Pancreas Transplantation – the Asian Experience

A Registry Report

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Contents

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Part I

Pancreas Transplantation in Deceased Donor

Duck-Jong Han, Chang Hee Jung, Joo Hee Jung, Takashi Kenmochi, and Yi-Ming Shyr

Introduction

Incidence

Diabetes mellitus is a leading public health concern in oriental countries and around the world. According to the Centers for Disease Control, more than 15 million people in the United States, or 5.9% of the population, have diabetes and 798,000 new cases are diagnosed each year (Fig. 1) [1].

Since 2000, it has been estimated that the worldwide prevalence of diabetes in adults has risen from 4.6% to about 9%. In 2019, about 460 million people were estimated to live with diabetes and a further increase is projected [2].

Korea

The prevalence of diabetes in Korea is almost the same with the States as 5.92% of the population. It is estimated that the diabetic population is rapidly increasing by 10% each year. The incidence of new type 1 diabetic patients was estimated to be 3.28 per 100,000 people in Korea [3]. While the prevalence of type 2 diabetes is estimated to be 13.8% in Korean adults aged more than 30 years old in 2020 (Diabetes Fact Sheet in Korea 2020) [4].

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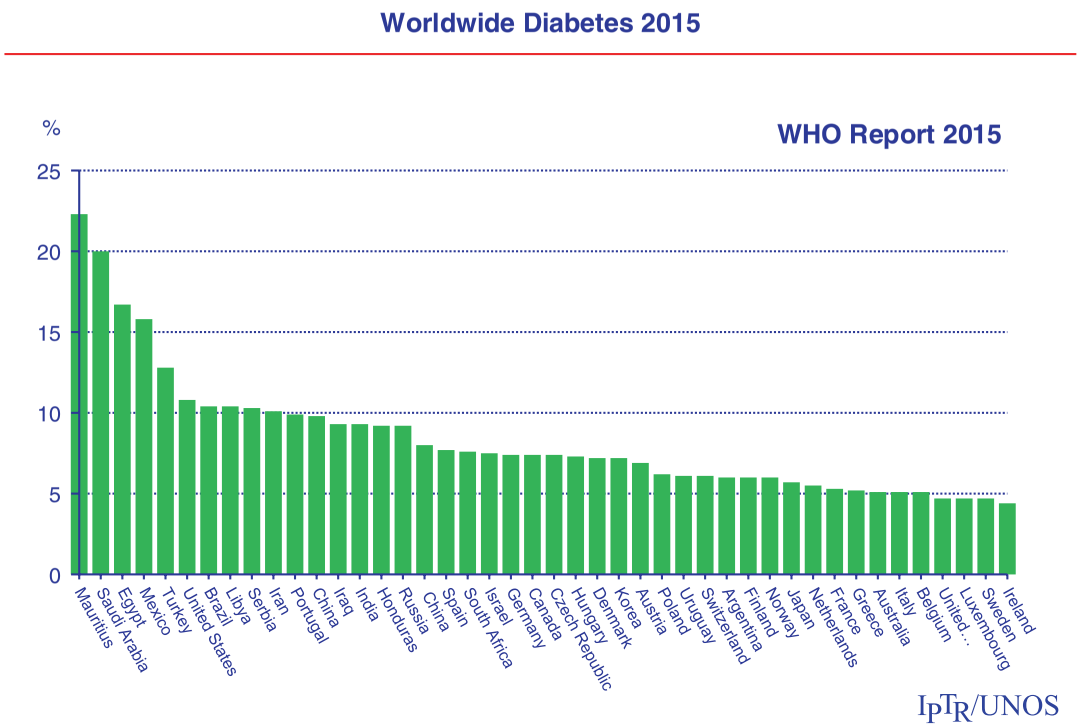

Fig. 1 The incidense of worldwide diabetes reported in WHO (2015)

Japan

In Japan, the prevalence of diabetes at the age of 20 years and older is 12.1% (male; 16.3%, female; 9.3%) of the population accounting for 10 million patients [5]. On the other hand, looking at type 1 diabetes in Japan, it is difficult to know the number of patients nationwide because medical institutions are not obliged to report. A research group of the Ministry of Health, Labor and Welfare, "Survey on the actual condition of type 1 diabetes, objective diagnostic criteria, and research on the creation of severity evaluation focusing on daily life and social life" led by Tajima N of Jikei University, had been conducting fact finding surveys on type 1 diabetes for 4 years since 2014. The research group calculated estimates from various surveys [6]. According to a survey by the research group, the estimated number of patients who received medical treatment for type 1 diabetes in 2017 is about 115,000 (51,000 male and 64,000 female). The prevalence rate is about 0.09% (about 90 per 100,000 population). In addition, according to an estimate using the research group's receipt information/specific medical examination information database (NDB), the number of patients with type 1 diabetes is approximately 141,000, and the prevalence rate is approximately 0.11%. According to the "2014 Patient Survey" by the Ministry of Health, Labor and Welfare, the total number of patients who received medical treatment for type 1 diabetes (insulin-dependent diabetes mellitus) was about 109,000, and the prevalence rate was about 0.09% [7]. The survey group has different estimates depending on the survey method, but the number of patients with type 1 diabetes (all ages) was about 100,000–140,000, and the prevalence rate was about 0.09–0.11% (about 90 per 100,000 population).

Taiwan

There are about 2,000,000 diabetes mellitus (DM) patients and the diabetic population is increasing by 25,000 new cases every year. DM is the fifth leading cause of death according to the Ministry of Health and Welfare, Taiwan. The prevalence rate of Type 1 DM is about 1.5/100,000 in Taiwan.

Definition

While hyperglycemia is the defining characteristic of diabetes, the underlying pathogenesis leading to hyperglycemia differs significantly among the various forms of the disease. Common to all is the presence of defects in insulin secretion and/or insulin action.

Type 1 diabetes occurs when the pancreatic beta cells are destroyed and the patient develops profound or absolute insulin deficiency. Nearly all cases are autoimmune in origin. This form of diabetes accounts for approximately 5–10% of diabetes. The disease most often appears in childhood, but patients of any age may present with type 1 diabetes. A mixture of genetic and envi-

ronmental factors are believed to lead to the autoimmune destruction that causes type 1 diabetes. Over the past 10 years, the incidence of type 1 diabetes has increased.

Type 2 diabetes occurs as the result of defects in both insulin secretion and insulin action. This form of the disease represents about 90% of prevalent cases of diabetes. The incidence of type 2 diabetes in children has been dramatically increasing in recent years [8].

Korea

Our body has the function of maintaining the blood glucose level within a certain range during fasting and after a meal. When fasting without food intake, blood glucose level is controlled so that it does not drop too low. After a meal, ingested nutrients are used as an energy source in muscle, fat, and liver, or the remaining energy is stored in the form of fat or sugar source (glycogen) so that there is not too much glucose in our blood. In order to properly maintain the blood glucose level, a hormone secreted from the pancreas called insulin must play a central role.

Diabetes mellitus is a disease characterized by insufficient secretion and action of insulin, thus causing problems in various blood vessels and organs.

There are various causes of diabetes mellitus, but currently, it is classified into four major categories [8]: (1) Type 1 diabetes, (2) Type 2 diabetes, (3) Gestational diabetes, and (4) Other types of diabetes.

Type 1 diabetes was also called "pediatric diabetes" or "insulin-dependent diabetes" in the past. However, currently diabetes is not classified by age or insulin use because there are cases of insulin-dependent type 2 diabetes, and type 1 diabetes can develop at any age, not limited to children or adolescents. Type 1 diabetes is a state in which glucose in our body does not function normally due to insufficient insulin, caused by selective destruction of beta cells, the insulin-secreting plants in the pancreas. The cause of the destruction of the pancreatic beta cells is not clear yet, but most of them are known to be caused by so-called autoimmune mechanism, in which immune cells in our bodies attack the beta cells. The reason why this "autoimmune mechanism" is activated is also not clear. It is presumed to be caused by a complex combination of prenatal "genetic predisposition" and various postnatal "environmental factors." However, not all type 1 diabetes is due to "autoimmune mechanisms," and the cause often happens to be unknown. This is called "idiopathic" type 1 diabetes, and its treatment and prognosis are not much different from those due to "autoimmune mechanisms." Commonly, type 1 diabetic patients need insulin supply in some way (external insulin injection via drug and injection or internal insulin supply such as pancreatic transplantation) to survive.

Type 2 diabetes is more complex in its causes than type 1 diabetes, and treatment methods also vary widely depending on the patient. In the past, type 2 diabetes was also referred to as "adult-onset diabetes" or "noninsulin-dependent diabetes," but these terms are not currently used because it can develop not only in adults but also in children and adolescents and sometimes requires insulin therapy.

The causes of type 2 diabetes are complexly divided into 8–11 reasons, which can be broadly summarized into two main reasons.

First, it is "relative insulin deficiency" phenomenon that occurs due to problems with secretion of insulin, which is responsible for glucose utilization and storage. This can lead to a very dangerous consequence of "absolute insulin deficiency" similar to that of type 1 diabetes. Therefore, internal or external supply of insulin is essential for treatment of diabetes and survival of patients.

Second, it is "insulin resistance" phenomenon caused by failure of insulin to work properly. It is considered a major cause of type 2 diabetes, and the risk of developing the disease increases as the body becomes obese.

Japan

According to the research group of the Ministry of Health, Labor and Welfare described above, among type 1 diabetes [9], type 1 diabetes which is particularly difficult to control and requires special consideration both physically and socially, is defined as "type 1 diabetes with depleted insulin secretion." The research group targeted 139 patients with type 1 diabetes whose intrinsic insulin secretory capacity was analyzed in detail in the glucagon stimulation test, and various factors that affect the severity index from the viewpoint of hyperglycemia, hypoglycemia, and glycemic fluctuation.

As a result, it was clarified that the endogenous insulin secretory capacity (C-peptide) is an index that correlates with the severity index of type 1 diabetes.

C-peptide is a substance that is formed during the production of insulin, and is produced in approximately the same proportion as insulin. Examining the amount of C-peptide excreted reveals how much insulin is secreted. There is a test to measure fasting serum C-peptide and a test to measure the amount of C-peptide by collecting urine for 24 h.

If the former is 0.6 ng/mL and the latter is 20 μg/day or less, it is a guideline for insulin dependence.

According to the research group, if the fasting C-peptide is less than 0.1 ng/mL, it is considered to be "type 1 diabetes with depleted insulin secretion." Furthermore, as a method for evaluating insulin secretion in detail, there is a glucagon stimulation test. If the ΔCPR (difference between 6- and

0-min CPR measurement after 1 mg glucagon injection) is 0.5 ng/mL or less, it is defined to be type 1 diabetes with depleted insulin secretion.

Diabetes patients who are completely depleted of insulin secretion, such as childhood-onset type 1 diabetes, need to be treated with intensive insulin or pancreas/islet transplantation for a lifetime.

Taiwan

In Taiwan, the diagnosis of DM is based on two of the followings: (1) (HbA1c) ≥ 6.5, (2) Fasting plasma sugar ≥126 mg/dL, (3) 2-h glucose tolerance test ≥200 mg/dL, (4) Typical symptoms of hyperglycemia and random plasma sugar ≥200 mg/dL.

DM Complication

Diabetes mellitus is associated with devastating complications that increase both the mortality and morbidity of those suffering from the disease. Because of its high prevalence and the severity of its associated complications, diabetes has become one of the costliest diseases to treat in Korea and Westernized countries.

The complications of diabetes are from vascular complication and are largely classified as follows:

- Microvascular complications: Retinopathy causing visual impairment, nephropathy causing chronic kidney disease, and sensory abnormalities, such as numbness in hands and feet, and motor disorders from neuropathy.
- Macrovascular complications: Coronary artery disease causing myocardial infarction, cerebrovascular disorders, peripheral artery disease from arteriosclerosis.

Heart disease is the leading cause of diabetes-related deaths and people with diabetes die from heart disease two to four times more often than people without diabetes. This is one of the leading causes of end-stage renal disease in Korea [10].

Excessive hyperglycemia is a major risk factor for the development of diabetic retinopathy [9]. Diabetes is the leading cause of new blindness [11]. But cataracts and glaucoma related to diabetes are also responsible for vision loss. Foot ulcers that occur as a result of diabetic neuropathy are estimated to affect about 15% of all patients with diabetes at some point during their lifetime [12]. In addition, approximately 85% of lower extremity amputations are proceeded by a foot ulcer [13]. In Korea, almost half (44.8%) of the people who had lower limb amputation were diabetic [10].

Of the microvascular complications, renal complications are especially very serious and can be caused by a combination of long-term uncontrolled hyperglycemia, hypertension, and dyslipidemia. Patients cannot feel the symptoms until the kidneys lose much of their original function, and because diagnosis is only possible through various tests including blood tests, the disease is often detected after the condition has significantly progressed. The same is true of other vascular complications, but it is generally difficult to return to the previous state once they occur, so it is best to detect early and prevent them through regular examinations first. Once renal complications have occurred, realistic treatment is to replace the kidney function with external methods such as hemodialysis or peritoneal dialysis. In addition, if there is an appropriate donor, kidney transplantation may be performed, and simultaneous kidney and pancreas transplantation may be performed to solve the insulin problem.

The burden of modern diabetic management is dialysis like. Standard diabetic management entails at least four blood sugar determinations a day, with at least twice daily insulin injections and supplementary injections according to blood sugar levels.

In the Diabetes Control and Complication Trial, even in the intensive treatment arm under the most ideal conditions, 15% of the patients went on to develop secondary complications [14]. Retinopathy, neuropathy, and nephropathy are at least as morbid, if not more so, than the side effects of chronic immunosuppression.

Rational of PT

Although an intensified insulin regimen improves glycosylated hemoglobin concentrations and reduces the rate of long-term complications, it does not prevent them. The goal of pancreas transplantation is to safely restore normoglycemia by the provision of sufficient β cell mass. Transplantation of a pancreas, unlike liver, lung, and heart, is not a life-saving operation. But it improves the quality of life because patients do not need to inject insulin on a daily basis or regularly monitor glucose concentrations with finger sticks, and hypoglycemic unawareness is no longer a problem. The long-term advantages of this surgical procedure have to be balanced against the potential morbidity and mortality associated with diabetes, and the side effects from the long-term immunosuppression that is needed to prevent alloimmunity and autoimmune recurrence (Figs. 2 and 3). The risk of immunosuppression is particularly relevant for recipients of pancreas transplants alone (PTA; unlike patients with uremic diabetes who are also given a kidney transplant), since the only benefit of immune suppression in this category is insulin-free euglycemia [15].

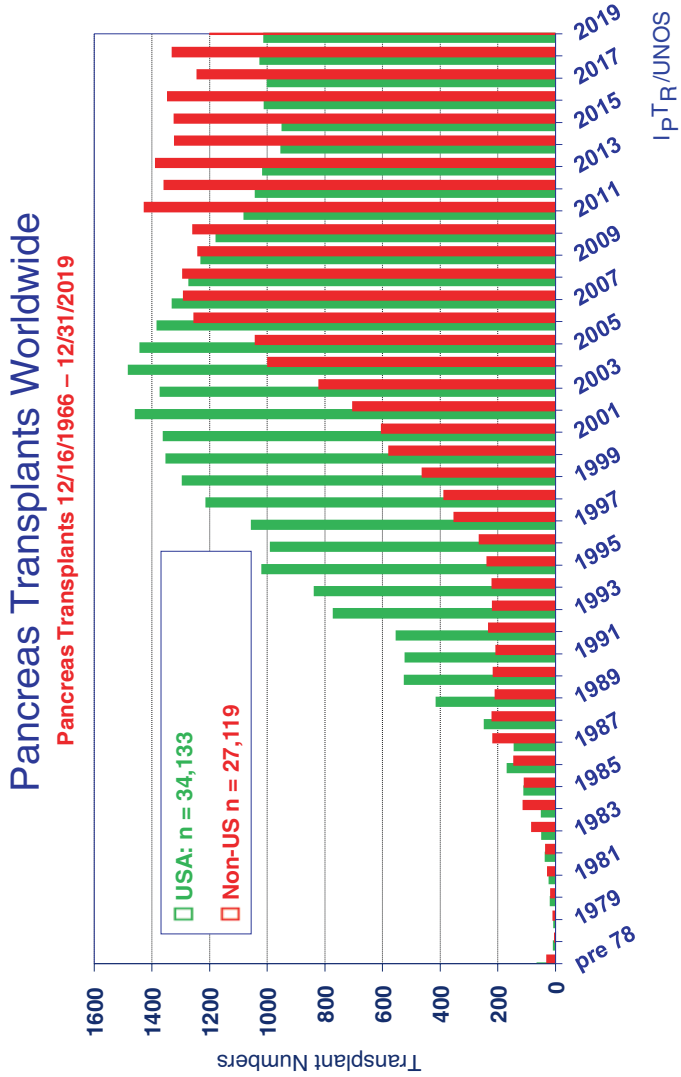

Fig. 2 The annual number of pancreas transplantation performed between US and non US

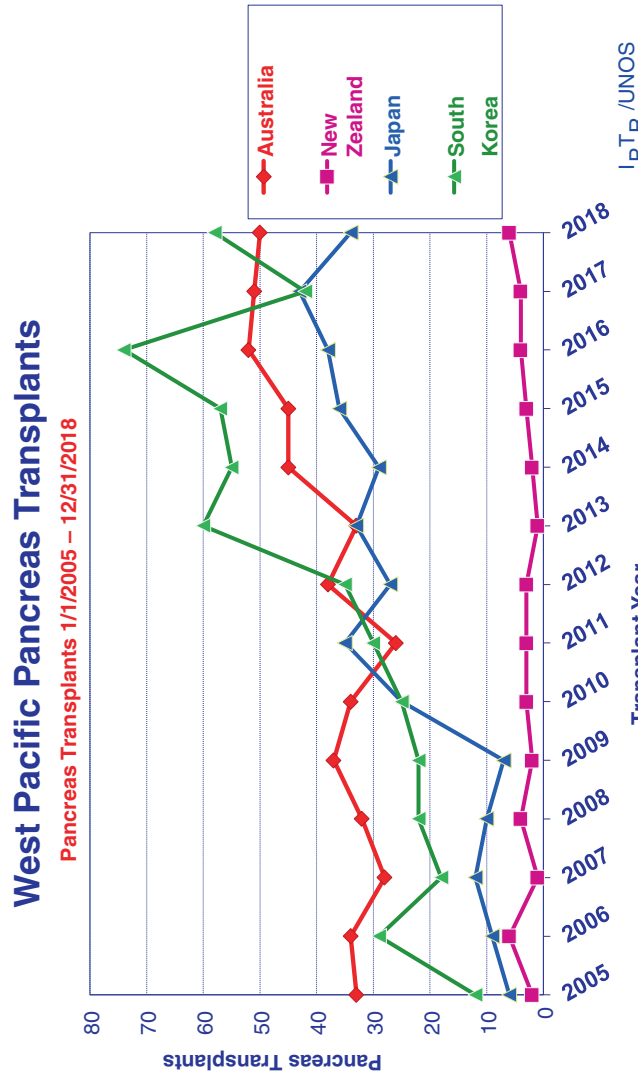

Fig. 3 The annual number of pancreas transplantation performed in west pacific countries

Diabetes per se is sufficient for a patient to opt for a β-cell transplant, accepting the risks of immunosuppression over those of diabetes [1]. Certainly for patients with ongoing diabetic problems, the quality of life improves with β-cell replacement.

