contact to the surgical procedure (hence cold ischemia time). The patient and his closest relatives should be aware of the expected duration of the intervention, median hospital stay, and most important post-transplant cares and outpatient visits.

Also, and for as long as they remain on the waiting list, the patient should be made aware of the importance of maintaining regular communication with the transplant center. The high incidence of complications that may occur in these diabetic patients, especially if they are affected by chronic renal failure and are also waiting for a simultaneous kidney transplant, requires strict monitoring and follow-up as long as they are not transplanted. Ideally, they should be visited by a member or collaborating doctor of the transplant team every 3–4 months. Only in this way, it is possible to detect possible events that may represent a temporary contraindication for the intervention.

4.3. Pancreas allocation

Solid organ allocation protocols are the major influence on patients' waiting-list vintage. In the UK, the introduction of a new nationwide allocation system in December 2010 significantly reduced the number of long-lasting patients and increased the number of islet transplants [11]. These protocols must comply with national legislations and logistic constraints. Several factors must be taken into account, such as donor demographics, donor center, geographical proximity to transplant center, and recipient priority indexes. In the UK protocol, weighting factors included expected organ travel time, recipient sensitization, dialysis vintage, waiting-list time,

HLA mismatching, and donor BMI (differential weighting for islet or whole-organ transplantation). Other allocation protocols, such as the US and the Eurtotransplant, also include in their weighting factors donor, recipient and center characteristics.

5. Donor selection

Pancreas blood supply is performed under low-flux conditions. This low blood flow rate increases the risk of surgical complications, such as thrombosis and ischemia. In addition, exocrine pancreas produces a large amount of protein cleavage enzymes, making it very susceptible to ischemia-reperfusion injury during transplantation. Pancreas present the highest donor discard rate among abdominal solid organ transplantations, with up to 33% of all pancreas being discarded by surgical teams prior to pancreas extraction, and an additional 50% being discarded following the extraction due to macroscopic appearance.

In an attempt to standardize donor acceptance criteria and predict short-term pancreas graft function, several scoring systems have been developed. P-PASS was one of the first to be described and was used in the Eurotransplant area to increase sensitivity in allocation. It categorized donors in low (<17) or high (≥17) risk donors [12]. The initial enthusiasm was halted by the reports of its inability to predict short- and long-term graft survival [13].

In 2010, Axelrod et al. published a complex scoring system, including donor and recipient variables, which enabled to predict 1-year graft survival [14]. Despite the promising results, it lacked several key factors, which are thought to influence outcomes, such as previous cardiac arrest in donors after brain death and perfusion solution. In 2013, Finger et al. demonstrated that the presence of at least two factors such as BMI ≥30 kg/m², donor creatinine ≥2.5 mg/dL, donor age > 50 years, and preservation time > 20 h were associated with technical failure [15].

Donors after brain death (DBD) have been the most widely used deceased donors since late 1980s; donors after cardiocirculatory death (DCD) were the first deceased donors used for organ transplantation in many countries until a brain death diagnosis and its acceptance for organ donation was legislated. Since the mid-2000s, DCDs regained protagonism as a potential source to increase donor pool, with an increasing number of transplanted organs ever since. DCDs should be evaluated carefully, since the definition includes donors with different backgrounds. According to the Maastricht classification, DCD donors can be classified from type I–V (**Table 4**) [16]. For pancreas transplantation, both type II (uncontrolled) and type III (controlled) have been used. Results from single center and registry analysis suggest

Type of donor	Management of cardiac arrest
Type I—brought in dead	Uncontrolled
Type II—unsuccessful resuscitation	Uncontrolled
Type III—awaiting cardiac arrest	Controlled
Type V—cardiac arrest after brain-stem death	Uncontrolled
Type V—cardiac arrest in a hospital inpatient (added in 2000)	Uncontrolled

Table 4. Maastricht classification [16].

that DCD donors are a suitable source of organs for pancreas and islet transplantation in selected donors [17]. Age limit acceptance is usually lower for DBD donors (<45 years), and both warm and cold ischemia times should be strictly respected, at the risk of increased surgical complications.

Table 5 describes the acceptance criteria for both DBD and DCD donors at our center. In summary, all donors under 45 years without other risk factors, with BMI ≤ 30 kg/m², and transaminases and pancreatic enzymes <3× normal values are accepted for transplantation, regardless of being DBD or DCD. Beyond those criteria, individual evaluations are performed.

Characteristic	DBD donors	DCD donors
Donor age (years)	≤ 45 (46–55 evaluate individually)	≤ 45
Donor BMI (kg/m ²)	≤ 30	≤ 30
Expected cold ischaemia time (h)	≤ 12 h (>12 h evaluate individually)	≤ 8 h (>8 h evaluate individually)
Hepatic transaminases (times above normal value)	<3×s	<3×s
Pancreatic enzymes (times above normal value)	<3×s	<3×s
Warm ischaemia (minutes)	—	<ul style="list-style-type: none"> • Total (TWIT): <60 • Functional (FWIT): <30 • Hemodynamic instability (SBP <60 mmHg) prior to donation: <60
Clinical risk factors	<ul style="list-style-type: none"> • Arterial HT • Smoking • Alcoholism • History of pancreatitis 	<ul style="list-style-type: none"> • Arterial HT • Smoking • Alcoholism • History of pancreatitis

Table 5. Hospital clinic pancreas donor acceptance criteria.