Currently, there was consensus workshop in Igls, Auatria organized by IPITA(International Pancreas and Islet Transplantation Association) and EPITA(European Association) in which β cell replacement therapy could be considered as a treatment for β cell failure, regardless of etiology and without requiring undetectable C-peptide, accompanied by glycemic instability with either problematic hypoglycemia or hyperglycemia. They reported the Igls definition of functional and clinical outcome for β cell replacement therapy of pancreas and islet transplantation (Table 1) [16].

Korea

The fundamental treatment of type 1 diabetes is the "supply of insulin." The external supply of insulin is usually the main focus of treatment, and pancreas transplantation, which enables the internal supply of insulin by transplanting a healthy pancreas into the patient, is also considered a method of treatment. External insulin therapy includes subcutaneous injection of insulin directly by the patient and continuous supply of insulin using a machine called "insulin pump." Recently, the tentatively called "artificial pancreas" treatment, which maintains stable blood glucose levels by using an insulin pump and a continuous automatic glucose monitoring device, is also increasing in use.

Because of the complexity of the cause, type 2 diabetes has a variety of treatments, largely classified into "lifestyle therapy," "oral drug therapy," and "non-insulin and insulin injection therapy."

"Lifestyle therapy" is the most important part of diabetes management and the treatment underlying all diseases, including regular exercise and weight control. For "oral drug therapy," drugs of five to six mechanisms have been developed and widely used, and "noninsulin injection therapy" has also recently been proven to be effective and safe and is widely used. In particular, the patient's convenience is greatly increased through weekly injection, and the number of cases that can replace insulin therapy for type 2 diabetes patients is increasing. However, the efficacy of "noninsulin injection therapy" in type 1 diabetes patients is yet to be known significantly.

Diabetes-related complications such as triopathy(retinopathy, nephropathy, neuropathy), and shortened patient life span cannot be solved even by intensive insulin therapy. Normoglycemia can be achieved by the provision of sufficient β cell mass following pancreas transplantation. In addition quality of life can be improved and a daily injection of insulin and monitoring of blood glucose can be avoided. Improved patient and pancreas graft survival by better immunosuppressants, refined surgical technique, and better patient care induce the pancreas transplantation as a recommended treatment option both in Type 1 and type 2 diabetic patients nowadays. However, the side effects of immunosuppressants have to be considered prior to major surgery.

Table 1 Igls definition of functional and clinical outcomes for β-cell replacement therapy

β-cell graft functional status	HbA1c, % (mmol/mol)[a]	Severe hypoglycemia, events per year	Insulin requirements, U/kg/day	C-peptide	Treatment success
Optimal	≤6.5 (48)	None	None	>Baseline[b]	Yes
Good	<7.0 (53)	None	<50% Baseline[c]	>Baseline[b]	Yes
Marginal	Baseline	<Baseline[d]	≥50% Baseline	>Baseline[b]	No[e]
Failure	Baseline	Baseline[f]	Baseline	Baseline[g]	No

Baseline, pretransplant assessment

[a]Mean glucose should be used to provide an estimate of the HbA1c in the setting of marked anemia or administration of dapsone

[b]Should also be >0.5 ng/mL (>0.17 nmol/L) fasting or stimulated

[c]Should also be <0.5 U/kg/day; might include the use of noninsulin antihyperglycemic agents

[d]Should severe hypoglycemia occur after treatment, then continued benefit may require assessment of hypoglycemia awareness, exposure to serious hypoglycemia (<54 mg/dL [3.0 mmol/L]), and/or glycemic variability/lability with demonstration of improvement from baseline

[e]Clinically, benefits of maintaining and monitoring β-cell graft function may outweigh risks of maintaining immunosuppression

[f]If severe hypoglycemia was not present before β-cell replacement therapy, then a return to baseline measures of glycemic control used as the indication for treatment may be consistent with β-cell graft failure

[g]May not be reliable in uremic patients and/or in those patients with evidence of C-peptide production before β-cell replacement therapy

Following the fully informed consent, pancreas transplant is decided and scheduled, and registered to KONOS (Korean Network for Organ Transplantation System).

Compared with Western countries, the number of pancreas transplantation is increasing in Asian countries according to the current IPTR report (Figs. 4 and 5) [17].

Japan

In type 1 diabetes, the secretion of insulin secreted by pancreatic β-cells is reduced to depleted, so the basis of treatment is to replace the deficient insulin. Otherwise, the energy necessary for survival will not be supplied from sugar as a source, and life cannot be maintained. In order to prevent the occurrence and progression of complications, it is necessary to perform daily insulin treatment so that the occurrence of hyperglycemia and hypoglycemia can be suppressed as much as possible and the blood glucose state with little fluctuation can be maintained. The main purpose of insulin treatment is to maintain appropriate glycemic control with little fluctuation by mimicking the physiological insulin dynamics as much as possible. In order to achieve this, it is necessary to perform intensive insulin treatment with frequent injection therapy (MDI) or continuous subcutaneous insulin infusion therapy (CSII). In addition to this, self-monitoring of blood glucose (SMBG) should be performed at least four times a day to understand fluctuations in daily blood glucose levels. Insulin treatment and glycemic control measures have made rapid progress, but neglecting insulin treatment for even 1 day can lead to metabolic disorders such as diabetic ketoacidosis. Also, injection of excessive amounts of insulin disproportionately to dietary intake and exercise, causes severe hypoglycemia.

Treatment and management of type 1 diabetes, where insulin treatment is essential for life, is not easy. In particular, when insulin secretion is depleted, the blood glucose level fluctuates greatly, increasing the risk of not only hyperglycemia but also hypoglycemia. The former causes complications and the latter reduces the patient's quality of life and is sometimes life-threatening.

The research group demonstrated, "In order for type 1 diabetic patients to prevent the onset and progression of complications while preventing hyperglycemia and hypoglycemia, it is necessary to further improve the medical and welfare system. It will hinder employment, schooling, marriage, etc. Social awareness activities are also required to prevent this from happening."

In Japan, there is a "Pediatric Chronic Specific Disease Treatment Research Project," and patients with type 1 diabetes who develop the disease before the age of 18 are subsidized for their own medical expenses in order to reduce the burden of medical expenses at home. Its public interest and value as a welfare business are highly evaluated. On the other hand, under the current system,

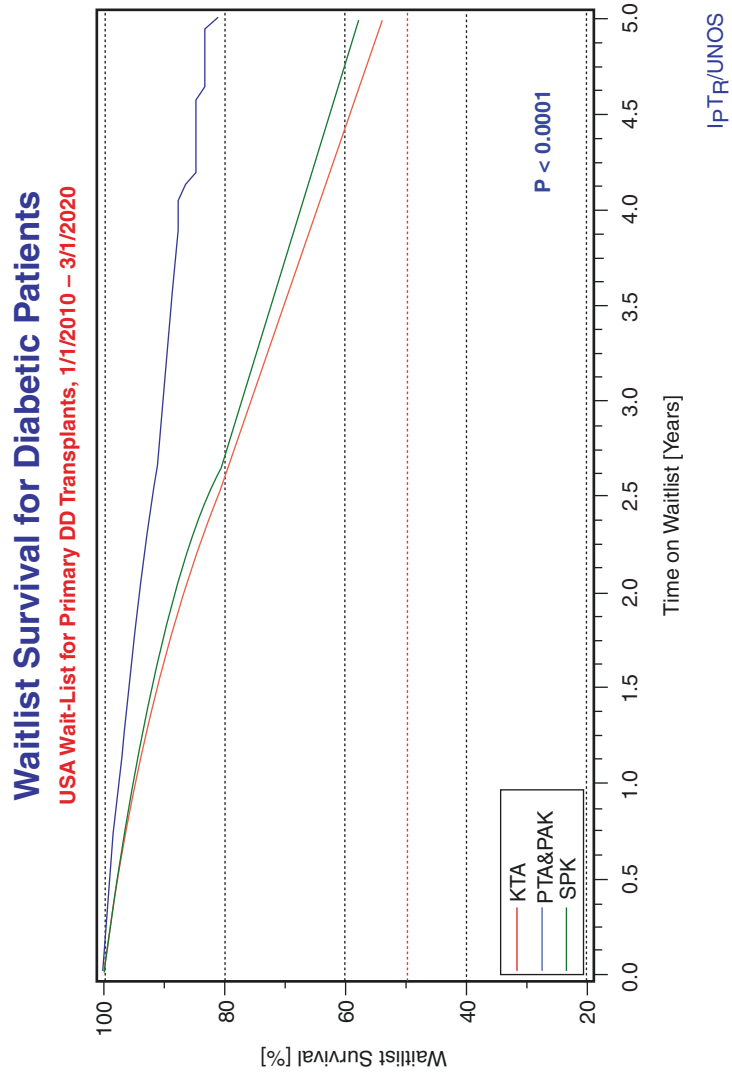

Fig. 4 The survival of diabetic patients waitlisted for transplantation

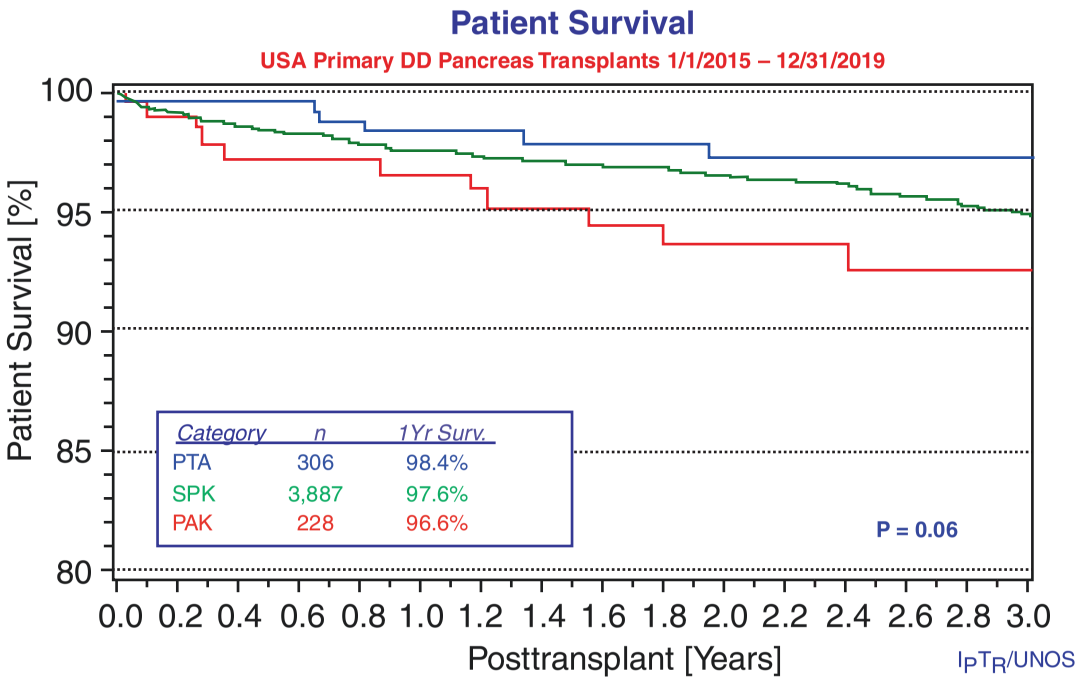

Fig. 5 The patient survival after deceased pancreas transplantation (US)

public subsidies for treatment costs are available until the age of 20 years, after which the medical treatment will be switched to medical insurance. For this reason, adult type 1 diabetic patients are forced to bear a heavy social and economic burden.

The prognosis of type 1 diabetes that develops in childhood is improving rapidly, and many patients with type 1 diabetes are living well without complications even after they grow up. However, according to a survey conducted by Tajima N. as described above, due to the rising medical costs associated with medical progress, 28% of patients think they cannot receive appropriate treatment. Medical advances such as the emergence of new insulin preparations, advances in glucose meters, insulin pump therapy (CSII), and continuous glucose measurement (CGM) have greatly improved glycemic control and prognosis in patients with type 1 diabetes. However, at the same time, it is also causing an increase in medical expenses. In a survey comparing 1997 and 2015, the share of medical expenses in households increased from 6.9% to 10.1% for more than 20% of the patients. As a result, in order to reduce the burden of medical expenses, some patients say that they "reduce blood glucose measurement," "reduce the number of consultations," "reduce the amount of insulin," and "cannot do CSII." Both adversely affect the treatment of type 1 diabetes.

Taiwan: Rationale of DM

Type 1 diabetes mellitus (DM) is usually diagnosed at the age of 10–20 years. Among the various types of DM, type 1 DM presents the most serious symptoms which, besides the classical triad of increased appetite, increased thirst, increased urination, are often associated with bodyweight loss and easy fatigue, and sometimes may lead to serious complications such as ketoacidosis, coma, or even death. For those patients with no pancreas or severe pancreas dysfunction, they still can survive with careful treatments with insulin injection, adequate replacement of pancreatic enzymes, and regular nutritional intake. However, retinopathy can occur in about 30% of patients with type I diabetes, nephropathy requiring hemodialysis in 40%, and neuropathy in 60% about 30 years after the onset of diabetes. Moreover, cardiovascular diseases may develop. DM-related complications are usually the causes of disability and death in diabetic patients. Therefore, to improve or eliminate the diabetic complications, a pancreas transplant may be the option to cure diabetes when the diabetes is poorly controlled by insulin injection or when the complications are severe. Currently, Pancreas transplant has emerged as the most effective treatment to establish durable normoglycemia for patients with diabetes mellitus, especially those with established end-stage renal disease.

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History of Pancreas Transplantation

Duck-Jong Han, Joo Hee Jung, Takashi Kenmochi, and Yi-Ming Shyr

General

Insulin independence in a type 1 diabetic was first achieved on December 17, 1966, when William Kelly and Richard Lillehei transplanted a duct-ligated segmental pancreas graft simultaneously with a kidney from a cadaver donor into a 28-year-old uremic woman at the University of Minnesota [1, 2]. The pancreas segment (body and tail) was transplanted extraperitoneally to the left iliac fossa, with anastomosis of the graft celiac axis to the left common iliac artery. The graft splenic vein was left attached to its junction with the superior mesenteric and portal vein; each was anastomosed end to side to the recipient's iliac vein with ligation of the intervening segment. Posttransplant immunosuppression consisted of azathioprine (8 mg/kg/day tapered to 4 mg/kg/day by day 3) and prednisone slowly tapered from 150 mg/day. Cobalt60 950 rads (300, 200, and 150 rads on consecutive days) was administered to the pancreas graft in an attempt to suppress exocrine function, again based on the experiments of Merkel [3]. The recipient was insulin-free for only 6 days and then needed increasing doses of insulin. On February 14, 1962, the pancreas (along with the kidney) was removed.