6. Surgical techniques

William Kelly and Richard Lillehei performed the first pancreas transplant at the University of Minnesota on December 17, 1966 [18]. In the last decades, the progress in immunosuppressive treatment has been parallel to a decrease in postoperative complications, to an improvement in the surgical technique, and ultimately to a better survival of both the graft and the patient.

The correct evaluation of the viability of the pancreas at the time of extraction in the donor is one of the basic pillars to obtain good results in the recipient. This must invariably be accompanied by a correct surgical technique during the extraction and implantation of the organ.

6.1. Pancreas extraction

Adequate donor selection is crucial in pancreas transplantation, as described in the previous section. The extraction technique is of well-documented importance for a successful outcome [19]. Whether it is advocated for an enteric or bladder drainage, it requires the extraction of the entire pancreas and a segment of the duodenum with its vascularization—perfused by the celiac trunk and superior mesenteric artery—and drained by the portal vein. As this vascularization is shared with the liver, surgical techniques have been developed to allow the simultaneous extraction of both organs. In specific cases of hemodynamic instability, rapid or block extraction must be performed in order to perfuse the preservation solution as quickly as possible.

The surgery begins with a xipho-pubic incision, with sternotomy and opening of the pericardium. The first step is to carry out a thorough examination of all the organs to identify any pathology that contraindicates the donation. It is important to have vascular control to allow rapid cannulation in case of instability, performing the dissection and individualization with ligatures of the aorta above the iliac bifurcation and the infrarenal cava, as well as the inferior mesenteric vein, in the case of portal vein being cannulated through it. The superior mesenteric artery is then dissected, located above and to the left of the confluence of the left renal vein with the cava, and a vessel loop is passed around it.

A first visual evaluation of the organ is performed, after the opening of the smaller sac, sectioning the gastrocolic ligament, to expose the entire anterior surface of the body and tail of the pancreas, together with palpation of the pancreatic head. The next phase comprises the dissection of the hepatic hilum to identify the possible anatomical variants of the hepatic artery. The most frequent are the right hepatic artery from the superior mesenteric artery and the left hepatic artery that derives from the stomatologic coronary artery. The common bile duct is dissected and sectioned at its most distal part. An incision is made in the gallbladder fundus and physiological serum injected into the fundus from the bile duct. The gastroduodenal artery and the hepatic artery are identified and dissected at the celiac trunk. In addition, the left gastric artery and the coronary vein are also identified, as well as all the lymphatic vessels in the upper border of the pancreas. The splenic artery is individualized and referenced with 6/0 prolene suture to prevent its retraction in the pancreas. A silk ligature must be passed through the abdominal aorta above the celiac trunk, following the blunt dissection of the esophageal hiatus. Finally, the dissection of the portal vein is carried out after identifying the stomatatic coronary vein. It is important to perform the Kocher maneuver in order to access the entire duodenum and the posterior aspect of the pancreatic head. The dissection of the pancreas must be done through the “no touch technique.” For the release of the pancreatic inferior aspect, mobilization of the entire transverse colon to the splenic angle is required. Subsequently, all the ligaments that fix the spleen to the retroperitoneum are sectioned for its separation from the kidney and the left adrenal gland, as well as the fixation of the body and tail to the retroperitoneum. Likewise, the section of the short gastrosplenic vessels and the dissection of the duodenum below the pylorus and at the level of the fourth portion is completed, for its subsequent sectioning to these two levels by means of a self-suture device.

Once the dissection is completed intrathoracically and abdominally, and prior to cannulation, intravenous sodium heparin (3 mg/kg) is administered. The aorta is then cannulated above the bifurcation, together with the cannulation of the portal system (through the inferior, superior, or portal mesenteric vein) and the supraceliac aorta is clamped to initiate perfusion of the aorta with preservation solution, at which time the vena cava is drained after opening it intrathoracically or through a drainage cannula placed in the inferior vena cava. At this time, crushed ice is placed on the organs to keep them at a suitable temperature. After completing the infusion, pancreas and liver are separated in situ. It is generally accepted that the celiac trunk must go with the liver. The splenic artery divides right after its origin from the celiac trunk. The aorta, at the level of the superior mesenteric artery, is sectioned laterally to visualize the origin of the renal arteries. The superior mesenteric artery must be ligated after the origin of the inferior pancreaticoduodenal artery. In short, the aortic patch is divided into two—the liver with the celiac trunk, and the pancreas—with the superior mesenteric artery. The infrahepatic vena cava is sectioned above the origin of the renal veins. The suprahepatic vena cava is divided along with the diaphragm that surrounds it. Finally, the portal is divided halfway between the liver and the pancreas. Finally, the pancreas is removed once the liver is removed. Some surgeons prefer to perform the extraction of both organs en block and perform their separation on the bench.

The iliac vessels (common iliac arteries/veins together with their bifurcations) are extracted and sent along with pancreas and liver grafts if they are needed for vascular reconstructions during the implant.

The organ is introduced in a sterile bag with preservation solution at 4°C. This bag is protected by inserting it into two other bags and transported to the recipient hospital. Bench surgery can be performed at the extraction site or later at reference hospital.

6.2. Bench surgery

During the bench surgery, the duodenum-pancreatic graft is prepared. This must remain in conditions of hypothermia at 4°C until its implantation.

After ligation of the splenic vessels, splenectomy is performed. If a fatty pancreas is found to be present, it should be removed carefully, making the necessary sutures to minimize the hemorrhage during reperfusion. It is advisable to invaginate the line of staples of the duodenal ends (with continuous 3/0 silk suture, although it is variable depending on the group), to ensure maximum suture tightness and avoid further fistulas.

In case of absence of celiac trunk (usual in simultaneous liver and pancreas extractions), it will be necessary to carry out reconstructions of the arterial vascularization of the pancreas that allow a good anastomosis with the iliac vessels of the recipient.

There are different techniques of vascular reconstruction of the pancreatic graft:

1. Anastomosis of the arteries of the pancreas with a segment of the iliac bifurcation of the donor. It is the most used modality in the USA and Europe.

2. Spleno-mesenteric termino-terminal anastomosis between the splenic artery and the distal end of the superior mesenteric artery of the graft. For some groups, it constitutes the technique of choice for its simplicity.
3. Spleno-mesenteric termino-lateral anastomosis between the splenic artery and the superior mesenteric artery of the graft.

Once the bench surgery is performed, graft is perfused with about 100 cc of preservation solution and is ready to be implanted in the recipient.

6.3. Pancreas implantation

The simultaneous kidney and pancreas transplantation is the most frequent transplant modality performed worldwide. The surgical technique used for the implantation of the renal graft does not differ from that used for kidney transplant alone. For pancreas transplantation, although the surgical technique is not standard among centers, there is unanimous agreement in implanting the complete organ, including the second portion of the duodenum.

Traditionally, the intraperitoneal position has been preferred by most groups. In the last decade, different authors have suggested the implant of the graft in a retroperitoneal location, advocating a more physiological position [20].

The pancreas should be implanted prior to the kidney, given its worse tolerance to cold ischemia. The best way to perform the transplant is with a supra-umbilical midline laparotomy, from a point midway between the xiphoid and the umbilicus up to 2–3 cm of the pubis. The complete pancreas with a small portion of the donor's duodenum, which contains the Vater's ampulla, is located laterally in the right iliac fossa of the recipient. The cranial or caudal position of the head of the pancreas depends on each group. Placing the pancreas on the left side increases the risk of graft thrombosis.

The intervention begins with the dissection of the ureter and the right iliac vessels. These should be dissected and mobilized widely to facilitate subsequent vascular anastomoses. Hemostasis must be carefully performed, and the major lymphatic vessels must be ligated. To facilitate the venous anastomosis of the portal, it is advisable to mobilize the distal vena cava and the right iliac vein.

Once the iliac vessels are dissected, the venous anastomosis is performed first, between the portal vein of the graft and the most proximal part of the right primitive iliac vein or on the cava before the iliac bifurcation. Before starting the anastomosis, the vena cava is perfused with heparin (1 mg in 100 cc). The termino-terminal venous anastomosis is performed with two continuous sutures of Prolene 5/0.

The arterial anastomosis is then carried out between the right primitive iliac artery of the recipient and the superior mesenteric artery or the segment of the iliac artery of the graft, depending on the bench surgery performed. From the beginning of the anastomosis, the graft should be kept refrigerated by compresses of crushed ice. Once the arterial anastomosis is completed, the vessels are sequentially declamped, first the vein and then the artery. Pancreas should recover a normal coloration immediately.

Systemic venous drainage is most widely used. Some groups advocate the use of portal venous drainage for the hypothetical benefit of maintaining a more physiological insulin level and thus avoiding the hyperinsulinemia attributed to the systemic drainage. However, technically, it is more complex and its potential metabolic advantages are still controversial.

Pancreatic exocrine secretion can be drained to the urinary tract or to the intestinal tract.

The urinary drainage (duodenocistostomy) contributed extraordinarily to consolidate the pancreas transplant, since it allows to monitor the rejection by the determination of pancreatic enzymes in the urine. However, the high incidence of complications associated with it require the conversion to enteric drainage in 15–30% of cases [20].

Therefore, today, enteric drainage is the technique of election. The most common method of enteric drainage is the one in which the anastomosis is performed between the duodenum of the graft and the jejunum of the recipient, with the pancreatic graft positioned intraperitoneally. The enteric anastomosis can be performed to the proximal jejunum or to the distal ileum, in a termino-terminal, termino-lateral, or a latero-lateral anastomosis. The use of direct anastomosis is currently more widely used than Roux-en-Y anastomosis. However, Boggi et al. [21] have shown excellent results with the use of a Roux-shaped “Y” latero-lateral duodenojejunoscopy (DY), with the retroperitoneal position of the pancreatic graft, and portal venous drainage. Exocrine drainage techniques to the stomach have also been described [22]. Duodenoduodenostomy (DD) is an interesting option for the drainage of digestive secretions when the pancreas is placed behind the right colon and is oriented in the cranial direction [23]. For the placement of the graft in the retroperitoneal position, the right colon is released medially together with the Kocher maneuver, so that the native duodenum is widely exposed. After the correct mobilization of the duodenum of the recipient, the latero-lateral anastomosis (2.5–3 cm) is performed between the duodenum of the graft and the second and third duodenal portion of the recipient with a double suture, one internal for the mucosa with resorbable material (Vicryl 3/0) and a seromuscular external one, with nonabsorbable suture (3/0 silk). After this, the right colon is repositioned to its usual position so that the pancreas remains immobile [24].

After the end of the intestinal anastomosis, the peritoneal cavity is washed with povidone-iodine serum. Some groups perform the wash with antibiotic solution to minimize the risk of peripancreatic infection and mycotic aneurysms. The peritoneum is then closed and the surgical field is prepared for the kidney implant on the left side.

6.4. Surgical complications

The absence of complications after pancreas transplantation depends largely on the detailed knowledge of both the donor and the recipient. Therefore, to minimize morbidity, postoperative care begins at the pre-operative and intraoperative periods.