In that first pancreas transplant, Kelly was the lead surgeon and Lillehei was assistant [2]. But, in the second pancreas transplant, on New Year's Eve 1966, Lillehei was the lead surgeon [2, 4]. In that 32-year-old recipient, the donor's whole pancreas and attached duodenum were transplanted extraperitoneally to the left iliac fossa. (As with the first transplant, the kidney was transplanted extraperitoneally to the recipient's right iliac fossa.) The donor's celiac axis and superior mesenteric artery on a small cuff of aorta were anastomosed end to side to the left common iliac artery, and the portal vein was anastomosed end to side to the left common iliac vein. The proximal duodenal end was closed blindly and the distal end (duodenum with the first portion of jejunum) was brought out as a cutaneous graft duodenostomy-jejunostomy. Immunosuppressive therapy for that recipient was with azathioprine and prednisone (as for the first recipient), but no posttransplant graft irradiation was administered. The second time, a more prolonged state of pancreas graft function was achieved. But, rejection treatment (consisting of prednisone boluses and graft irradiation) had to be instituted 3 and 8 weeks posttransplant. The recipient was on insulin when

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she died 4.5 months posttransplant from sepsis. Lillehei performed a total of 13 pancreas transplants, the last on January 11, 1973 [5] (Fig. 1). In his first four transplants, Lillehei managed the exocrine secretions with a cutaneous graft duodenostomy; in the next eight, with internal exocrine drainage using a Roux-en-Y duodenojejunostomy (Fig. 2). Indeed, the technique he employed in his 5th through 12th cases is nearly identical to the contemporary methods of pancreaticoduodenal transplantation with enteric drainage described. Regarding the recipient category, of those first 13 pancreas transplants, 9 were done with a simultaneous kidney transplant (SPK category); 4 (3 in nonuremic patients) were done without a kidney (PTA category). Interestingly, most complications were associated with the kidney graft: First, kidney rejection occurred in almost all SPK recipients without evidence of pancreas graft rejection. Worldwide after those first four pancreas transplants at the University of Minnesota, the next

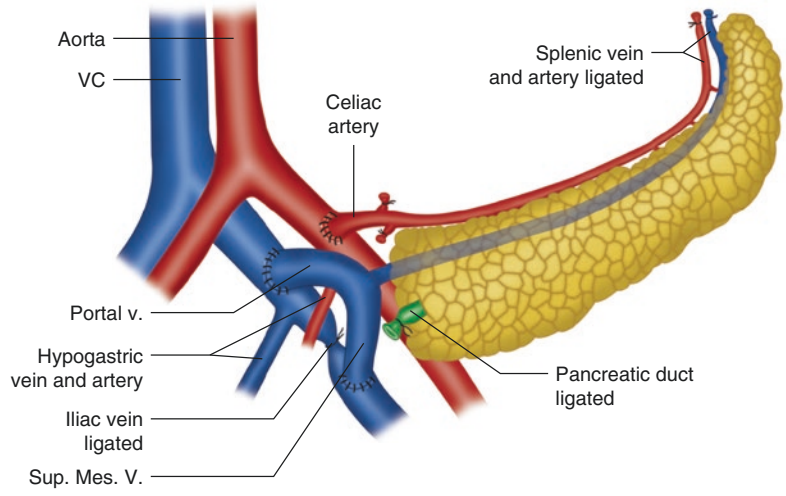

Fig. 1 First deceased segmental pancreas transplantation by Dr. Kelly (University of Minnesota)

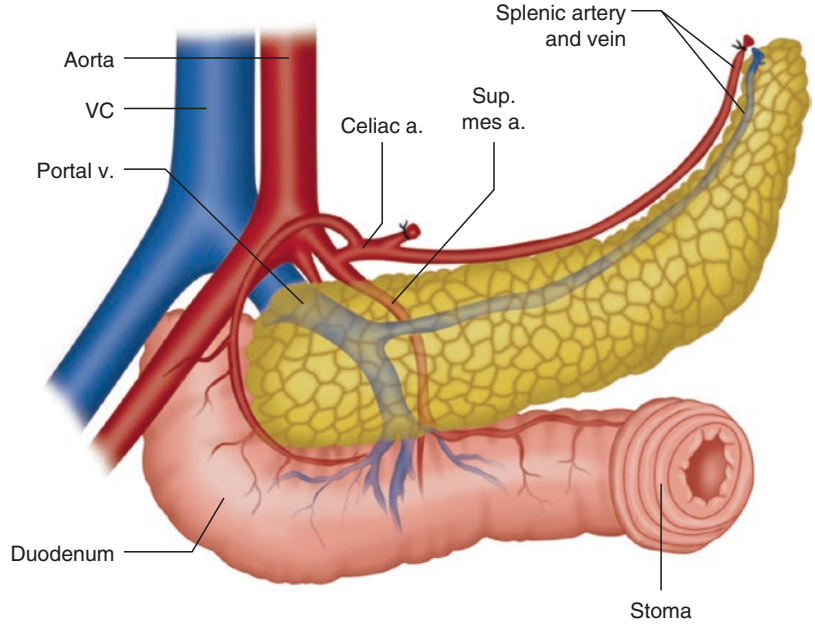

Fig. 2 Deceased whole pancreas transplantation by Dr. Lillehei (University of Minnesota)

four transplants (May through September 1968) were performed in South America [6–8]: three in Brazil (one at the University of Rio de Janeiro, two at the University of Sao Paulo) and one in Argentina (Buenos Aires Hospital). Of those four South American solitary pancreas grafts, only one functioned for 4 months, but it was subsequently lost to rejection [6]. In 1969, two other US institutions performed one SPK transplant each: one at the University of Colorado (Merkel and Starzl) and one at the University of California, Irvine Medical Center (Connolly) [6, 9]. The first pancreas transplant in Europe (along with a kidney transplant) was performed in 1972 at Guys Hospital in London [6]. Until December 31, 1970, only 25 pancreas transplants had been performed at six institutions worldwide. Of these 25 grafts, only 1 (from Lillehei's original series) functioned for almost 1 year, and none for more than 1 year. On November 24, 1971, the first pancreas transplant using urinary drainage via the native ureter was performed by Marvin Gliedman at Montefiore Hospital in New York. In 1973, Gliedman et al. published the results of four segmental pancreas transplants in which the pancreatic duct had been anastomosed to the recipient's ipsilateral native ureter [10]. Gliedman and associates performed a total of 11 ureteral drained pancreas transplants in the early 1970s [11], 8 in uremic patients: 3 received SPK transplants: in 5, the pancreas was grafted prior to a kidney transplant. Of this series, one graft functioned for 22 months, another for 50 months—until then, the longest pancreas graft survival recorded [12].

Interestingly, Merkel et al. in 1973 reported a segmental PTA with end-to-side ductoureterostomy without the need to sacrifice the kidney in a nonuremic diabetic recipient [13]. Two new techniques were introduced in the mid and late 1970s: open drainage and duct injection. Open duct drainage in contrast to duct injection preserves the function of exocrine pancreatic tissue, and pancreatic secretions are absorbed by the peritoneum if the enzymes are not activated. The first two open drained pancreas transplants were performed on February 3, 1976, by Bewick at Guys Hospital in London[102] and on July 25, 1978, at the University of Minnesota [14]. The latter recipient lived for 18 years until she was thrown off a horse and died with a functioning graft [15]. In 1978, Dubernard et al. reported on a technique in which the pancreatic duct of the segmental pancreas graft was injected with neoprene, a synthetic polymer. The first transplant using duct injection was performed on October 22, 1976, fittingly in Lyon, the city of Claude Bernard, who more than a century earlier had injected paraffin into animal pancreases and showed that diabetes did not occur despite the glandular atrophy induced [16]. By the end of the 1970s and during the early 1980s, duct injection became the most common technique for drainage of exocrine secretions, in particular in Europe. By the time of the first report of the International Pancreas and Islet Transplant Registry at the Lyon meeting in March 1980, only 105 pancreas transplants had been performed worldwide [17] in the United States and [18] outside the United States (mainly in Europe) [19]. Segmental grafts were favored by most at the time, based on the perception that the complications Lillehei described were related to the duodenum, although a critical examination of his cases showed that the majority of complications were related to the kidney graft [5]. In 1983 Hans Sollinger at the University of Wisconsin reported on a technique that over the next decade in one variation or another was the most used method for managing pancreatic exocrine secretions: bladder drainage [20]. In the initial clinical publication on the technique in 1984, Sollinger et al. stated that a significant decrease in urinary amylase might be a sensitive indicator for early pancreatic rejection [21]. In 1987, Nghiem and Corry at the University of Iowa described the technique of bladder drainage via a graft-to-recipient duodenocysostomy for whole pancreaticoduodenal grafts, preparing the donor organ as described by Lillehei for his first 12 cases [5, 16]. They pointed out that the anastomosis from the duodenum to the bladder is safer than the duodenojejunostomy, since the leak can easily be controlled by reoperation, whereas a gastrointestinal leak would be catastrophic. Bladder drainage via the graft duodenum was quickly adopted by most US centers. The

Stockholm group reported that for segmental grafts, using a Roux-en-Y loop for the pancreaticoenteric anastomosis and a pancreatic duct catheter for temporary protection, the complication rate was lowered [22, 23]. Thus, in 1984, Starzl et al. [24] reintroduced the technique of enteric-drained whole-organ pancreaticoduodenal transplants as originally described by Lillehei [25]. From the mid-1980s to the mid-1990s, bladder drainage became the most common technique worldwide, for SPK transplants because of its safety, for PTA for this reason and because a decrease in urine amylase activity could be used as a sensitive, if nonspecific, marker of rejection that preceded hyperglycemia by several days [26–28]. IPTR analyses consistently showed higher survival rates or a lower incidence of rejection failure for bladder than for enteric-drained solitary pancreas transplants [29]. The late 1990s then saw a shift again from bladder to enteric drainage [29] in particular for SPK transplants. Enteric drainage is a more physiologic way to drain pancreatic exocrine secretions, and improvements in antimicrobial and immunosuppressive therapy reduced the risks of complications as well as rejection. In addition, the chronic complications of bladder drainage (e.g., urinary tract infections, hematuria, acidosis, dehydration) led to the need for enteric conversion in 10–15% of bladder-drained recipients [29].

Gastric drainage as described by Calne et al., in 1984 and used in a few cases by Tyden et al. [30]; and drainage via the recipient gallbladder as reported by Helmut Wolfe from Berlin in the 1980s (personal communication). In regard to venous drainage of pancreas grafts, portal would be the most physiological but from the first cases of Kelly and Lillehei[88] until Calne reported using the recipient splenic vein as the outflow for a gastric-duct-drained segmental pancreas graft venous effluent in 1984 [31], the systemic venous system was accessed. Following Calne's case [31], other groups drained segmental grafts into the portal system, specifically the superior mesenteric vein in Stockholm [30], the splenic vein in Barcelona [32], and the inferior mesenteric vein at the University of Minnesota [33]. In 1992, Rosenlof et al. from the University of Virginia [34] and Shokou-Amri et al. from the University of Tennessee [35] described the use of portal drainage at the junction of the recipient's superior and splenic veins in recipients of enteric-drained whole-organ pancreaticoduodenal transplants. Subsequently, Gaber et al. reported on a large series of cases from the University of Tennessee [36] touting its metabolic and possible immunologic advantages, features also noted at the University of Maryland, another large program that has converted to doing portal drainage almost exclusively [37]. The issue of whether to use a segmental or a whole-organ pancreas graft has also evolved over time.

Most transplants in the late 1960s and early 1970s were whole-organ grafts. Segmental transplants became more common in the late 1970s and early 1980s. Since the mid-1980s, whole-organ transplants with a duodenal segment (rather than a duodenal button or patch) have been standard. Segmental transplants have not completely disappeared but are primarily used with living donors (LDs). Pancreas transplants with LDs began at the University of Minnesota in the late 1970s [38] and have been done in all three recipient categories [39, 40]. The first LD pancreas after kidney (PAK) transplant was performed on June 20, 1979, the first LD PTA on May 14, 1980, and the first LD SPK transplant on March 10, 1994. All three firsts were at the University of Minnesota, the same institution where LD laparoscopic distal pancreatectomy was introduced in 2001 [41].

The first case reported worldwide of robotic distal pancreatectomy and nephrectomy for living-donor pancreas-kidney transplantation was successfully performed in 2006 at the University of Illinois at Chicago. The application of minimally invasive techniques has allowed an increased acceptance of the procedure among potential donors and may, therefore, increase the number of donors for this life-saving transplant [42].

As an aside, recurrence of autoimmune isletitis in pancreas grafts with selective destruction of ß-cells in the absence of rejection was first described at the University of Minnesota in 1984 for segmental transplants from LDs [43], either

from an HLA-identical sibling to a minimally immunosuppressed recipient or from an identical twin to a nonimmunosuppressed recipient [44]. The level of immunosuppression to prevent autoimmune recurrence of disease is probably less than that necessary to prevent rejection in most pancreas allograft recipients. One other technical modification that relies on transplanting segmental grafts is the split-pancreas procedure. In 1988, a cadaver pancreas graft was split into two segments (head and body-tail) and successfully transplanted in two recipients with negative cross-matches to the donor despite high panel reactive alloantibody levels [45]. The split-pancreas procedure preceded the now common split-liver procedures by 1 year. Living-donor kidney transplantation and cadaveric pancreas transplant can be done simultaneously. Each organ would come from different donors, either fortuitously having a cadaver pancreas available at the time of a scheduled LD kidney transplant, as was first done at the University of Minnesota in the 1980s, or with the LD kidney donor on call to come in when a cadaver pancreas becomes available for the recipient. A relatively large series in the latter category was reported by Farney et al. from the University of Maryland in 2000 [46]. Unlike in kidney transplantation, discussion of surgical techniques in pancreas transplantation dominated the seminars organized to forward the field in the first decades that followed the first case. Also critical to progress in the field was the development of multiorgan donor procurement, improvements in the diagnosis and treatment of rejection, advances in immunosuppressive protocols for induction and maintenance therapy, and antimicrobial prophylaxis and treatment, all of which evolved over time. Early diagnosis of pancreas rejection had been difficult from the beginning. In SPK from the same-donor transplants, serum creatinine could be used as a marker, because rejection usually (there were exceptions [47] involved both organs and usually manifested in the pancreas first. The introduction of bladder drainage resulted in a better marker for rejection: urine amylase. As for other solid-organ transplants, graft biopsy has been the gold standard for diagnosing rejection right from the beginning. Percutaneous ultrasound or CT-guided biopsies have now become the gold standard for tissue diagnosis in pancreas transplantation. The introduction of the calcineurin inhibitors (cyclosporine in the 1980s and tacrolimus in the 1990) significantly increased the number of pancreas transplants. Starzl et al. first reported the use of tacrolimus in pancreas allograft recipients during the investigative period in 1989 [48]. After FDA approval, the first report on the use of tacrolimus for pancreas transplantation was by Shaffer et al., successfully reversing ongoing acute rejection in two SPK recipients [49]. By the late 1990s, over 80% of all pancreas recipients worldwide were on tacrolimus-based maintenance immunosuppressive regimens [29, 50]. Likewise, in the mid-1990s mycophenolate mofetil replaced azathioprine as the mainstay immunosuppressant or coimmunosuppressant for more than three decades [51]. The combination of tacrolimus and mycophenolate mofetil became the most popular maintenance therapy regiment for pancreas transplant recipients, but rapamycin is also being used in pancreas recipients [52]. Induction therapy with anti-T-cell preparations to prevent early pancreas graft rejection was used in some of the first cases according to information in the IPTR database [53].

Korea

From October 1992 to Dec 2019, 739 cases of pancreas transplantation were performed in Korea.

First cadaveric pancreas and kidney transplantation was performed in 28-year-old female IDDM patients who suffered from insulin dependent diabetes at the age of 17, became end-stage renal disease state, and treated with hemodialysis for 1 year. Following deceased SPK in Asan Medical Center (AMC), she stopped using insulin from immediate post operative period. Since then ca 10 cases of pancreas transplantation were performed a year until 2005, and more than 50 cases per year were performed since 2013 in Korea. The first deceased PTA was performed in AMC in 1992, and first simultaneous deceased

pancreas and living-donor kidney was performed in AMC in 2009. The first living-donor SPK was performed in AMC in 2006, since then 23 (3.3%) cases were performed in Korea until Dec 2019.

From October 1992 to Dec 2019, 475 cases of pancreas transplantation were performed at Asan Medical Center. Among these, 21 (4.4%) were LDPT [54]. One IDDM female recipient underwent ABO-incompatible SPK from her father (A to B) in 2012. Three other centers (Seoul National University Hospital, Yangsan Busan University Hospital, and Samsung Medical Center) have performed more than 50 pancreas transplantations each.

Japan

The history of pancreas transplantation in Japan is also the history of the Japan Pancreas and Islet Transplantation Association (JPITA). JPITA was established in 1982 and was led by Professor Idezuki Y (University of Tokyo), who participated in the world's first pancreas transplantation performed by Kelly WD and Lillehei RC in 1966 [2, 55]. Because of clinical practice was not possible in Japan due to the lack of acceptance for brain death in our country, a lot of basic studies and large animal experiments were performed and clinical preparations were also being performed. Idezuki Y (University of Tokyo) [56], Nozawa M (Meikai University) [57], Ito T (Osaka University) [58], Teraoka S (Tokyo Women's Medical University) [59], Fukao K (University of Tsukuba) [60], Asano T (Chiba University) [61], and Kuroda Y (Kobe University) [62] were actively conducting research. After that, the president of JPITA has been inherited to Inoue K (Kyoto University), Teraoka S (Tokyo Women's Medical University), Gotoh M (Fukushima Prefectural Medical University), and Ito T (Osaka University). And now I, Kenmochi T (Fujita Health University) is the sixth president of JPITA.

The first heart transplantation from brain death donor was performed in Japan in 1968. However, the brain death became a social problem. Since then, organ transplantation from brain dead donor could not be performed. Under this environment, Professor Fukao K at the University of Tsukuba performed the first pancreas transplantation (SPK) from brain dead donors in Japan in 1984 [63]. However, the pancreas graft was removed 168 days later due to the rejection of the transplanted kidney and peritonitis. Afterwards, he died in 357 days due to complications such as bleeding. Thereafter, the problem of brain death was discussed again in society, and organ transplantation from brain dead donor was not performed because brain death had not yet reached a social consensus. From 1992 to 1994, 14 pancreas transplantation (SPK 10 cases, PAK 4 cases) were performed from non-heart beating donors led by Teraoka S of Tokyo Women's Medical University. Despite using marginal donor, six cases showed a prolonged graft survival [64].

The Organ Transplant Law was finally enacted in Japan in 1997, and organ transplantation from brain death became possible. The system of clinical pancreas transplantation was established in Japan, led by "The Central Coordination Committee of the Pancreas Transplantation in Japan." The Committee was composed of members recommended by the Japan Diabetes Society, Japanese Society of Nephrology, the Japanese Society for Transplantation, and the Japanese Pancreas and Islet Transplantation Association, and the chairman was selected from the members recommended by the Japan Diabetes Society. The first chairman was Kanazawa Y (Jichi Medical University), followed by Iwamoto Y (Tokyo Women's Medical University) and Awata T (Saitama Prefectural University). The committee prepared the recipient's indication criteria, donor indication criteria, and recipient selection criteria for pancreas transplantation. Thirteen institutions were certified to perform pancreas transplantation in Japan in 1998. Judgment of the indication of the recipient was carried out at "The Local Expert Medical Board for Pancreas Transplantation Indication," which is a branch of the Central Coordination Committee. Recipients were finally registered to the Japan Organ Transplant Network (JOT). For the performance of pancreas transplantation, a national team was

organized by "The Expert Surgeon Board of the Pancreas Transplantation in Japan (ESBPT)," which is also a branch of the Central Coordination Committee, and a system was established to support the transplantation at each institution. The first chairman of ESBPT was Idezuki Y (University of Tokyo). Secretaries were Ito T (Osaka University), Ishibashi M (Nara Medical University) in addition to Sugitani A (Kyushu University) and Furukawa H (Kobe University), who returned from studying at Pittsburgh. Thereafter, Nakajima I (Tokyo Women's Medical University) and Kenmochi T (Chiba University) joined as secretaries. There were many factors of marginal donor such as old age, cerebrovascular disease as a cause of death, and cardiac arrest episode in Japan. In order to maintain the blood flow in the head of the pancreas graft, the common hepatic artery and gastroduodenal artery of the pancreatic graft were bypassed by I-graft using the donor's iliac artery [65]. Also, in order to share the information and improve the results of the pancreas transplantation, ESBPT holds a review meeting twice a year, verifying and discussing the results of all cases of pancreas transplantation performed in Japan. This national team system is still functioning. The second chairman of ESBPT was Ishibashi M (Nara Medical University) and now Kenmochi T (Fujita Health University) is the third chairman.

As of January 2021, the following 18 certified facilities for pancreas transplantation are available in Japan; 1. Hokkaido University Hospital, 2. Tohoku University Hospital, 3. Fukushima Prefectual University Hospital, 4. Dokkyo University Hospital, 5. Niigata University Hospital, 6. Dokkyo Medical University Hospital, 7. Tokyo Woman's University Hospital, 8. Tokyo Medical University Hospital, 9. Nagoya 2nd Red Cross Hospital, 10. Fujita Health University Hospital, 11. Kyoto University Hospital, 12. Kyoto Prefectual University Hospital, 13. Osaka University Hospital, 14. Kobe University Hospital, 15. Hiroshima University Hospital, 16. Kagawa University Hospital, 17. Kyushu University Hospital, and 18. Nagasaki University Hospital. Among these, the high volume centers that perform pancreas transplantation more than 50 cases are Fujita Medical University, Kyushu University, Tokyo Women's Medical University, and Osaka University.

In 2000, the first pancreas transplantation (SPK) from DBD donor after the enforcement of the Organ Transplant Law, was performed by Ito T et al. at Osaka University Hospital. However, under the Japanese Organ Transplant Law, it was necessary to express the intention of donation at brain death in writing before his/her life, so the annual number of pancreas transplants from brain dead donor was less than 10 cases per year nationwide. During this period, due to the shortage of DBD donors, Kenmochi T et al. performed the first living-donor pancreas transplantation (LDPT) in Japan at Chiba-East National Hospital in 2004 [66]. Until December 2019, 27 LDPTs have been performed at five centers in Japan. Among these, 18 cases (66.7%) have been performed at Chiba-East National Hospital. Since the Organ Transplantation Law was revised and enforced in 2010 allowing donation of brain dead organs with the consent of the family, the number of DBD donor increased to several times and, thereafter, very few cases of LDPTs have been performed.

Based on the experience and good results of ABO-incompatible living-donor kidney transplantation in Japan, ABO-incompatible LDPT (SPK) was first introduced in 2006 by Kenmochi [67].

By the end of 2019, 410 cases of deceased donor pancreas transplantation and 27 living pancreas transplantation with total of 437 cases had been performed Until December 2019.

Taiwan

The first pancreas transplant, simultaneous pancreas and kidney transplant (SPK), was successfully initiated at Taipei Veterans General Hospital on September 19th of 2003. Before that, the first pancreas transplant was tried, but failed on April 1st of 1984 at Chang Gung Memorial Hospital. Thereafter, the pancreas team and professor Yi-Ming Shyr at Taipei Veterans General Hospital became the first team and surgeon qualified to

perform human pancreas procurement and transplant in Taiwan by Taiwan Department of Health on August 31st of 2007. Until November 27th of 2020, there are 167 cases of pancreas transplant performed at Taipei Veterans General hospital, including 38 SPK, 78 pancreas transplant alone (PTA), 28 pancreas before kidney transplant (PBK), 20 pancreas after kidney transplant (PAK), and 1 pancreas after liver transplant (PAL). The technical success rate in our pancreas transplant is 97%, with 1-year pancreas graft survival rate of 97.4%, 5-year pancreas graft survival rate of 87.2%, and 10-year pancreas graft survival rate of 70.4%.

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Indication of Pancreas Transplantation (Donor and Recipient)

Takuya Awata, Takashi Kenmochi, Yi-Ming Shyr, and Duck-Jong Han

Cadaveric Donor

General

The vast majority of pancreas grafts are obtained from cadaver, heart-beating donors, and small portion from living donor. Although pancreas grafts from non-heart-beating donors have been successfully transplanted, this practice has been extremely limited [1, 2]. The suitability of a cadaver pancreas donor is based on general criteria common to all organ procurements as well as on specific pancreas-related factors.

Diagnosis of Brain Death

Complete, irreversible loss of brain function and brain stem function manifests clinically as complete apnea, brain stem areflexia, and cerebral unresponsiveness. The cause for the absence of clinical brain function must be known and must be demonstrably irreversible. Reversible causes of brain stem depression, such as hypothermia and drug intoxication (due to alcohol, sedatives, or paralytic agents), must first be excluded. The American Academy of Neurology defines brain death as "an irreversible loss of the clinical function of the brain, including the brain stem" and has promulgated guidelines for the clinical diagnosis of brain death as follows:

Prerequisites

1. Clinical or neuroimaging evidence of an acute central nervous system catastrophe that is compatible with clinical diagnosis of brain death.
2. Exclusion of complicating medical conditions that may confound clinical assessment (e.g., no severe electrolyte, acid base, or endocrine disturbance).
3. No drug intoxication or poisoning.
4. Core temperature equal to or greater than 32 °C.

Three Cardinal Findings

1. Coma or unresponsiveness.
2. Absence of brain stem reflexes (pupil, ocular, corneal, pharyngeal, and tracheal).
3. Apnea.

Confirmatory Laboratory Tests (Not Mandatory)

1. Electroencephalogram.
2. Contrast or isotope angiography.

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3. Isotope scanning.
4. Transcranial Doppler uItrasonography.

Even in the presence of negative serological test resuIts, extreme prudence should be used if an organ donor has a history of social behavior that increases the risk of transmissible infectious disease. In particular, because human immunodeficiency virus (HIV) infection is universally considered an absolute contraindication to organ donation any donor potentially at risk for the transmission of this deadly and highly contagious disease must be screened with extreme care.

A history of alcohol abuse is concerning, especially in relation to possible liver or pancreas donation. Some centers consider a history of heavy drinking an absolute contraindication to pancreas procurement, but others prefer to surgically explore the potential donor and base the final determination on the gross appearance of the organ at the time of procurement [3, 4].

A medical history of malignancy constitutes an absolute contraindication to organ donation, with the exception of primary brain tumors (without history of ventriculoperitoneal shunt), skin cancers other than melanoma, and carcinoma in situ of the cervix. The presence of malignancy may be unknown to the family and attending physicians, so a careful search for malignancy must be performed by the procurement coordinator (looking for possible skin melanomas) and procuring surgeons. The risk of causing a tumor in the recipient by transplanting organs from a donor affected by malignancy is very high (overall, about 50%) [5].

In the past, documented sepsis in the potential donor was universally considered an absolute contraindication to donation. Recently, because of the worsening donor shortage, many centers have taken a different approach toward selected donors with infection. Documentation of HIV infection (based on positive serological test resuIts), tuberculosis, and herpes simplex virus encephalitis are still considered absolute contraindications to donation because of the high chance of fatal disseminated disease in the recipient.

Bacteremia as a resuIt of localized infection (e.g., line sepsis, bacterial meningitis, or cellulitis affecting an extremity) is not a contraindication to donation, provided that proper antibiotic therapy is instituted in both the donor and recipient. However, untreated bacterial infections from *Staphylococcus, Klebsiella, Escherichia coli,* or *Pseudomonas* in donors have been linked to the development of serious infections (in particular, mycotic aneurysm at the vascular anastomoses) in recipients [6–8]. Fungal infections are even more dangerous in this regard; documented systemic fungal sepsis is a contraindication to donation. In pancreas transplantation, an additional problem is that the donor duodenum (a standard component of the whole pancreas graft) is frequently contaminated by *Candida* species, especially in donors with a prolonged intensive care stay before their death. In a large retrospective study of intra-abdominal infectious complications in pancreas recipients, *Candida* was a frequent and aggressive pathogen [9]. To minimize this serious risk, many transplant centers routinely irrigate the donor duodenum with amphotericin B through the nasogastric tube at the time of pancreas procurement. The presence of antibodies to syphilis, which are usually detected by a rapid plasma reagin (RPR) test, is not a contraindication to donation. However, for recipients of organs from RPR positive donors standard antisyphilis prophylaxis with penicillin for 2 weeks posttransplant is currently recommended [10]. Hepatitis B serological tests are a standard component of the donor workup. The transmission of hepatitis B through organs procured from hepatitis B surface antigen (HBsAg) positive donors is well documented. Such donors must not be used for pancreas transplants because the pancreas is not a life-saving organ [11, 12]. If the donor is HBsAg negative, HB-core antibody (anti-HBc) negative, and anti-HBs positive, it means that he or she had a vaccination or that the HB virus (HBV) infection cleared spontaneously. Such a donor can be safely used if a history of vaccination or hepatitis B immunoglobulin (HBIG) administration can be confirmed.

If the donor's serological test results are positive for anti-HBc (with or without concomitant positivity for anti-HBs), HBV DNA may be present in the blood and may cause infection in liver recipients [13, 14]. For extrahepatic organ recipients, the risk of disease transmission is small but present if the donor is anti-HBs positive but significantly increased if the donor is anti-HBs negative. If the donor is HBsAg negative but anti-HBc positive, then further tests are required to establish if the positivity depends on immunoglobulin IgG or IgM. The presence of IgM suggests a recent HBV exposure and is a contraindication to donation. If the donor's anti-HBc positivity is due to IgG, donation can be considered if the potential recipient is HBsAg positive.

In general, HCV positivity is a contraindication to pancreas donation. Still, the use of pancreas grafts from HCV-positive donors into HCV-positive recipients has not been properly investigated to date. Positive serological test results for cytomegalovirus (CMV) are not a contraindication to pancreas donation, although they may predispose to a higher incidence of CMV disease in recipients.

The initial selection of a cadaver pancreas donor is based on ABO group compatibility and on a documented negative crossmatch. HLA matching is not critical for SPK transplants. But, for solitary pancreas transplants the degree of match is an important prognostic factor for graft survivaI [15]. A number of organ-specific issues must be addressed before the pancreas graft can be accepted. Even elective surgical procedures involving the pancreas are notoriously associated with a high rate of technical complications (e.g., pancreatitis, fistula pseudocyst, necrosis). In the setting of pancreas transplantation, these unavoidable problems are compounded by ischemia reperfusion injury, immunologic factors, and aggressive immunosuppressive therapy. Further, the quality of the donor graft is key to the rate of early postoperative complications such as thrombosis, pancreatitis, infection, and leaks. Following factors are associated with a lower quality of pancreas grafts and thus an increased incidence of technical complications.

Donor age is important for all organs, but pancreas donor age requirements are, in general, more strict.

The main concern with a young pancreas donor is the small size of the graft and the increased risk of vascular complications because of the small size of the vessels. Most centers require a minimum donor weight of 30 kg or above. The most compelling evidence of the deleterious effect of older donor age on pancreas graft outcome was initially provided by Gruessner et al. [16]. In their review of 445 pancreas transplants performed in the cyclosporine era at the University of Minnesota, they found that donor age above 45 years was a significant risk factor for vascular thrombosis, intra-abdominal infections, anastomotic or duodenal leaks, and relaparotomy. These technical complications not only significantly decrease graft survival but also are related to increased recipient mortality. In the tacrolimus era, donor age above 45 years had no larger a significant impact on outcome. In a recent University of Pittsburgh study [17] the use of 22 pancreas grafts from donors older than 45 years did not increase the incidence of posttransplant complications and did not result in worse patient and graft survival rates as compared with "optimal" grafts from younger donors. The Pittsburgh authors contended that the most important variable in determining suitability of a pancreas graft is inspection by an experienced pancreas transplant surgeon.

The ideal donor for organ transplantation is a young trauma victim with no associated morbidity.

In the University of Minnesota report previously mentioned, cardio-cerebrovascular cause of donor death was found to be an independent risk factor for increased incidence of vascular thrombosis in PAK recipients [18]. Most donors in that report who died of cerebrovascular causes were older than 45 years, so dissecting out the impact of donor age vs donor cause of death was difficult.

It is safe to state that donors dying from cerebrovascular complications, especially those who are older and who have comorbid conditions, should be assessed carefully.

Organ donation from poisoned brain-dead donors is poorly documented. Overdoses of barbiturates, benzodiazepines, and acetaminophen are frequent in suicide attempts [19]. Accidental exposure to methanol, cyanide, or carbon monoxide is also a common cause of death due to acute poisoning [20]. Brain death progression in this condition is usually related to hypoxic lesions after cardiopulmonary resuscitation or to direct brain damage due to the toxin. In evaluating such patients as potential donors, it is important to carefully evaluate the toxic exposure with respect to specific organ injury. Acute methanol intoxication may increase serum amylase levels or the incidence of pancreatitis and pancreatic necrosis [21].

A transplant should be considered only after correction of acidosis. Moreover, the inspection of the pancreas during procurement is crucial. Carbon monoxide poisoning is often followed by hyperamylasemia (in up to 40% of cases), usually transient and independent of damage to the pancreas [21]. According to the literature, the patient survival rate with pancreas grafts from selected poisoned donors is similar to the rate with pancreas grafts from nonpoisoned donors [22].

Hyperglycemia in the absence of a history of pancreatic endocrine insufficiency is often seen in brain-dead patients.

More than 50% of brain-dead potential pancreas donors have blood glucose levels greater than 200 mg/dL. Several authors have suggested that hyperglycemia in cadaver donors may adversely affect outcome posttransplant, but usually this condition is unrelated to the endocrine functional status of the pancreas graft. Onset of hyperglycemia may be directly related to trauma as a consequence of the destruction of areas in the central nervous system related to metabolic functions. Further, hyperglycemia can be the result of injury-related stress and the release of hormones (e.g., endogenous steroids, catecholamines). The liberal administration into the donor of large amounts of exogenous glucose solutions and corticosteroids can also lead to highly elevated glucose levels.

Most transplant centers consider donor hyperglycemia a benign disorder; in the absence of a clinical history of diabetes, it is not a contraindication to donation, even in severe cases. However, hyperglycemia may be a sign of relative endocrine pancreas insufficiency, which represents a significant risk factor for long-term pancreas graft survival. Unfortunately, potentially helpful indicators such as HbAlC or C-peptide levels are not readily available in the emergency setting of organ procurement. The literature supports the concept that hyperglycemia per se is not a contraindication to pancreas graft procurement [16, 23, 24]. Shaffer et al. found that donor hyperglycemia (>200 mg/dL) does not impair long-term pancreas graft survival or glucose control as measured by HbAlc levels [25].

Hyperamylasemia is frequently associated with head trauma, a common cause of brain death in organ donors. It is sometimes a consequence of direct salivary gland trauma. Other causes of hyperamylasemia include pancreatitis, metastatic cancer, and severe renal insufficiency, all circumstances that contraindicate organ donation. Isolated elevation of serum amylase levels without significant comorbidity does not appear to contraindicate pancreas donation. The literature clearly shows that isolated elevation is not predictive of posttransplant graft function [26].

With modern organ preservation, based on flush and cold storage with the University of Wisconsin solution, pancreas grafts can be safely transplanted up to 30 h after procurement. Several studies in the last 10 years as weIl registry data have found no added morbidity related to the length of cold ischemia, within a 30-h limit [17, 27]. However, other authors have reported an increased incidence of vascular thrombosis with prolonged cold ischemia. Further, Gruessner et al. showed that, in the specific case of PTA recipients, increased length of cold ischemia time correlates with an increased rate of intra-abdominal infections and posttransplant laparotomies (but not with vascular thrombosis) [28].

Most transplant centers do not consider the need for vasopressors an absolute contraindication to donation.