The first 24–48 h is the most crucial for the graft and the recipient due to (a) the surgical trauma to which the patient has been subjected, (b) the ischemia-reperfusion phenomena of the transplanted organ, and (c) immunosuppression. As expected, the combination of these three insults, especially in a diabetic patient with vascular complications, constitutes a challenge for the entire medical and surgical team.

Surgical complications are relevant since they can lead to graft loss. From 1983 to 1987, 25% of the pancreas transplants performed in the world were lost due to technical reasons [25]. However, in the last decade, the percentage of surgical morbidity has decreased drastically [6].

In general, the main complications of pancreas transplantation, in addition to the general complications of solid organ transplants, include those that are more specific as a consequence of certain organ characteristics: low vascular flow and exocrine component.

There are a number of factors that significantly increase the risk of developing surgical complications such as a donor and recipient body mass index $>30 \text{ kg/m}^2$, organ preservation time $>20 \text{ h}$, cause of death of the non-traumatic donor, and to a lesser extent the intestinal drainage of pancreatic exocrine secretion.

Following are the main surgical complications:

- Vascular complications: arterial or venous thrombosis represents one of the most frequent causes of early graft loss (5–10%). The incidence of thrombosis ranges from 5 to 10% in the simultaneous transplantation of pancreas-kidney and 10–20% in isolated pancreas transplantation. It usually happens to be a venous thrombosis (60%) and appears in the first few days of transplant evolution [26].

The causes are still not fully understood: technical mistakes when performing vascular anastomoses, prothrombotic disorders and hypercoagulability, microvascular injuries produced during the period of extraction and preservation of the graft, as well as hemodynamic instability that reduce the intrinsic flow. It has also been associated with factors related to the donor, as the age and the cause of death, or a prolonged cold ischemia time.

Doppler ultrasound in expert hands is the most available image technique to diagnose thrombosis. Computed tomography is used for the evaluation of vascular anastomoses as well as to rule out the presence of other abdominal complications. Arteriography may be used to confirm the diagnosis in cases of partial or total pancreatic vessel thrombosis and even interventional radiology may be necessary.

In cases of total thrombosis, thrombolysis or thrombectomy should be attempted urgently by performing interventional radiology, and in cases where this is not possible or fails, surgical thrombectomy or transplantectomy should be performed. In partial venous thrombosis, if the thrombus occupies more than two-thirds of the lumen of the vessel, endovascular treatment may be attempted, and in the rest, heparinization. This has made it possible to reduce graft loss due to venous thrombosis to less than 1% [27].

Other vascular complications of the pancreatic graft include hemorrhage, arteriovenous fistulas, pseudoaneurysms, and stenoses of the anastomoses. **Table 6** summarizes the most important complications observed in pancreas transplant recipients for each period.

- Intestinal complications: they usually present at the anastomosis of the duodenal segment. Its incidence has decreased considerably in recent years, and currently less than 1% of the grafts are lost due to this cause [28]. Its incidence ranges at 5–20% in bladder drainage and between 5 and 8% in the intestinal drainage. Early fistulas are usually attributed to ischemia or technical failure, while later fistulas are usually caused by infections or acute rejection.

They represent the second cause of relaparotomy after hemorrhage. The treatment depends on the type of derivation of the exocrine secretion and the importance of the leak.

- Graft pancreatitis: increase in serum amylase and lypase is common after pancreas transplantation, due to both factors inherent to the donor and lesions that the pancreas can suffer during extraction, preservation, implantation, and reperfusion. They are usually self-limited and do not tend to have an impact on the graft outcome. However, hyperamylasemia may be indicative of true graft pancreatitis, with symptoms that may include fever, abdominal pain, ileus, and abdominal distension. Pancreatitis that appears after the first weeks following transplantation is usually secondary to an acute rejection or infections (such as cytomegalovirus—CMV). In patients with bladder drainage, they can also be attributed to reflux of urine through the pancreatic duct. As a consequence of graft pancreatitis, fistulas, peripancreatic collections or abscesses, and pancreatic pseudocysts may occur.

Post-transplant period	Complications
Pre-trasplant	Graft damage during organ procurement: <ul style="list-style-type: none"> • Vascular lesions (splenic artery, SMA, portal vein) • Duodenal lesion • Damage to pancreatic capsule or parenquima
Peri-transplant	Acute surgical or post-surgical complications: <ul style="list-style-type: none"> • Vascular lesion (recipient severe atheromatosis) • Hemorrhage • Pancreatitis • Inadequate graft perfusion • Cardiovascular morbidity
Post-trasplant	Vascular complications <ul style="list-style-type: none"> • Graft thrombosis (60% venous, 40% arterial) • Late vascular complications (anastomosisstenosis, pseudoaneurisms, arteriovenous fistulas) • Vascular complications of kidney graft (in SPK) Infection of surgical wound Incomplete healing of surgical wound Intra-abdominal infection Fistulas due to duodenal leaks Graft pancreatitis Pancreatic pseudocysts Panreatic leak Hemorrhage (intra-abdominal, bladder, gastrointestinal) Urological complications Infections (bacteria, viral, fungal)

Table 6. Complications according to the time of appearance.

- **Infections:** they are frequent in this group of transplant recipients (80% throughout the first year), and they play an important role in the patient and graft survival. Diabetes, surgery, and immunosuppression are factors that predispose these patients to suffer infections of all types. Pancreas transplantation presents a risk of infection by CMV of 13–17%, largely due to the use of potent induction immunosuppression. CMV infection is associated with increases in mortality, the rate of rejection, and the presentation of other types of infections. The incidence of intra-abdominal infections is 10–30%, most of them polymicrobial, with fungi present in less than 10% [29]. The current prophylaxis schemes (against bacterial, viral, and fungal infections), established from the moment of intervention, have managed to reduce its incidence in the short term. However, they still need to be monitored in the longer term.

7. Perioperative management

Recipients of pancreas transplantation are diabetic patients most often with a disease vintage over 10 years and frequently with secondary macro- and microvascular complications. The cardiovascular risk is superior to those of general population or recipients of kidney transplant alone. The perioperative management is of crucial importance not only to avoid the risk of hemodynamic instability and periods of low perfusion of the graft, but is also vital for organs such as brain and heart.

7.1. Volume, acid-base and electrolyte, and hemodynamic stability

Volume and electrolytes should be monitored closely during the first 48 h and fluids administered accordingly to avoid hypovolemia or acid-base and electrolyte imbalances. Although an individualized assessment should be performed in each case, it is considered appropriate to maintain a central venous pressure between 5 and 10 mmHG. The administration of fluids with dextrose should be avoided, as it may prolong the need for insulin.

Since most patients are also recipients of a kidney transplant, close monitoring of urinary output must be performed simultaneously. In the event of polyuria (urinary output >150 ml/h), aggressive volume reposition should be performed, usually at a rate of 1:1 during the first 24 h, and thereafter at a rate of 0.7:1 to avoid prolonging the polyuria. Fluid solution should be selected according to acid-base and electrolyte homeostasis, with 0.9% or 0.45% sodium chloride often being the first line of treatment.

In the event of delayed graft function and oliguria (urinary output <50 ml/day), fluids should be restricted to those needed for the minimum daily calories and electrolyte intake to avoid hastening the need for dialysis intended for volume management. When needed, dialysis modality (continuous vs. intermittent) should be discussed with the nephrologist and risk benefits must be weighed—intermittent dialysis may be performed with the need for anticoagulation, and with low ultrafiltration volumes, reducing the risk of surgical complications, while continuous dialysis reduces hemodynamic instability and therefore decreases the risk of reducing organ perfusion.

Anemia is frequent among patients with ESRD. It is important to maintain adequate levels of hemoglobin (Hgb >10 mg/dl), especially in the case of postoperative bleeding. Controversy exists regarding the need for immediate anticoagulation (vide Section 8—prophylaxis).

Both hypotension and hypertension should be avoided. A systolic blood pressure < 100 mmHG increases the risk of arterial and venous thrombosis of the graft, especially in the immediate postoperative period. On the other hand, prolonged severe hypertension can lead to a stroke or myocardial infarction and may increase the risk of intra-abdominal hemorrhage. It is advisable to maintain the systolic pressure between 120 and 160 mmHg during the first 24 h post-transplant to ensure adequate perfusion of the graft and minimize the risk of adverse effects.

7.2. Graft function

The immediate evaluation of the graft (both pancreatic and renal, in the case of SPK) can be monitored in various ways. The protocol accepted by most centers combines the use of laboratory parameters together with image tests. The decrease in blood levels of blood urea nitrogen (BUN), creatinine, amylase and lipase is required, together with blood glucose levels within normality, to consider that the grafts function correctly (in case of SPK). Blood levels of amylases and lipases provide additional information regarding pancreatic injury. In the immediate postoperative period, blood levels of pancreatic enzymes may be elevated, with normal blood glucose levels, which translates into an ischemia-reperfusion injury, and usually resolves spontaneously. In cases of exocrine drainage to urinary bladder, the level of amylases in urine can be monitored. A decrease of 50% or more is suggestive of rejection or pancreatitis.

7.3. Image diagnosis

In the post-transplant period, radiological examinations should be performed to evaluate graft perfusion and exclude surgical complications, such as collections or thrombosis. Most centers rely on ultrasound as their preferred method, since it is easy to use, nontoxic, and may be performed as often as needed. When available, computerized tomography may provide further information, such as contrast-enhanced evaluation of arterial perfusion and venous drainage, as well as exclude possible hemorrhages. Herein, we describe in detail advantages of each option.

7.3.1. Color Doppler Ultrasound

It is the initial imaging technique for control and monitoring of pancreas transplantation. The study with electronic data capture (EDC) allows to assess the size and the structure of the graft, the presence of liquid collections (study in B mode), and the perfusion of the parenchyma (resistance index), as well as the permeability of the vascular anastomoses (Doppler study). An extension of the study can also be done with the ultrasound signal enhancer, if it is considered appropriate by the sonographer who performs the study. It is advisable to make a basal study, between 24 and 48 h post-transplant, and a follow-up study, every 3–4 days until the patient's discharge.

7.3.2. Abdominal CT scan

In some cases, Doppler ultrasound may be technically limited (abdominal distension, obesity) or the study might need to be extended, such as in the patient with abdominal pain, fever, and/or graft dysfunction, intra-abdominal collection not accessible to ultrasound drainage, intra-abdominal collection drained by ultrasound, but without adequate clinical response. If a vascular pathology or bleeding is suspected, a contrast-enhanced CT scan is advised.

7.3.3. Interventional radiology

Interventional radiology may be used for diagnostic confirmation and/or treatment (thrombectomy) of a partial arterial and/or venous thrombosis of the graft.

7.4. Monitoring of vascular thrombosis

Thrombosis is the most common vascular complication in the initial post-transplant (8–10 days post-transplant) period. Therefore, early diagnosis is important to establish adequate treatment.