However, if the donor used high-dose, powerful vasoconstrictor agents (e.g., epinephrine or norepinephrine) most transplant surgeons would hesitate. At least one report correlated the need for dopamine with worse long-term graft function [2, 24].

As stated above, the appearance of the pancreas at the time of procurement is paramount. Acute or chronic pancreatitis, pseudocysts, or extensive fatty infiltration preclude pancreas procurement. Evidence of direct traumatic injury to the pancreas contraindicates procurement, but minor capsular laceration may be tolerated.

The issue of pancreatic edema is even more controversial. No convincing data on this issue is available in the literature, mostly because the decision to use or not use an edematous graft is a subjective one.

The vast majority of pancreas transplant surgeons consider donor obesity to be at least a relative contraindication to donation. Grafts with fatty degeneration are widely considered more likely to develop posttransplant pancreatitis, thrombosis, and infection. Impact of donor obesity on graft outcome warrants systematic study. Unfortunately, reliable data is not currently available.

Korea

The vast majority of pancreas grafts are obtained from cadaveric, heart-beating donors, and small portion from living donor.

The initial selection of a cadaver pancreas donor is based on ABO group compatibility, age of less than 45 year old, no history of diabetes or hyperglycemia, and normal HbA1C apart from normal medical workup. As most centers, a minimum donor weight requirement is 30 kg or above. Hyperglycemia in the absence of a history of pancreatic endocrine insufficiency is often seen in brain-dead patients. Isolated elevation of serum amylase levels without abnormal pancreatic function does not appear to contraindicate pancreas donation. Donor obesity (BMI > 30) is a relative contraindication to donation.

A medical history of malignancy is an absolute contraindication to organ donation, with the exception of primary brain tumors (without history of ventriculoperitoneal shunt), skin cancers other than melanoma, and carcinoma in situ of the cervix as described in General section (Table 1).

Documentation of HIV infection (based on positive serological test resuIts), tuberculosis, and herpes simplex virus encephalitis are considered absolute contraindications to donation.

Untreated bacterial infections from *Staphylococcus, Klebsiella, Escherichia coli,* or *Pseudomonas* in donors have been linked to the development of serious infections. Fungal infections including candida are contraindications due to aggressive pathogenecity.

The transmission of hepatitis B through organs procured from hepatitis B surface antigen (HBsAg) positive donors, and HCV positivity are contraindications for pancreas donation.

Acute or chronic pancreatitis, pseudocysts, or extensive fatty infiltration preclude pancreas procurement. Evidence of direct traumatic injury to the pancreas contraindicates procurement, but minor capsular laceration may be tolerated.

On a documented negative crossmatch, HLA matching is not critical for SPK transplants. There is no autoantibody (glutamic acid and decarboxylase 65: GADA). Grafts with fatty degeneration are widely considered more likely to develop posttransplant pancreatitis, thrombosis, and infection. The most important variable in determining suitability of a pancreas graft is

Table 1 Deceased donor selection criteria for pancreas transplantation (Korea)

Contraindications
Systemic active infection
Positive for HIV antibody
Positive for HBV, HCV
Creutzfeldt–Jakob disease and its suspicion
Malignant tumors (excluding primary brain tumor and those considered to be cured)
History of diabetes
Carefully consider the indications if the following diseases or conditions are involved
Abdominal trauma with bacterial infection
Functional or organic disorders of the pancreas
Age of 45–50 years or younger is desirable

inspection by an experienced pancreas transplant surgeon involved in donor organ harvest.

Japan

In Japan, both brain-dead donors (DBD) and non-heart beating donors (DCD) are indicated for the donors of pancreas transplantation. The criteria for indication in DBD donors are shown in Tables 2 and 3 shows the indication criteria for DCD donors

Table 2 DBD donor criteria for Pancreas Transplantation (Japan) (Health Bureau, Ministry of Health, Labor and Welfare, Health. Issue No. 798, July 30, 2001)

1. Contraindications
(a) Systemic active infection
(b) Positive for HIV antibody, HTLV-1 antibody, HBs antigen, HCV antibody, etc.
(c) Creutzfeldt–Jakob disease and its suspicion
(d) Malignant tumors (excluding primary brain tumors and those considered to be cured)
2. Carefully consider the indications if the following diseases or conditions are involved
(a) Abdominal trauma with bacterial infection
(b) Functional or organic disorders of the pancreas
(c) History of diabetes
3. Age: 60 years or younger is desirable

Table 3 DCD donor criteria for Pancreas Transplantation (Health Bureau, Ministry of Health, Labor and Welfare, Health. Issue 0114 No. 3, January 14, 2010. Japan)

1. Contraindications
(a) Systemic active infection
(b) Positive for HIV antibody, HTLV-1 antibody, HBs antigen, HCV antibody positive, etc.
(c) Creutzfeldt–Jakob disease and its suspicion
(d) Malignant tumors (excluding primary brain tumors and those considered to be cured)
2. Carefully consider the indications for transplantation if the following diseases or conditions are involved.
(a) Abdominal trauma with bacterial infection
(b) Functional or organic disorders of the pancreas
(c) History of diabetes
(d) Temporary cardiac arrest
(e) Hypotension
(f) Hypoxemia
(g) Anuria
(h) Hypernatremia
(i) Administration of noradrenaline and dopamine of 15 μg/kg/min or more
(j) Abnormal values of pancreatic function and liver function
3. Age: 60 years or younger is desirable.

[29]. The age of 60 years or younger is recommended both in DBD and DCD donors. Although the indication criteria are stricter in DCD donors as compared to DBD donors, pancreas transplantation from DCD donors is rarely performed due to the recent increased number of DBD donors. If the donor fulfill the criteria, the JOT coordinator asks a medical consultant for pancreas transplantation to determine if it is possible to proceed. The final donor indication is decided by each transplant team. Currently, patients aged 60 years or older, BMI 30 kg/m^2 or higher, HbA1c 6.0% or higher, and long cardiac arrest time tend to rarely used for pancreas transplantation.

Under the DBD donor Criteria for Pancreas Transplantation [30], contraindications are (1) Systemic active infection, (2) Positive for HIV antibody, HTLV-1 antibody, HBs antigen, HCV antibody, etc., (3) Creutzfeldt–Jakob disease and its suspicion, 4. Malignant tumors (excluding primary brain tumors and those considered to be cured).

Careful consideration is needed for the indications of transplantation if the following diseases or conditions are involved: (1) Abdominal trauma with bacterial infection, (2) Functional or organic disorders of the pancreas, or (3) History of diabetes.

60 years or younger is desirable.

Under the DCD donor criteria for Pancreas Transplantation [31], contraindications are (1) Systemic active infection, (2) Positive for HIV antibody, HTLV-1 antibody, HBs antigen, HCV antibody positive, etc., (3) Creutzfeldt–Jakob disease and its suspicion, or (4) Malignant tumors (excluding primary brain tumors and those considered to be cured).

Carefully consider the indications for transplantation if the following diseases or conditions are involved:

(1) Abdominal trauma with bacterial infection, (2) Functional or organic disorders of the pancreas, (3) History of diabetes, (4) Temporary cardiac arrest, (5) Hypotension, (6) Hypoxemia, (7) Anuria, (8) Hypernatremia, (9) Administration of noradrenaline and dopamine of 15 μg/kg/min or more, or (10) Abnormal values of pancreatic function and liver function.

60 years or younger is desirable.

Taiwan

Pancreas donor is not considered for the following conditions: (1) Age >55 years old or <5 years old, (2) Body mass index (BMI) >30, (3) Diabetes mellitus (DM) disease, (4) Pancreatitis disease, (5) Alcoholism, (6) Malignancy, except for those from skin or central nervous system, (7) Chronic infection disease, (8) Drug addiction (intravenous injection), (9) Prolonged hypotension, (10) High-dose vasopressor, (11) Severe systemic infection

Recipient

General

Most pancreas transplants have been done in patients with type 1 diabetes who are absolutely β-cell deficient. However, pancreas transplants have also been done in type 2 diabetes. The patient became insulin dependent even though C-peptide type was present pretransplant, indicating persistence of at least some endogenous β-cell dysfunction (Figs. 1 and 2) [32]. Successful

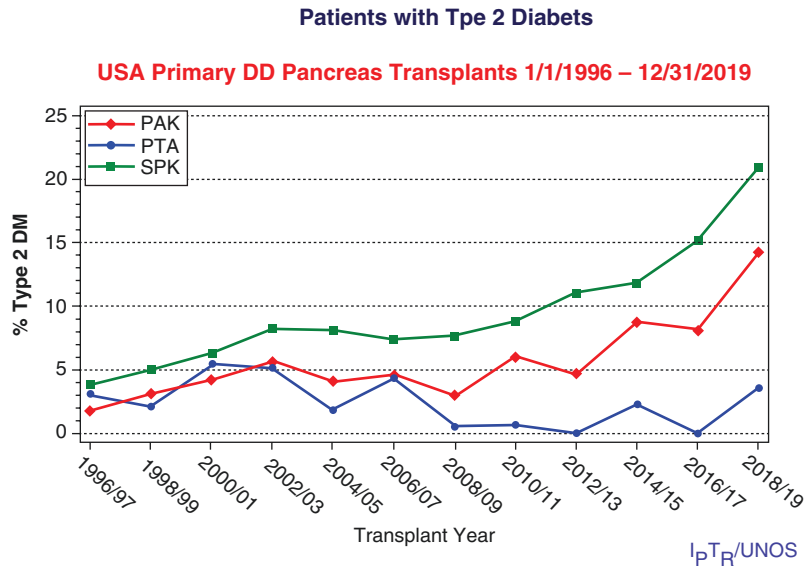

Fig. 1 Type 2 DM in US primary DD pancreas transplant (1996–2019)

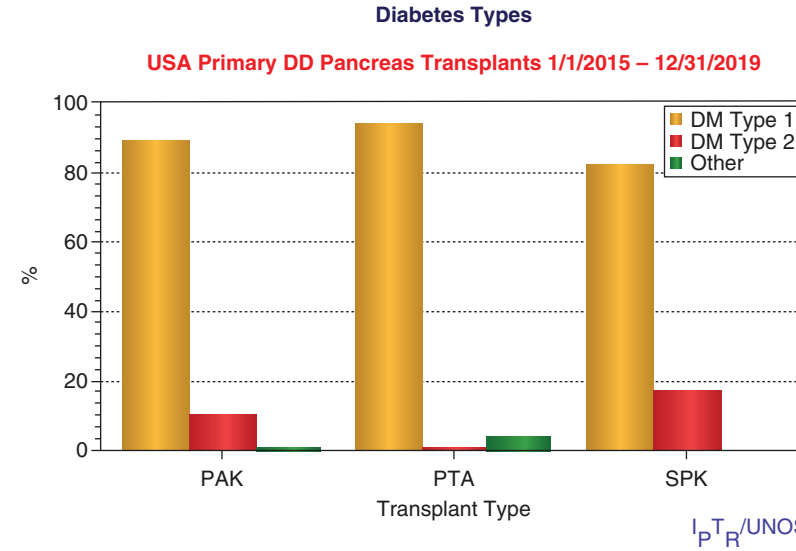

Fig. 2 The proportion of type 2 DM in US primary DD pancreas transplant (1996–2019)

insulin independence following pancreas transplantation in type 2 diabetes is already reported [33–36].

Benefit of a transplant is obvious when the problems of diabetes clearly exceed the potential side effects of chronic immunosuppression [37]. Patients with hypoglycemic unawareness with frequent reactions to exogenous insulin lead a dangerous existence [38].

Patients with progressive secondary complications of diabetes are also destined for blindness, amputations, and kidney failure that exceed the usual side effects of immunosuppression. Beta-cell replacement as early as possible is desirable.

Pancreas transplant recipients can be divided into two broad classifications: those with nephropathy to such a degree that they also undergo a kidney transplant, either simultaneously or sequentially, and those, usually without end-stage renal disease, who undergo only a pancreas transplant.

Among the traditional categories of SPK, PAK, and PTA, in the SPK category, the most common scenario is for both organs to come from same cadaveric donor, with a small percentage being from a living donor. However, simultaneous cadaveric donor pancreas and living donor kidney transplants have also been done in whom ABO compatible living donor is available.

Living donor SPK transplant is the good option for uremic diabetic patients [39]. As a preemptive transplant, it avoids dialysis and induces insulin independence with one operation and with the lowest rejection rate.

A pancreas transplant is performed to treat diabetes mellitus, most commonly in conjunction with a kidney transplant for patients with kidney failure or dysfunction secondary to diabetic nephropathy.

For diabetic individuals with preserved kidney function, the decision to undergo a pancreas transplant must balance the risks of long-term immunosuppression with the risks of long-term insulin therapy. The decision is easiest for those with brittle diabetes who have rapid fluctuations in blood sugar levels, frequent episodes of diabetic ketoacidosis, or significant hypoglycemic unawareness [40]. For such patients, a successful pancreas transplant becomes a lifesaving procedure.

There are few absolute contraindications to a pancreas transplant. Factors that represented absolute contraindications in the past now may no longer be contraindications or are only relative contraindications. Nonetheless, untreated malignancy, active infections, and significant noncompliant behavior still represent obvious contraindications.

Because immunosuppression would likely favor the growth of existing malignant cells, untreated cancers are a contraindication to transplant. For most malignancies, candidates should be free of recurrence for 2 years before the transplant, a period that will eliminate about two thirds of recurrences. However, for most malignant melanomas, and for some breast carcinomas and colorectal cancers (depending on tumor stage), a longer waiting period may be prudent. For example, if there was evidence of nodal involvement with a breast or colon cancer a waiting time of 5 years may be more appropriate. Yet, for certain tumors—such as in situ carcinomas, basal cell skin cancers, and incidentally discovered small renal cell cancers, no waiting time is likely required because the chance of recurrence of such tumors, once treated, is exceedingly small.

An active infection (which, like a malignancy, could rage unchecked in the presence of immunosuppressive medications) is also a contraindication to a transplant. One important part of the pretransplant evaluation is to search for occult infections, which may respond to therapy or may be an absolute contraindication to the transplant. Common examples of occult infections that should be looked for are dental caries, urinary tract infections, dialysis access site infections, and chronic pulmonary infections. Pulmonary tuberculosis may be completely masked until patients receive immunosuppressive agents [41]. Pretransplant, all potential recipients must have a detailed history done looking for risk factors, a chest x-ray, and a purified protein derivative (PPD) skin test. Depending on the findings, treatment with antituberculosis agents may be required both before and after the transplant.

All candidates should be tested for infection with the human immunodeficiency virus (HIV). Other viruses that should be tested for during the pretransplant evaluation include the members of the herpes family, such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex. These are not contraindications, but diagnosing them is important to obtain prognostic information on the likelihood of infections with these viruses posttransplant. This information can then be used to guide decisions on prophylactic therapy posttransplant. Cytomegalovirus is the most common opportunistic infection that affects recipients posttransplant. Recipients who are seronegative and subsequently receive an organ from a seropositive donor have the highest likelihood of developing CMV posttransplant [42]. Similarly, EBV-negative patients who receive an organ from an EBV-positive donor have a higher incidence of developing posttransplant lymphoproliferative disorder (PTLD) [43].

Another important group of viruses that need to be tested for pretransplant are the hepatitis viruses, specifically, hepatitis B and C. Immunosuppressive medications can certainly increase hepatitis B virus replication posttransplant. Even patients who have cleared the virus pretransplant have experienced return of hepatitis B surface antigen posttransplant [44]. The pretransplant evaluation of hepatitis B-positive patients should likely involve a liver biopsy to determine the histological appearance of the liver and the severity of damage; serum tests should be done to determine the histological appearance of viral replication (as indicated by the presence of hepatitis B virus [HBV] DNA and hepatitis B e antigen). Candidates with cirrhosis or significant fibrosis on liver biopsy should likely not proceed with a transplant because they are at risk for liver failure posttransplant. Those with less severe histology, but evidence of active viral replication, should receive antiviral therapy pretransplant to slow the degree of replication. Antiviral therapy should then be continued posttransplant.

Overall survival is worse for recipients who are hepatitis C positive because of an increased number of deaths secondary to liver failure. Candidates who are hepatitis C positive should, therefore, have a liver biopsy pretransplant. Candidates with cirrhosis should not proceed with a transplant.

Defining absolute psychiatric contraindications to a transplant is difficult. Candidates who display signs of psychosis and are unable to give informed consent should be seen by a psychiatrist before being considered for a transplant. Those with other major cognitive or psychiatric disorders should undergo proper psychiatric evaluation to help determine their ability to follow posttransplant regimens. Ongoing substance abuse should be addressed and treated; abstinence should be documented before proceeding with the transplant. Another important part of the psychosocial assessment is to evaluate for signs that may indicate future noncompliance.

Risk factors that may suggest future noncompliance include significant mood or anxiety disorders, substance abuse, severe personality disorders, and inadequate psychosocial support systems [45].

Korea

Most of the pancreas transplants have been done in IDDM patients who are absolutely β-cell deficient and requiring insulin. However pancreas transplants have been done in non-obese type 2 diabetic patients who use insulin for glucose control even though C-peptide type was present pretransplant, indicating persistence of at least some endogenous β-cell function. In early diabetic stage without diabetic complication, pancreas transplant can be done in the case in whom blood glucose is hardly controllable by exogenous insulin use, hypoglycemia unawareness, and early development of diabetic complication. In these conditions, post-transplant immunosuppressant should be understandable compared with insulin therapy. Diabetes with end-stage renal disease will be the ideal candidate for SPK under the physical condition available for major operation. Pancreas transplant following kidney transplantation can be performed if the patient wants insulin off or to avoid the diabetic complication afterwards.