If a first post-transplant imaging study to confirm the vascular permeability of the graft (splenic and mesenteric artery/vein) is not achieved due to bowel distention, the decision whether or not to extend the radiological procedure will be based on pancreas functionality: (1) in normal functioning graft the study is repeated in 24–48 h, (2) if dysfunctional the study is extended to a non-invasive imaging technique, such as angio-CT. Some groups advocate performing angio-CT as standard monitoring image technique due to its ability to establish a grading score for venous thrombosis [30]. In our experience, in the presence of an experienced radiologist, Doppler ultrasound, with or without contrast-enhanced ultrasound (CEUS), is a reliable screening technique.

During the first 48-h post-transplant, the patient usually stays in the intensive care unit, to be transferred later to the conventional hospital ward if there have been no adverse effects. Progressively, the oral intake is introduced and the abdominal drainage is removed. Before hospital discharge, it is important to give a detailed description of medication and home care to the patient.

8. Immunosuppression and prophylaxis

8.1. Immunosuppression

Advances in immunosuppression protocols during the last two decades significantly increased short- and long-term pancreas graft survival. The purpose of immunosuppression is control alloimmune response, and protocols often include a combination of different drugs to minimize the damage to the graft and the risks to the patient. They are similar in all solid organ transplants. Nonetheless, it is of particular relevance in pancreas transplant recipients due to the increased risk of acute rejection, especially in recipients of pancreas transplant alone (PTA). The greatest burden of immunosuppression is then usually administered in the recipients of a PTA.

Immunosuppression is usually divided into two major categories—induction and maintenance. The former represents treatments used in the peri-transplant period alone, with the objective of inhibiting both the innate and adaptive immune response when the graft is first exposed to recipient immune system. The drugs used are the same as for other solid organ transplantations and have been described in other chapters. The next section describes how and what drugs are used in pancreas transplantation:

8.1.1. Induction therapy

This consists of the administration of a polyclonal or monoclonal antibodies and is currently assumed as standard treatment for pancreas transplantation. These decrease the incidence of acute rejection or delay its onset, and reduce the number of steroid-resistant rejections. Depleting T-cell antibodies may be polyclonal, most widely used, such as rabbit anti-thymocyte globulin (Thymoglobulin®/ATG-Fresenius®) or monoclonal, such as the anti-CD52 alemtuzumab (Campath®); among non-depleting monoclonal antibodies, anti-IL-2 receptor (anti-CD-25; basiliximab) is the most frequently used.

There is no consensus on which is the best protocol. Depleting antibodies appear to increase graft survival by reducing acute rejection risk [8] and are the most widely used. Nonetheless, due to financial constraints and also due to an increased infection and cancer risk associated with T-cell depleting agents, some groups use monoclonal anti-IL-2 antibodies in low-immunological risk simultaneous pancreas-kidney transplantation.

8.1.2. Maintenance treatment

As an adjunctive treatment to induction therapy, and as long-term maintenance immunosuppression, a combination of three drugs is most often used: a calcineurin inhibitor (CNI), an anti-proliferative, and steroids.

The discovery of cyclosporine 35 years ago marked a new era in solid organ transplantation. The incidence of acute rejection was drastically reduced, and despite an increased risk for renal calcineurin toxicity and subsequent renal failure, the patient and graft survivals observed a spectacular improvement. Tacrolimus (or FK-506), also a CNI, exhibits a better and more potent immunosuppression profile and is currently considered the drug of choice in pancreas transplantation. CNIs act by inhibiting the transduction of the first signal between antigen-presenting cells and T-cells. Several comparative studies have shown a lower incidence of acute rejection, as well as a lower severity of rejection and a better survival of the pancreatic graft in the short and long term, in those patients treated with tacrolimus.

CNI is often associated with an anti-proliferative agent. Their action focuses on a different pathway of the T- and B-cell activation and proliferation. Azathioprine, the first to be used, arrests cell cycle in the G2 phase, inhibiting the progress to the M phase and subsequent clonal expansion. On the other hand, antimetabolite agents (mycophenolate-mofetil or mycophenolate sodium) inhibit nucleotide synthesis, removing the substrate to DNA replication, finally achieving the same result as azathioprine—prevents cell proliferation. Finally, the latest agent to be introduced to solid organ transplantation were mammalian target of rapamycin

(mTOR)-inhibitors (sirolimus and everolimus). Both act as anti-proliferative drugs by inactivating the mTOR pathway following the receptor CD28 activation by antigen-presenting cells.

Steroids are perhaps the most widely used immunosuppressive drugs for organ transplantation. Steroids present a pleiotropic effect, with an action on both innate and adaptive immune responses. Steroids reduce antigen-presenting cells' cytokine transcription and secretion, reducing the ability of innate immune system to further recruit polynuclear cells. It also inhibits activation of mononuclear cells, such as T- and B-cells. Despite the great immunosuppressive profile, side effects mandate that these are reduced or withdrawn from maintenance treatment.

Triple therapy using one agent from each category has achieved excellent results. The most widely used combination is steroid, tacrolimus, and mycophenolate. An mTOR-inhibitor may be used instead of mycophenolate, but careful management of side effects should be undertaken. Although the results obtained with this association seem to be superimposable, as far as patient and graft survival is concerned [31], the incidence of complications attributable to rapamycin in the immediate post-transplant is greater, so this combination is not as widely used in the initial period of the transplant. However, it is a good option for long-term use.

Several studies have suggested that steroids can be suppressed as maintenance therapy, especially in patients receiving a calcineurin inhibitor associated with an antimetabolite or an mTOR-inhibitor, without affecting the survival of the grafts. However, there is no consensus regarding this topic [32], due to some reported increased risk of rejection following withdrawal. It seems reasonable that the decision to suppress steroids is focused for the moment on those patients with low-immunological risk, and it should be attempted during the first year of transplantation.

8.2. Prophylactic treatments

In pancreas transplantation, prophylactic treatments are usually wider than those used in kidney transplantation. As previously stated, pancreas low blood flow, complex vascular anastomosis, the duodenal enteric anastomosis, and the increased infection risk due to persistent hyperglycemia prior to transplantation increase the need for thrombotic and infectious prophylaxis.

Antithrombotic prophylaxis: graft thrombosis is one of the most frequent early complications in pancreas transplantation. Therefore, most transplant centers perform prophylaxis. There is no standard protocol among different centers, but the most frequent is the use of heparin and/or aspirin. Some centers use low doses of intravenous heparin, unlike others who use subcutaneous low-molecular-weight heparin. In both cases, it is important to monitor coagulation parameters and adjust dose to renal function due to uremia-induced anticoagulation and/or anticoagulation used during dialysis sessions. Heparin is often associated with low-dose aspirin, which could be continued in the long term to reduce global cardiovascular risk.

Antimicrobial prophylaxis: infection remains one of the main causes of morbidity and mortality after pancreas transplantation. That is why it is usual to use a wider prophylaxis in these patients. At transplantation and during a variable period of time, broad-spectrum antibiotics to cover Gram negative, Gram positive, and anaerobic are recommended. They are used for 3–5 days and several associations are possible, usually cephalosporin + ampicillin or vancomycin or carbapenem + vancomycin depending on local post-transplant epidemiology. Antifungal prophylaxis with fluconazole is also often performed. Currently, some prophylactic guidelines have replaced fluconazole with a new drug, micafungin, with the advantage of avoiding interaction with tacrolimus. Since most patients receive induction treatment with polyclonal antibodies, which is well known to increase the risk of infections, especially viral infections, antiviral prophylaxis with valgancyclovir for CMV is also advisable. Finally, prophylaxis to pneumocystis jirovecii with trimetoprim-sulfamethoxazole for 6 months is the treatment method, as used in kidney transplantation.

9. Long-term outcomes and complications

Pancreas transplant outcomes have increased in the last decades, with a median graft survival using current protocols up to 15 years. In order to achieve these outcomes, close ambulatory controls must be performed during the first year, with increasing the time between outpatient visits if follow-up is unremarkable. It is usual to perform a weekly control during the first 3 months post-Tx, biweekly until 6 months, and between 6 and 12 months on a monthly basis. They focus primarily on functional graft monitoring, immunosuppression, and complications secondary to diabetes.

To assess pancreatic graft functionalism, baseline glycemia, glycosylated hemoglobin (HbA1c), as well as serum amylases and lipases is determined in each outpatient follow-up. In the post-transplant period, after hospital discharge and again 1 year after transplant, it is convenient to perform an oral glucose tolerance test (OGTT). Subsequently, and as a follow-up guideline, the intervals between these analyses varies according to the teams. It is also advisable to perform a C-peptide determination to monitor insulin secretion throughout the follow-up, as well as the determination of anti-glutamic acid decarboxylase (GAD), in order to detect a possible recurrence of diabetic disease. Both should be checked at least once a year.

During patient follow-up, it is important to control secondary complications of diabetes. Despite having a functioning pancreas graft, recipients should continue to monitor secondary complications present prior to pancreas transplantation, such as diabetic retinopathy or macrovascular complications. Some patients experience an improvement of complications present prior to transplantation, particularly in neuropathic symptoms. As to macro- and microvascular complications, most lesions tend to stabilize [33]. Therefore, it is advisable to perform an annual ophthalmological examination, regularly assess neuropathy of both peripheral and autonomic nervous system, as well as having a special surveillance to the complications related to the vasculopathy, appearance of precordial pain, or peripheral ischemic lesions.

Not least important, patients should be advised to maintain a proper diet to avoid weight gain, promote physical activity, avoid sun exposure, prohibit or limit the consumption of alcohol and smoking, recommend suitable footwear to avoid chafing and periodic podiatric check-up, and, in women of childbearing age, recommend measures of contraception to avoid pregnancy during the first 1–2 years of the transplant.

9.1. Acute and chronic rejection

The incidence of acute rejection is higher in pancreas transplant than those reported in kidney transplantation. The actual incidence must be individualized according to transplant modality, recipient immunological risk, induction and maintenance immunosuppression, and transplant follow-up period.

Overall 1-year rejection incidence varies between 14.7% [34] and 21% [10]. PTA and PAK are associated with significantly higher incidence of acute rejection than SPK recipients [34]. Other risk factors include pancreas re-transplantation [10], absence of induction therapy or basiliximab and induction agent [8], donor age, number of HLA donor-recipient mismatch [10], and the presence of donor-specific antibodies (DSA) [35, 36].

In SPK recipients, monitoring of renal function and/or the performance of a renal biopsy had been advocated as an indirect method to establish the diagnosis and treatment of pancreas' acute rejection, since for many years it has been considered that acute rejection was present in the majority of the cases simultaneously in both grafts. However, it is now well documented that isolated rejection of one of the two organs occurs in up to 36% of cases [37].