There are a few absolute contraindications to a pancreas transplant (Table 4). Conditions that represented absolute contraindications are untreated malignancy, active infections, and significant noncompliant behavior.

In certain tumors such as in situ carcinomas, basal cell skin cancers, and incidentally discovered small renal cell cancers, no waiting time is likely required.

Common examples of occult infections that should be looked for are dental caries, urinary tract infections, dialysis access site infections, and chronic pulmonary infections, such as pulmonary tuberculosis.

After the experience of fatal scedosporiosis following multi organ transplantation from nearly drowned donor, prophylaxis of voriconazole (200 mg BID/day) for the prevention of this disease occurrence was a routine practice for the safety of recipients [46, 47].

Patients with progressive secondary complications of diabetes are also destined for blindness, amputations, and kidney failure that exceed the usual side effects of immunosuppression. Diabetes per se is sufficient for a patient to opt for a β-cell transplant, accepting the risks of immunosuppression over those of diabetes. Living donors for solitary pancreas transplants are now used if the recipient is highly sensitized (panel reactive antibody >80%) and has a low probability of receiving a cadaver graft; must avoid high-dose immunosuppression; or has a nondiabetic identical twin or a 6-antigen-matched sibling [30].

Pancreas transplant recipients can be divided into two broad classifications: those with nephropathy to such a degree that they also undergo a kidney transplant, either simultaneously or sequentially, and those, usually without end-stage renal disease, who undergo only a pancreas transplant. The traditional categories are as follows: SPK transplant, PAK transplant, PTA, and kidney after pancreas (KAP) transplant. In the SPK category, the most common is for both organs coming from same cadaveric donor, with a small percentage being from a living donor. However, simultaneous cadaveric donor pancreas and living donor kidney transplants have also been done. As a pre-emptive transplant, it avoids dialysis and induces insulin independence with one operation and with the lowest rejection rate.

Table 4 Recipient selection criteria for deceased donor pancreas transplantation—Korea

Conformity conditions
ABO blood type: Candidates are ABO blood type identity and compatible
Lymphocyte crossmatch (Whole lymphocyte or T lymphocyte) negative
Priority
If there are multiple transplant applicants (recipients) that meet the conforming conditions, the priority is as follows.
(1) Relatives
Priority is given to organs to relatives based on the act on organ transplantation
If the intention is indicated, the relative will be given priority
(2) ABO blood type
Priority is given to those who are ABO blood type identical over those who are compatible
(3) Number of HLA matching
Priority is given to those with the highest ranking calculated by the number of HLA DR or A, B matching
(4) Rule of kidney sharing to pancreas transplantation
SPK recipient has a priority to be shared one kidney if HLA types with one or more matches in the DR locus
(5) Waiting period
Give priority to those who have a long waiting period
(6) Others: history of organ donation in patient or relatives, retransplantation, young age(< 18 year old), highly sensitized patients

Japan

Indication for the recipient of pancreas transplantation is shown in Table 5.

Central Coordination Committee for Pancreas Transplantation in Japan revised and reported the criteria of the recipient for pancreas transplantation at 2010.7.5 [48].

As an indication, (1) Diabetes patient with end-stage renal disease and decreased serum C-peptide levels is indicated for simultaneous pancreas and kidney transplantation (SPK) or pancreas after kidney transplantation (PAK). (2) Diabetes patient with normal renal function, decreased serum C-peptide levels, and unstable blood glucose levels under control by diabetologist is indicated for solitary pancreas transplantation (PTA).

Table 5 Criteria of the recipient for pancreas transplantation. Central committee for pancreas transplantation in Japan, 2010.7.5 revised

Indication
#1. Diabetes patient with end-stage renal disease is indicated for simultaneous pancreas and kidney transplantation (SPK) or pancreas after kidney transplantation (PAK).
*Decreased serum C-peptide levels.
#2. Diabetes patient with normal renal function is indicated for solitary pancreas transplantation.
*Decreased serum C-peptide levels.
*Unstable blood glucose levels under control by diabetologist.
Age: <60 years is preferable.
Contraindications
#1. Progressive retinopathy
#2. Active infection, active liver dysfunction, active peptic ulcer
#3. Malignancy
#4. Unapproved case by regional committee for indication

Table 6 Recipient selection criteria for deceased donor pancreas transplantation—JOT, 2020

1. Conformity conditions
(a) ABO blood typeCandidates are ABO blood type identity and compatible.
(b) Lymphocyte crossmatch (whole lymphocyte or T lymphocyte) negative
2. Priority
If there are multiple transplant applicants (recipients) that meet the conforming conditions, the priority is as follows.
(a) RelativesPriority is given to organs to relatives based on the Act on Organ Transplantation.If the intention is indicated, the relative will be given priority.
(b) ABO blood typePriority is given to those who are ABO blood type identical over those who are compatible.
(c) Number of HLA matchingPriority is given to those with the highest ranking calculated by the number of HLA DR or A,B,C matching.
(d) Rule of kidney sharing to pancreas transplantation. SPK recipient has a priority to be shared one kidney if HLA types with one or more matches in the DR locus.
(e) Waiting periodGive priority to those who have a long waiting period.
(f) Transport time

Age: <60 years is preferable.

As contraindications, (1) Progressive retinopathy, (2) Active infection, active liver dysfunction, or active peptic ulcer, (3) Malignancy, and (4) Unapproved case by regional committee for indication are considered.

The best indications of pancreas transplantation are simultaneous pancreas and kidney transplantation (SPK) or pancreas after kidney transplantation (PAK) for the diabetes patient with end-stage renal disease and decreased serum C-peptide levels. Decreased serum C-peptide levels (CPR) were defined that fasting CPR is <0.3 ng/mL and stimulated CPR with glucagon stimulation test is <0.5 ng/mL. Solitary pancreas transplantation (PTA) may be indicated to the diabetes patients with normal renal function. However, in PTA, unstable blood glucose levels and a frequent hypoglycemic unawareness even under control by authorized diabetologist are necessary in addition to decreased serum C-peptide levels. This is because that the purpose of PTA is rather an improvement of quality of life (insulin independency) than life saving.

Patients who meet the indication category undergo a detailed examination and are judged by the Local Expert Medical Board for Pancreas Transplant Indication in Japan. The eligible recipient is finally registered in JOT and waits for transplantation. When a donor developed, the recipient is selected in the process showed in recipient selection criteria for deceased donor pancreas transplantation (JOT, 2020) (Table 6) [49].

As conformity conditions: (1) Candidates are ABO blood type identity and compatible, and (2) Lymphocyte crossmatch (whole lymphocyte or T lymphocyte) negative is mandatory As a priority, if there are multiple transplant applicants (recipients) that meet the conforming conditions, the priority is as follows.: Priority is given to organs to relatives based on the Act on Organ Transplantation. If the intention is indicated, the relative will be given priority. Priority is given to those who are ABO blood type identical over those who are compatible. Priority is given to those with the highest ranking calculated by the number of HLA DR or A,B,C matching. SPK recipient has a priority to be shared one kidney if HLA Dr locus is matched at least one. Priority is given to those who have a long waiting period and short transport time of the grafts.

Taiwan

According to Taiwan National Health Insurance Administration, indication for pancreas transplantation recipient is Type 1 DM or low serum peptide with diabetic complications such as nephropathy, retinopathy, neuropathy, and cardio-cerebral vasculopathy (Table 7).

Type 1 DM or low serum peptide with frequent life-threatening hypoglycemia or hyperglycemia.

Type 1 DM or low serum peptide with disability in school learning, working, and living.

Type 2 DM requiring insulin control, but less than 1.5 units/kg/day, and kidney transplantation.

Contraindications of pancreas transplantation for recipient are age >65 years old, uncontrollable infection, human immunodeficiency virus (HIV) infection, untreated tuberculosis, or malignancy.

Following are exceptions in malignancy: early or low malignancy, intraductal papillary mucinous neoplasm (IPMN) of the pancreas, neuroendocrine tumor of the pancreas, incidental renal carcinoma, in situ carcinoma(excluding bladder), or Dukes' A colon cancer, basal cell carcinoma, disease-free interval >5 years for malignant melanoma, breast cancer, gastrointestinal, carcinoma, or lung cancer, or disease-free interval >2 years for other malignancy. Another contraindications are autoimmune disease treated with prednisolone>10 mg/day or other immunosuppressants, poor compliance, unresolvable psychosocial problems, severe psychiatric disorder, major medical conditions prohibiting a major operation, uncorrectable severe cardio-cerebrovascular, or peripheral vascular disorder preventing self-care, or drug or alcohol abuse.

According to Taiwan Organ Registry and Sharing Center, allocation of the deceased pancreas graft is based on the Scoring system for pancreas graft allocation in Taiwan shown in Table 8 [50].

Table 7 Indications and contraindications of recipient (Taiwan)

Indications in Taiwan

1. Type 1 DM or low serum peptide with diabetic complications such as nephropathy, retinopathy, neuropathy, and cardio-cerebral vasculopathy.
2. Type 1 DM or low serum peptide with frequent life-threatening hypoglycemia or hyperglycemia.
3. Type 1 DM or low serum peptide with disability in school learning, working, and living.
4. Type 2 DM requiring insulin control, but less than 1.5 units/kg/day, and kidney transplantation.

Contraindications of pancreas transplantation for recipient:

1. Age >65 years old
2. Uncontrollable infection
3. Human immunodeficiency virus (HIV) infection
4. Untreated tuberculosis
5. Malignancy, except the following conditions:
   (a) Early or low malignancy: Intraductal papillary mucinous neoplasm (IPMN) of the pancreas, neuroendocrine tumor of the pancreas, incidental renal carcinoma, in situ carcinoma (excluding bladder), Dukes' A colon cancer, basal cell carcinoma
   (b) Disease-free interval >5 years for malignant melanoma, breast cancer, gastrointestinal carcinoma, lung cancer
   (c) Disease-free interval >2 years for other malignancy
6. Autoimmune disease treated with prednisolone >10 mg/day or other immunosuppressants
7. Poor compliance, unresolvable psychosocial problems, or severe psychiatric disorder
8. Major medical conditions prohibiting a major operation
9. Uncorrectable severe cardio-cerebrovascular or peripheral vascular disorder preventing self-care
10. Drug or alcohol abuse

Table 8 Scoring system for pancreas graft allocation in Taiwan

Scoring system	Level	Score
Waiting time	0.5 per year	1 (upper limit)
HLA mismatch	0 ABDR mismatch	12
	1 ABDR mismatch	10
	2 ABDR mismatch	8
	3 ABDR mismatch	6
	4 ABDR mismatch	4
Age of recipient	<18 y/o	3
	18–55 y/o	2
	>55 y/o	0
Family member of previous organ donation	Within third-degree relative	1
ABO blood type	Identical	1
Hepatitis B	HBsAg (+) recipient	−1
Hepatitis C	Anti-HCV (+) recipient	−1

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Preoperative Evaluation and Management

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CAD Donor

General

Potential pancreas donor must also fulfill criteria for donation as illustrated in previous donor indication section.

Any patient who is likely to remain permanently unconscious on life support, as a result of irreversible intracerebral damage, should be considered a potential organ donor [1]. Usually, these are healthy individuals who have suffered massive cerebral trauma or intracerebral hemorrhage and are declared brain-dead. Less common causes of brain death are hypoxic brain damage and primary cerebral tumors. After the patient is declared brain-dead, relatives must give formal consent for organ donation before the procurement team can begin its work. After prompt resuscitation, the potential donor must be stabilized.

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Although stabilization is usually achieved, the procurement team should always be ready for emergency organ procurement if the donor cannot be stabilized. Hemodynamic stability and electrolyte homeostasis are challenges for the clinicians involved in the donor's care before and during organ retrieval. Hypotension, hypothermia, electrolyte imbalances, and cardiac dysfunction are common. Hypotension is frequent, especially at the time of initial referral. Severe blood loss is a common cause of hypovolemia in trauma victims. The lack of neuroregulation of the vasomotor response due to cerebral damage may exacerbate hemodynamic instability.

Administration of large volumes of colloids and blood products in combination with crystalloid solutions is the first step in donor resuscitation to correct hypotension and establish adequate urinary output. A central venous catheter, an arterial line, and not infrequently a pulmonary artery catheter are essential in monitoring the resuscitation process. Aggressive fluid administration is preferable for kidneys to maintain diuresis. However, the pancreas (like the heart, lung, and liver) needs adequate, but not excessive, central venous and arterial perfusion pressures. The risk of pulmonary edema must also be judged. Preliminary evaluation of organ suitability may guide donor care, in particular if one or more organs are clearly unsuitable.

Hemodynamic instability may persist after adequate fluid resuscitation; vasopressor support

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is frequently needed. Administration of low to moderate doses of dopamine hydrochloride (1–5 mic/kg/min intravenously) is the first line of support. The goal is to maintain a minimum systolic blood pressure of 90 mmHg, especially during the initial period of volume replacement. When the blood volume is restored and the blood pressure stabilized, vasoactive drugs should be discontinued if at all possible. If a high concentration of dopamine (10 mic/kg/min or more) is required, a pulmonary artery catheter should be placed without delay to determine cardiac filling pressures, cardiac output, and systemic vascular resistance. Volume expansion results in increased urine output; diuretics usually are not needed. Moreover, polyuria is frequent in brain-dead patients, usually caused by osmotic diuresis (due to mannitol use or hyperglycemia), use of diuretics, or development of diabetes insipidus. Hypernatremia, hypokalemia, or hyperosmolarity caused by polyuria must be promptly corrected. Serum potassium levels should not fall below 3.5 mEq/L. If glycosuria and hyperglycemia occur, the donor should be treated with intravenous insulin (4 units every 100 mg/dL of blood glucose elevation above 200 mg/dL). Correcting hyperglycemia is in particular important from the pancreas procurement standpoint to avoid undue stress to the ß-cells. To control hypernatremia, hypotonic infusions should replace the isotonic solutions used for volume expansion. Diabetes insipidus is diagnosed if the urine output exceeds 500 mL/h, accompanied by a urine-specific gravity value less than 1005, hypernatremia, and increased serum osmolality. If polyuria persists, despite adequate hypotonic fluid, vasopressin should be used (initial dose, 1 U/h, increased up to 2 U/h in order to maintain urine output close to 200–300 mL/h). Electrolyte and arterial blood gas analyses are frequently required during these large fluid shifts. Arterial oxygen saturations should be no less than 95% and PCO2 levels should be 40–45 mmHg. Hematocrit should be maintained at levels above 30%. Hypothermia is common in organ donors because of the loss of the thermoregulatory function of the hypothalamus. It may cause cardiac arrhythmias and depression. Further, hypothermia impairs cellular metabolism and oxygen release and leads to hypotension, which further decreases tissue and organ perfusion. To prevent hypothermia, the room temperature should be maintained at 75 °F or above, body surfaces should be constantly well covered, and topical warming devices should be liberally used. Fluids should be warmed before intravenous infusion.

In summary, standard donor care is most likely adequate to preserve the pancreas graft in optimal condition.

However, special emphasis must be placed on avoiding excessive fluid administration that could lead to pancreatic edema as well as on preventing and aggressively treating hyperglycemia.

Korea

Potential pancreas donor must be compatible with criteria for donation as illustrated in previous donor indication chapter.

After the patient is declared brain-dead, relatives must give formal consent for organ donation. After prompt resuscitation, the potential donor must be stabilized by administration of large volumes of colloids and blood products in combination with crystalloid to correct hypotension and establish adequate urinary output.

In contrast to kidneys, the pancreas (like the heart, lung, and liver) needs adequate, but not excessive, central venous and arterial perfusion pressures.

Polyuria is frequent in brain-dead patients, usually caused by osmotic diuresis, use of diuretics, or development of diabetes insipidus. Electrolyte imbalance such as hypematremia, hypokalemia, or hyperosmolarity caused by polyuria must be promptly corrected.

Hypothermia impairs cellular metabolism and oxygen release and leads to hypotension.

In parallel to donor care above mentioned, medical history of donors, especially episode of hyperglycemia is searched very carefully. Donors underwent a general medical work-up for cardiopulmonary function and renal function test especially in SPK donor, and immunologic test which included ABO blood typing, HLA

typing, cross-matching of donor T-lymphocytes and recipient serum. Evaluation of pancreatic exocrine and endocrine function for insulin secretory and resistance (serum amylase and lipase, fasting plasma glucose, fasting hemoglobin [Hb] A1C levels, and C-peptide), and measurement of islet cell autoantibodies (anti-GAD antibodies) were done. Donor BMI is limited below 27 kg/m^2.

Final decision of donor is carry out by the transplant surgeon involved at the time of donor harvest in OR by inspection of pancreas parenchyma such as consistency, degree of fatty infiltration, and absence or presence of parenchymal injury.

Japan

Donor evaluation consists of four steps of primary evaluation, secondary evaluation, tertiary evaluation, and final evaluation. The primary evaluation is performed by the JOT coordinators to confirm that the indication is satisfied. If they are uncertain about indication, consultation to a medical consultant for pancreas transplantation should be done to make a decision. The secondary evaluation is made by the transplant surgeon based on the information obtained from the donor hospital, that is, blood biochemical data, urine findings, and imaging findings such as ultrasound and CT scan. The third evaluation is made by the transplant surgeon (transplant facility doctor) who directly performs ultrasound sonography immediately before organ procurement. The final evaluation is to actually observe and determine the pancreas at the time of donor operation. The degree of arteriosclerosis, the size and the hardness of the pancreas, the dilation of the pancreatic duct, the presence or absence of a tumor, the degree of fatty change, etc., are comprehensively judged to finally decide whether to use for transplantation.