To diagnose pancreatic graft rejection, the only biochemical markers available are pancreatic enzymes (amylases and lipases), which are elevated in most of these episodes. Lipase increase is more specific than amylase [10]. On the other hand, in acute rejection, it is possible to observe changes in graft size and eco-structure, with an increase in the resistance index when performing a Doppler ultrasound. Both parameters allow to establish the diagnosis of suspected acute rejection, but they are not specific enough to establish confirmation. This sometimes leads to unnecessary or incomplete empirical treatments, with the consequent repercussion for the patient and the graft. In addition, pancreatic rejection, as recently observed, can also be mediated by antibodies, which requires a different and specific treatment.

Currently, pancreatic biopsy is considered the gold standard for etiologic diagnosis of graft dysfunction. In our center, pancreatic graft biopsy is performed per protocol at 3 weeks and 12 months post-transplant, or indicated in the following circumstances (**Figure 1**): (1) patients in whom the existence of an acute rejection of the pancreatic graft is suspected due to biochemical parameters (increase in serum glycemia, amylases, and lipases), and/or ultrasound (increase in size, changes in the graft structure, and involvement of the graft), (2) in whom the existence of a chronic rejection is suspected due to a persistent increase in amylases or serum lipases, progressive increase in glycemia and glycosylated hemoglobin, and/or progressive decrease in C-peptide secretion, and (3) in whom the recurrence of diabetic disease is suspected due to detection or progressive increase of anti-GAD antibodies, and pathologic oral glucose tolerance test. To establish the severity of the histological lesion of acute rejection, the Banff scheme should be taken as reference [38].

Pancreas' acute rejection can be successfully treated using steroids, polyclonal antibodies, and/or plasma exchange and immunoglobulins. Nonetheless, up to 20% of grafts may be lost during the first year following an acute rejection [10].

9.2. Diabetes relapse

Type 1 diabetes is the most frequent indication for pancreas transplantation. As described in the first section of this chapter, DM1 is an autoimmune disease, characterized by autoantibodies directed to β cells. Disease relapse in pancreas graft is a well-known risk for graft failure. It has been reported in up to 7% of all transplant recipients [39]. Induction and maintenance immunosuppression are likely the reason for such a low incidence. Some factors have been associated with an increased risk for disease relapse, such as donor-recipient sharing of HLA-DR alleles, particularly HLA-DR3 [39], and the increase in autoantibodies, particularly ZnT8A, predicts the risk of disease relapse [40]. As with primary disease, no treatment is established for the management of disease relapse. Increase in baseline immunosuppression maybe attempted. If a pancreas re-transplantation is indicated, recipients must be advised of the risk of relapse in the new graft.

10. Islet transplantation

In addition to pancreas transplantation, β cell mass transfer may be performed through islet transplantation. This procedure consists of islet cell isolation from pancreas as potential donors using both mechanical and enzymatic digestion protocol, following which islets are separated using a Ricordi chamber [41]. Isolated islets are infused into recipient's portal vein, without the need for vascular and/or enteric anastomosis, reducing the surgical risks of the procedure.

The attractiveness of a minimally invasive procedure and the possibility of multiple infusions without the surgical risks associated with whole-organ pancreas transplantation have positioned islet cell transplantation as a promising treatment for patients with diabetes. Despite these advantages, islet transplantation presents two critical drawbacks when compared to whole-organ transplant. Islets obtained from a minimum of 2–3 pancreas are often needed in order to achieve euglycemia [41], increasing organ demand, and risk of recipients' sensitization. Additionally, islets direct engraftment into a vascularized bed exposes β cells to platelets and lymphocytes. Instant blood-mediated inflammatory reaction (IBMIR) is a well characterized event associated with innate immune reaction and coagulation and complement activation following islet transplantation, leading up to 25% of total islet cell mass loss following vena cava infusion [42]. Moreover, it may increase the risk of rejection and reduces overall graft survival.

In early 2000, the Edmonton group published some promising results using an induction immunosuppression protocol [41]. By the end of 2015, over 15,000 procedures had been performed worldwide [5]. Reported 1- and 5-year insulin independence is up to 80 and 50%, respectively [5].

Novel biocompatible implantation devices and gene editing tools foresee a bright future for islet transplantation. 3D-bioprinting is being used to build an islet-blood interface which enables β cell survival and insulin production, while avoiding immune activation and graft rejection [43]. On the other hand, generation of human-induced pluripotent stem cells (hiPSCs) has opened the door for personalized medicine and cell-based therapy. iPSCs can proliferate unlimitedly in culture and harbor the potential to generate all cell types in the adult body. Generation of hiPSC-derived β cells has been published by several groups, using different protocol, with varying degrees of success [44, 45]. The advantage is the possibility to generate tailor-made islet cells, particularly β cells, from recipient-derived hiPSC, evading the risk of allo-rejection. One can envision in the near future hiPSC-derived cells implanted in a biocompatible device for the treatment of type 1 diabetic patient.

For the time being, islet cell transplantation remains at an almost investigation level due to smaller insulin independence when compared to pancreas transplantation. Nonetheless, it is a suitable option for selected type 1 diabetic patients, and to those with a surgical contraindication for whole-organ transplantation. Finally, islet transplantation presents a promising future as the technique of election for β cell mass transfer.

11. Conclusion

Pancreas transplantation is the best treatment alternative for patients with end-stage renal disease and type 1 diabetes and may be found in the selected group of type 2 diabetic patients. Patient and graft survival have greatly increased in the last decades, particularly due to improvements in surgical procedures and immunosuppression protocols, with graft half-life of 15 years. Following transplantation, patients should be carefully monitored due to the risk of acute rejection, disease relapse, or diabetic secondary complications present prior to the transplant.

Conflict of interest

The authors decline any conflict of interests.

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