Donor management is performed to improve the function of the organs after transplantation. Basically, respiratory and circulatory management are performed to obtain stable circulatory dynamics. Management to preserve the function of donor organs is started after brain death judgment and obtaining the consent from the donor family. In order to maintain cardiac function, regulation of preload and afterload is performed.

ADH is administrated intravenously (0.5–1 U/h) via central venous route regardless of urine output. The dose of catecholamine is reduced as much as possible (Dopamine 10 mg/kg/min or less). Mean arterial pressure should be about 80 mmHg or systolic blood pressure should be more than 90 mmHg (but 120 mmHg or less). Central venous pressure should be kept in 5–10 cmH_2O. In principle, dopamine is used for low blood pressure. Blood transfusion is also performed depending on the situation of anemia. The hematocrit should be kept above 30%. Since noradrenaline reduces blood flow in abdominal organs, it should not be used as much as possible. Since increased dose of adrenaline also decreases myocardial adrenergic receptor density, it should not be used as much as possible. As for the management of respiration, PaO_2 should be kept from 70 to 100 mmHg or more (95% or more with SaO_2), $PaCO_2$ should be around 40 mmHg, pH should be kept between 7.35 and 7.45. Since nerve reflex to the airways (cough reflex, etc.) disappears, regular repositioning and bronchoscopic suction are important for the prevention of lung infections and atelectasis. Administration of ADH is also useful for good respiratory management.

In brain-dead patient, hypothermia and hypokalemia are easily occurred; it is, therefore, important to adjust body temperature and electrolytes. Position change to prevent pressure ulcers and careful treatment for catheter, airway system, wounds and pressure ulcers are also important to prevent infection.

Taiwan

The data of suitable potential donor for pancreas transplant should be uploaded to Taiwan Organ Registry and Sharing Center, and allocation of the deceased pancreas graft is based on the Scoring system for pancreas graft allocation in Taiwan as mentioned before.

Recipient

General

One crucial factor in ensuring successful outcomes after pancreas transplants is the comprehensive pretransplant evaluation of potential recipients including a complete history and physical examination.

Therefore, a more important goal of the pretransplant evaluation should be to prepare the potential recipient so that he or she is in the best possible condition by the time the transplant is performed. This preparation involves identifying any significant risk factors that could be altered and dealing with medical problems that may lead to complications peri- or posttransplant.

To minimize morbidity following pancreas transplantation, patient care actually begins pre and intraoperatively. In addition early post op management is important for the successful outcome with emphasis on avoiding preventable complication. Preoperative evaluation also allows for assessment of acute medical issues (e.g., infectious diseases) that would contraindicate surgery. In pancreas transplant recipients, significant emphasis must be placed on three areas; cardiovascular status, kidney function, and glucose control. Immediate preoperative cardiac evaluation is pivotal. Previous hospital records pertaining to cardiac evaluations and procedures (e.g., angioplasty, bypass). For this reason, patients should undergo appropriate cardiovascular evaluation every 6 months to 1 year while on waiting list. It may be necessary to proceed with additional noninvasive stress testing or directly with coronary arteriography. If revascularization (i.e., coronary artery bypass) is indicated, the pancreas transplant should be deferred. Because of diabetic micro- and macroangiopathy, attention must also be given to peripheral vascular disease and especially with respect to aortoiliac atherosclerosis. In uremic candidates, the need for hemodialysis must be determined prior to transplantation. Knowledge of dialysis status and preoperative fluid management (including electrolyte, acid base, and volume status) is vital to the proper choice of a uremic recipient for organs from a particular donor.

Cardiac disease is the number one cause of mortality after pancreas transplants. Most such deaths occur late posttransplant, but a significant number are seen in the early perioperative period. Often, these represent recipients with underlying coronary artery disease that was not detected or adequately treated pretransplant. These patients are then at higher risk for a perioperative myocardial event secondary to the stress of the surgical procedure itself. Therefore, a detailed and thorough pretransplant cardiac evaluation is critical. The presence of diabetes itself is a significant risk factor; the longer the history of diabetes, the greater the risk. Other significant risk factors include hypertension, hypercholesterolemia, smoking, and a family history of cardiovascular disease [2]. Uremia also increases the risk. Those with multiple risk factors or obvious cardiac symptoms (such as chest pains suggestive of angina) should undergo invasive cardiac testing with coronary angiography. Coronary angiography is sensitive but invasive and unnecessary in candidates found not to have coronary artery disease. The contrast material used for the procedure can be nephrotoxic; patients with borderline kidney function, but not yet on dialysis, may end up in overt kidney failure. The problem, however, is that noninvasive cardiac testing has a poor predictive value in transplant candidates. Therefore, in most candidates being evaluated for a pancreas transplant coronary angiography should be performed to rule out coronary artery disease. In select, young diabetic candidates with no risk factors other than their diabetes, a dobutamine stress echocardiogram may suffice as the initial screening test. Once coronary angiography has been performed, any identified lesions with greater than 75% stenosis should likely be treated pretransplant by bypass surgery, angioplasty, or stent placement.

Besides revascularization if indicated, transplant candidates should also undergo interventions to reduce or eliminate hypercholesterolemia, hypertension, and smoking. In some candidates, an echocardiogram may also be indicated pre-

transplant, including those with known valvular disease or clinical evidence of myocardial dysfunction (e.g., orthopnea, shortness of breath on exertion). The echocardiogram may reveal a significant decrease in the systolic ejection fraction(often secondary to coronary artery disease). If not, other causes should be sought such as valvular heart disease, constrictive pericarditis, or thyroid dysfunction.

If the ejection fraction is low and does not appear to be reversible, the transplant may be contraindicated. Medical problems can then potentially be dealt with pretransplant, thereby decreasing the overall risk. Diabetes is a major risk factor for atherosclerosis, so a detailed cardiovascular assessment is mandatory. The respiratory, gastrointestinal (GI), and genitourinary systems must also be carefully assessed. Given the high prevalence of peripheral vascular disease among diabetics, a thorough vascular evaluation must be performed pretransplant. The history and physical exam earlier are probably the most important tools for assessing vascular disease. A history of claudication, especially if it is in the region of the buttocks, may suggest iliac occlusive disease. The lower extremities should be carefully examined for evidence of vascular disease such as ulcers, gangrene, or prior amputations. Palpation of all lower-extremity pulses is essential.

A magnetic resonance angiogram (MRA) is a good initial test; it will delineate the location of the arterial lesions. If significant lesions are identified, the next step is angiography.

Aggressive risk factor management is important, in particular smoking cessation. Other interventions include management of hypertension and hyperlipidemia.

Pancreas transplant candidates are also at risk for carotid occlusive disease. A history of neurological events or a finding of a carotid bruit on physical exam should prompt further investigation of the cerebral circulation. Radiological imaging with a carotid Doppler study, with or without an MRA, is likely the best initial test. Symptomatic lesions should be dealt with pretransplant; a carotid endarterectomy may be required [3]. Any history of seizures must be documented pretransplant; several anticonvulsant medications can interact with the commonly used immunosuppressive agents. Immunosuppressive agents may lead to a drop in the level of anticonvulsant medications and subsequent seizures. Pretransplant, any necessary anticonvulsant medications should be changed to ones that do not interact with immunosuppression agents.

Problems with gastroparesis and chronic constipation are common in diabetic patients. Pretransplant assessment of the severity of these disturbances is vital. Often, symptoms worsen in the early posttransplant period because of the operative stress, abdominal surgery, and new medications. No routine investigation for peptic ulcer disease is warranted, but transplant candidates with significant symptoms or a recent history of ulcers should be investigated with an upper endoscopy pretransplant. Symptomatic cholelithiasis should also be dealt with pretransplant. Asymptomatic cholelithiasis does not require any specific intervention. A history of pretransplant pancreatitis is important to document, as this may be worse posttransplant secondary to medications such as azathioprine or prednisone. Contributing factors for pancreatitis, such as cholelithiasis, should be dealt with appropriately (usually cholecystectomy, either pretransplant or at the time of the transplant). Colorectal cancer screening should be performed when indicated, in accordance with national recommendations for nontransplant patients. Patients with documented episodes of diverticulitis may benefit from an elective sigmoid resection prior to transplant.

Chronic pulmonary disease may be a problem postoperatively because of increased risk for pulmonary infections and ventilator dependency. Pulmonary function tests are useful to help determine lung capacity and should be done pretransplant in any candidate with symptoms or significant risk factors (e.g., long-term smoking).

Pancreas grafts may be drained either enterically or into the bladder to manage the exocrine secretions. Connecting to the bladder may create problems if there is existing bladder dysfunction.

A neurogenic bladder may be a complication of long-standing diabetes. Urologic evaluation with manometry studies pretransplant is important for these patients to determine if they will improve with medications or if self-catheterization may be required. Diabetic recipients may suffer from problems with voiding, secondary to diabetic neuropathy. Candidates with symptoms of bladder dysfunction should be evaluated urodynamically by water cystomanometry. Any history of chronic or recurrent urinary tract infections or ureteral reflux should also be investigated pretransplant. Voiding cystourethrography is usually the best test to evaluate this. Hematuria should prompt cystoscopy and formal urologic evaluation. The presence of a penile prosthesis is not an uncommon situation. This is not a contraindication to transplant, but information regarding the type and location of the prosthesis should be obtained pretransplant. This will help avoid injuries to the prosthesis at the time of transplant.

Pancreas recipients have a significantly increased risk for fractures posttransplant. Diabetic female candidates are especially at risk for osteoporosis and pathologic fractures, a risk compounded by high steroid use early posttransplant. Such candidates should undergo bone mineral density screening in an effort to identify bone loss pretransplant. If identified, it should be treated with some form of calcium replacement therapy.

Obesity is not uncommon in diabetic pancreas transplant recipients. They are at higher risk for many different types of surgical and medical complications posttransplant. Surgical complications (including wound infections, wound dehiscence, relaporatomy, and bleeding) were all significantly higher in obese recipients [4]. Obesity also increases the long-term likelihood of cardiovascular disease. Therefore, all obese transplant candidates should be strongly encouraged to lose weight pretransplant.

Any missing immunizations should be done. Hepatitis B vaccine should be given to candidates who are surface antibody negative. Pneumococcal vaccine should be given to everyone unless it was received within the last 5 years. Keep in mind, however, that vaccinations have reduced efficacy in patients with kidney failure. Also, live vaccines should be avoided in immunosuppressed individuals (e.g., in a previous kidney transplant recipient who is now being evaluated for a pancreas transplant) [1]. Once a patient is determined to be a good candidate for a pancreas transplant, with no obvious contraindication, it is important to decide which type of transplant is best for that individual patient. First, the degree of kidney dysfunction and the need for a kidney transplant must be determined. Patients with stable kidney function (creatinine clearance >60 mL/min, creatinine <2.0 mg/dL, and minimal protein in the urine) are candidates for a pancreas transplant alone.

However, patients with moderate kidney insufficiency will likely require a kidney transplant also because further deterioration often occurs once calcineurin inhibitors are started.

1. Simultaneous cadaver pancreas and kidney (SCPK) transplant: This is the most common option nationwide. It has good documented long-term survival results for both the kidney and pancreas grafts. The recipient has the advantage of undergoing both transplants at the same time and therefore potentially becoming dialysis free and insulin independent at the same time. There is also an immunologic advantage: Acute rejection rates are significantly lower vs pancreas transplants alone [5]
2. Living-donor kidney transplant, followed weeks to months later by a cadaver pancreas after kidney (CPAK) transplant: ·If a living donor is available for the kidney transplant, then this is a good option for the uremic diabetic candidate [6]. Simultaneous living-donor kidney and cadaver pancreas (SLKCP) transplant: Candidates with an available living donor for the kidney transplant who have not yet progressed to dialysis can be placed on the cadaver pancreas transplant waiting list. When a cadaver pancreas becomes available, the living donor for the kidney is called in at the same time and both procedures are done simultaneously. Advantages include use of a living donor for the kidney, shorter waiting times, and one simultaneous operation [7].

Technically, this option may be more difficult to organize as it requires using two full surgical teams and two full operating rooms.

3. Living-donor simultaneous pancreas and kidney (LSPK) transplant: If one appropriate living donor is available for a both a kidney and hemipancreas, then this is another potential option. It is especially useful for candidates with a high level of preformed antibodies, who have difficulty finding a cadaver organ from the general population [8].

A pancreas transplant is a significant undertaking from the patient's point of view. Meticulous care and diligent followup are important to obtain optimal results. Patient education must be an integral part of the pretransplant evaluation.

Korea

Preoperative evaluation includes complete history and physical examination. Preoperative evaluation also allows for assessment of acute medical conditions (e.g., infectious diseases) and cardiovascular status, kidney function, and glucose control in addition to a general medical work-up.

Regarding the diabetic status, glucose control by fasting glucose and HbA1C, insulin requirement, and status of endogenous β-cell function assay by C-peptide and glucose challenge test should be done.

Previous hospital records pertaining to cardiac evaluations and procedures (e.g., angioplasty, bypass) are examined carefully. It may be necessary to proceed with additional noninvasive stress testing or directly with coronary arteriography or echocardiogram. Studies must be done to peripheral vascular disease and especially with respect to aortoiliac atherosclerosis.

Secondary complications of diabetes are also to be studied. Radiological imaging with a carotid Doppler study, with or without an MRA, is likely the best initial test. Problems with gastroparesis and chronic constipation are common in diabetic patients.

Gastroduodenal endoscope for evaluation of an upper GI tract and colorectal cancer screening should be done.

Pulmonary function tests are useful to help determine lung capacity and should be done pretransplant in any candidate with symptoms or significant risk factors such as long-term smoking.

Any history of chronic or recurrent urinary tract infections or ureteral reflux should also be investigated pretransplant; by voiding cystourethrography. They are at higher risk for many different types of surgical and medical complications posttransplant.

Surgical complications including wound infections, wound dehiscence, relaporatomy, and bleeding were all significantly higher in obese recipients. Obesity also increases the long-term likelihood of cardiovascular disease. Therefore all obese transplant candidates should be strongly encouraged to lose weight pretransplant.

Patients with stable kidney function (creatinine clearance >60 mL/min, creatinine <2.0 mg/dL, and minimal protein in the urine) are candidates for a pancreas transplant alone. However, patients with moderate kidney insufficiency will likely require a kidney transplant also because further deterioration often occurs once calcineurin inhibitors are started.

According to an availability of kidney donor in the family member, pancreas transplant can be categorized: (1) Simultaneous cadaver pancreas and kidney (SPK) transplant: Living-donor kidney transplant, followed by a cadaver pancreas after kidney (PAK) transplant: ·If a living donor is available for the kidney transplant, then this is a good option for the uremic diabetic candidate. (2) Simultaneous living-donor kidney and cadaver pancreas transplant: Candidates with an available living donor for the kidney transplant and cadaver pancreas becomes available, the living donor for the kidney is called in and both procedures are done simultaneously. (3) Living-donor simultaneous pancreas and kidney transplant, if one appropriate living donor is available for both kidney and hemipancreas. In uremic candidates, the need for hemodialysis must be determined

prior to transplantation. As described in donor evaluation, ABO typing and immunologic test which included HLA typing, cross-matching of donor T-lymphocytes and recipient serum, flow-cytometry antibody test (living donor only), and luminex assay for donor specific antibody screening should be done.

Patient education about transplantation operation itself, and perioperative care including lifelong medication especially immunosuppressants must be an integral part of the pretransplant evaluation.

Hepatitis B vaccine should be given to candidates who are surface antibody negative. Pneumococcal vaccine should be given to everyone unless it was received within the last 5 years (Table 1).

As mentioned in previous section of indication and selection section of recipient, prophylaxis of voriconazole (200 mg BID/day) for the prevention of fatal scedosporiosis occurrence in nearly drowned donor was a routine practice [7, 8].

Japan

As the time of registration, basic physical information of the recipient such as height, weight, blood type, HLA typing, and detailed diabetes history should be examined. To evaluate pancreatic endocrine function, daily excretion of urinary C-peptide and glucagon stimulation test are performed. Evaluation of glycemic control instability should be performed by continuous glucose measuring (CGM). We also investigate the frequency of hypoglycemic unawareness. A severe hypoglycemic attack is defined that the third-party assistance is required to help a patient when the attack occurs. In addition to the age of onset of diabetes, the mode of onset, the history of insulin treatment, and the history of hospitalization for ketoacidosis, anti-GAD antibody, and anti-IA2 antibody are measured as an immunological search to diagnose type 1 diabetes. Evaluation of diabetic nephropathy is important as a diabetic complication. Patients with dialysis or CKD stage 5 are indicated for SPK, and CKD stages 1 and 2 may be indicated for PTA. Regarding CKD stage 3, the indication of PT should be determined carefully because PT may worsen renal function. Regarding retinopathy, in the case of active reti-

Table 1 Pretransplant evaluation—Korea

History taking
DM history: Onset, insulin dose per day
DM related complication history: Nephropathy, retinopathy, neuropathy, vasculopathy such as coronary arterial disease (CAD) and cerebral vascular disease
Infection history: Active and chronic infection disease
Malignancy history: Remitted or unremitted malignancy
Co-morbid disease and current medication
Physical examination
Complete physical examination focusing on infection, malignancy, neuropathy, and vasculopathy
Laboratory evaluation
Respiratory evaluation: Chest X-ray, pulmonary function tests
Cardiac evaluation: EKG, Echocardiogram, consultation of cardiovascular doctors for any suspicious CAD if needed
Abdominal evaluation: Nonenhanced abdomen and pelvic CT
Vascular evaluation: Low abdominal CT scan for aorta and iliac arteries condition. Doppler scan for lower limb vessels
Gastrointestinal evaluation: Gastroduodenal endoscopy, stool examinations/colonoscopy (>40 years) if needed
Breast evaluation (female): Mammography or breast sonography
Pancreas profiles: Fasting glucose, HbA1c, C-peptide, amylase, lipase, GAD Ab, OGTT
Blood tests: Blood count, biochemistries
Urinary tests: Urinalysis, urine culture, urine cytology, VCUG (SPK)
Tumor marker tests: PSA
Hepatitis markers for Hepatitis A, B, and C
Bacteriology testing: Latent TB infection test (IGRA), PNS series
Viral Testing: Anti-HIV, CMV IgG/IgM, EB-VCA IgA/M
Blood typing: Blood type for A, B, AB, and O
Immunology Laboratory Tests: HLA A, B, Cw, DR, DQ typing, HLA Ab single bead class I, II on waiting
Pretransplant cross-matching testing (CDC and T flow in high PRA): When a donor is available
Consultation: Dentist, ENT, OB/GY, Infectionist, Social service/Psychiatrist, if necessary

nopathy, priority is given to ophthalmic treatment, and transplantation is possible when it is stable. As for neuropathy, evaluation of the degree both of peripheral neuropathy and autonomic neuropathy should be performed. Evaluation of atherosclerotic change is of utmost importance in performing PT operation. In particular, the coronary artery lesion should be evaluated reliably, and if ischemic heart disease is found by cardiac angiography or myocardial scintigraphy, coronary artery bypass grafting (CABG) or coronary stent treatment should be prioritized before transplantation. Echocardiography should confirm that cardiac function is normal. Screening for malignancy is also important, which is studied with gastrointestinal endoscopy, colonoscopy, abdominal ultrasonography, chest, abdominal CT, breast cancer screening, uterine cancer screening, tumor markers, etc.

In principle, patients visit the outpatient clinic every 3 months and are evaluated by interview and blood test concerning anemia, infection, renal function, glycemic control status, etc. In addition, the following examinations are performed annually to evaluate malignancy, arteriosclerosis, and cardiovascular complications: (1) Chest and abdominal X-ray, (2) Chest and abdominal CT, (3) Abdominal ultrasonography, (4) Viral antibody test: HBs antigen, HBs antibody, HBc antibody, HCV antibody, HIV antibody, HTLV-1 antibody, etc. (5) Gastroscope, (6) Tumor markers: CEA, AFP, CA19-9, PSA, etc. (7) Cardiovascular examination: stress electrocardiogram, echocardiography, myocardial scintigraphy, consultation with a cardiologist.

Pancreas transplant is an emergency operation, and when the recipient is hospitalized for transplantation, an evaluation should be performed immediately before transplantation. In addition to the examinations required for normal emergency surgery, the items to be examined are chest and abdominal CT, echocardiography, and evaluation by a cardiologist. Finally, the anesthesiologist determines whether or not transplant surgery is possible.

Taiwan

Pretransplant evaluation are DM history (type, onset age, duration), DM related complication history (nephropathy, retinopathy, neuropathy, vasculopathy such as coronary arterial disease (CAD) and cerebral vascular disease). Infection history (Active and chronic infection disease) and malignancy history (remitted or unremitted malignancy) should be taken. Complete physical examination is done focusing on infection, malignancy, neuropathy, and vasculopathy, and respiratory evaluation by chest X-ray, pulmonary function tests. Heart evaluation is done by electrocardiogram (EKG), consultation of cardiovascular doctors for any suspicious CAD. If needed, vascular evaluation by low abdominal CT scan for aorta and iliac arteries condition, and Doppler scan for lower limb vessels are done.

Abdominal evaluation is done with whole abdominal sonography, and gastrointestinal evaluation by upper gastrointestinal (UGI) endoscopy, and stool examinations/colonoscopy if needed. Phychomental evaluation is done by psychiatrist and social worker consultation if needed.

Breast evaluation (female) is done with mammography or breast sonography.

Pancreas are evaluated with fasting blood sugar (FBS), HbA1c, C-peptide, amylase, and lipase.

Blood tests are done for blood count, and biochemistries. Tumor marker tests are done for CEA, CA 19-9, AFP, PSA, CA 125, and CA 153. Hepatitis markers are studied with hepatitis A, B, and C markers.

Bacteriology testing should be done with latent TB infection test, and toxoplasma IgG/M, and viral testing for anti-HIV, anti-Human T-cell lymphotropic virus type-I/II (ANTI-HTLV-I/II), CMV IgG/M, EB-VCA IgA/M, HSV Ig G/M, and varicella zoster IgG/M.

Blood typing should be done (Blood type for A, B, AB, and O). And immunology laboratory tests are tissue typing for HLA A, B, DR, and Panel Reactive Antibody (PRA) on waiting. Pretransplant crossmatch testing is done when a donor is available (Table 2).

Table 2 Pretransplant evaluation for pancreas at Taipei Veterans General Hospital

DM history: Type, onset age, duration
DM related complication history: Nephropathy, retinopathy, neuropathy, vasculopathy such as coronary arterial disease (CAD) and cerebral vascular disease
Infection history: Active and chronic infection disease
Malignancy history: Remitted or unremitted malignancy
Physical examination: Complete physical examination focusing on infection, malignancy, neuropathy, and vasculopathy
Respiratory evaluation: Chest X-ray, pulmonary function tests
Heart evaluation: Electrocardiogram (EKG), consultation of cardiovascular doctors for any suspicious CAD if needed
Abdominal evaluation: Whole abdominal sonography
Vascular evaluation: Low abdominal CT scan for aorta and iliac arteries condition, Doppler scan for lower limb vessels
Gastrointestinal evaluation: Upper gastrointestinal (UGI) endoscopy, stool examinations/colonoscopy if needed
Phychomental evaluation: Psychiatrist and social worker consultation if needed
Breast evaluation (female): Mammography or breast sonography
Pancreas profiles: Fasting blood sugar (FBS), HbA1c, C-peptide, amylase, lipase
Blood tests: Blood count, biochemistries
Tumor marker tests: CEA, CA 19-9, AFP, PSA, CA 125, CA 153
Hepatitis markers: Hepatitis A, B, and C markers
Bacteriology testing: Latent TB infection test, Toxoplasma IgG/M
Viral Testing: Anti-HIV combo, anti-Human T-cell lymphotropic virus type-I/II (ANTI-HTLV-I/II), CMV IgG/M, EB-VCA IgA/M, HSV Ig G/M, Varicella Zoster IgG/M
Blood Typing: Blood type for A, B, AB, and O
Immunology Laboratory Tests: Tissue typing for HLA A, B, DR, Panel Reactive Antibody (PRA) on waiting
Pretransplant crossmatch testing: When a donor is available

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Surgical Aspects of Pancreas Transplantation

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Cadaveric Donor

General

The successful outcome of pancreas transplantation largely depends on the procuring surgeon's expertise [1]. It became obvious that perioperative coordination is essential, in particular when the pancreas and liver are procured by different teams.

A midline incision is made. After the falciform ligament is divided, the right colon is fully mobilized to expose the retroperitoneum, cava, aorta at its bifurcation, and duodenum. The infrarenal aorta is encircled, the inferior mesenteric artery is divided, the mesentery is reflected superiorly, and the superior mesenteric artery is identified at its base and encircled. The triangular ligament of the left lobe is mobilized to allow access to the supraceliac aorta.

After infrarenal and supraceliac control of the aorta is achieved, the porta hepatis is dissected. The common bile duct is divided close to the superior margin of the head of the pancreas. The hepatic artery is dissected from its bifurcation to the celiac artery; the gastroduodenal artery is ligated and divided. The splenic artery is identified and looped with a vessel loop. The portal vein is dissected free at its midpoint between the pancreas and liver. The nasogastric tube is advanced into the duodenum, and the duodenum is flushed with a solution of amphotericin, metronidazole, and gentamicin.

The patient is heparinized (20,000 U) and the distal aorta cannulated and ligated. The inferior mesenteric vein is cannulated, and the cannula is advanced up to the portal vein. The supraceliac aorta is clamped. Inferior vena cava is exposed supradiaphragmatically at its junction with the right atrium and incised. The right pleural cavity is opened. The aortic and portal cannulas are flushed with 3 and 2 L, respectively, of cold UW or other (HTK) solution. The abdomen is packed with slushed ice until the perfusion is complete.

Once flushing is complete, the ice is removed. The liver is carefully excised, taking the adjacent diaphragm. The portal vein is divided, leaving an adequate stump (1–2 cm) on the pancreas side. The splenic artery is divided close to its origin and tacked with a single nonabsorbable 6-0 suture to aid future identification.

The lesser sac is opened by sharp dissection along the greater curvature of the stomach toward the spleen. The short gastric vessels are divided with scissors. The spleen is mobilized carefully,

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dividing all its peritoneal reflections. The spleen is elevated. The avascular plane behind the pancreas is developed, both bluntly and sharply. The peritoneal reflection along the inferior border of the pancreas is divided. After removal of the perfusion cannula, the inferior mesenteric vein is ligated on the pancreas side. The attachments along the superior border of the pancreas toward the stomach are divided by sharp dissection. The Kocher maneuver is completed. Attachments to the anterior surface of the head of the pancreas, including the right gastric and gastroepiploic artery, are ligated. The duodenum is divided just distal to the pylorus using a GIA stapler. The third or fourth portion of the duodenum or proximal jejunum (right behind the ligament of Treitz) is divided in a similar manner. The mesentery and mesocolon are divided using a GIA stapler. The superior mesenteric artery is taken with a patch of the aorta without injury to the renal arteries. The pancreas is removed and packaged.

Meticulous surgical technique and attention to detail during the benchwork preparation are paramount to avoid grave technical complications posttransplant. Bench-work reconstruction involves these steps: splenic hilar dissection, duodenal segment preparation, ligation of mesenteric vessels, and arterial (or venous) reconstruction.

Korea

The most important aspect for the decision of whether the pancreas is appropriate for transplantation is the direct inspection of the pancreas at the time of recovery [2]. Initially, a portion of the head and body of the pancreas is exposed after dissection of the hepatogastric ligament. Subsequently, the greater omentum is separated from the transverse colon to open a lesser sac, and the whole pancreas is exposed for evaluation. The pancreas is given up for recovery if there is significant calcification, fibrosis, fat infiltration, and edema in the pancreas, or severe atherosclerosis in feeding arteries.

When the pancreas is considered to be suitable for recovery, dissection of the pancreas and duodenum is initiated. At first, the head of the pancreas, aorta, and inferior vena cava can be exposed after dissection with the Kocher maneuver. Anterior and posterior pancreaticoduodenal arteries are ligated. The right gastric artery is ligated as well as supraduodenal arteries. It should be cautious not to make an injury to an atypical right hepatic artery originating from a superior mesenteric artery. After ligation of supraduodenal arteries, a gastroduodenal artery from the common hepatic artery is exposed, which is tagged with prolene 6-0 at the time of recovery, and encircled with a vessel loop. Dissection should be progressed from gastroduodenal artery to celiac trunk to identify the origin of the splenic artery, which should be encircled with a vessel loop. The inferior mesenteric vein at the lower border of the pancreas should be identified and encircled with vessel loop. At the time of portal perfusion through the inferior mesenteric vein in liver harvest, it is important not to insert liver perfusion cannula deep into the pancreas.

The nasogastric tube is lowered to Treitz ligament, and proximal jejunum is clamped for duodenal irrigation with antibiotics and antifungals-mixed normal saline. After irrigation, the nasogastric tube is repositioned up to the stomach. The proximal duodenum is separated from the pylorus with GIA 60 stapler.

After perfusion of abdominal viscera with HTK or UW solution, the pancreas and the liver are usually separated in situ. The splenic artery is separated from the Celiac trunk at the origin, whereas the gastroduodenal artery is divided from the common hepatic artery at the origin. Both arteries should be tagged with 6-0 prolene before separation. The portal vein should be divided at an appropriate point to secure a proper length of the portal vein. After recovery of the liver, the superior mesenteric artery is separated at the origin from the aorta. At the time of the superior mesenteric artery division, it should be cautious not to injure both renal arteries. The inferior mesenteric vein is ligated at the lower border of the pancreas. Mesenteric root below uncinated process is divided with TA 90 stapler. Spleen is separated from the stomach by dividing short gastric arteries. Handling the spleen, distal pancreas and spleen are separated from adjacent

tissue. After recovery of the pancreas and followed by both kidneys, en bloc dissection of common, external, and internal iliac arteries should be performed and harvested for use as Y-graft in pancreas arterial reconstruction.

After identification of anatomy of the pancreas in bench procedure, distal portion of duodenum below the pancreatic attachment is separated from the mesentery. The proximal end of graft duodenum closed by stapler during the organ harvest is reinforced with 4-0 prolene suture. Stapled end of the mesenteric root is reinforced with 4-0 prolene continuous suture. Spleen is detached from the tail of the pancreas with double ligation of splenic artery and vein. Open end of gastroduodenal artery is closed. The divided portal vein is trimmed, and reconstruction of the splenic artery and superior mesenteric artery is carried out by Y-graft of donor bifurcated iliac artery into a single stoma as usual fashion. After ligation of trivial vessels and loose tissues surrounding the pancreas, the graft is kept in cold preservation solution until use (Fig. 1).

Japan

Because of operation by the certified 18 facilities under a multi-facility cooperation system for carrying out pancreas transplantation and performing a simulation of organ removal using pigs once a year, the procedure for procurement of pancreatic graft from the cadaveric donor is unified to some extent in Japan. Details procedure on the procurement of pancreatic graft from the cadaveric donor is published on the Japan Society for Transplantation website [3].

Laparotomy is made with from median sternotomy to the upper pubis following the chest thoracotomy. After Kocher's maneuver, the abdominal aorta and inferior vena cava (IVC) is taped just above the left and right bifurcations of

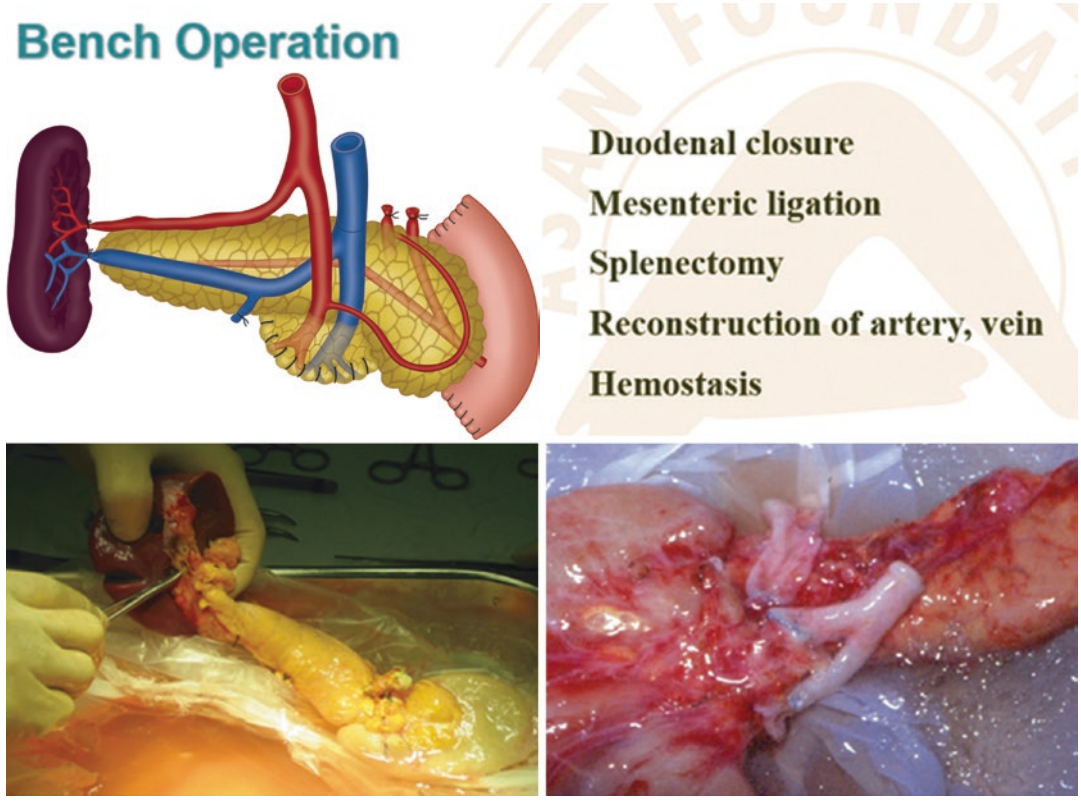


Fig. 1 Deceased donor pancreas transplantation-bench procedure (AMC)

the common iliac artery and vein. Then, the abdominal aorta is taped just below the diaphragm.

The greater sac is opened to observe the pancreas, and both kidneys are mobilized from the retroperitoneum to make a space for surface cooling. At 3 min after systemic heparinization (400 units/kg), cannulations to the abdominal aorta and inferior vena cava just above the bifurcations of the common iliac artery and vein are performed.

After the cannulation, the aorta is clamped (cross-clamp) at the position of just below the diaphragm. Blood is washed out from the cannula inserted to the inferior vena cava by perfusing of cold 2–3 L of UW solution by drip infusion from the cannula inserted from the abdominal aorta. Also, surface cooling of the abdominal organs is achieved with slush ice as soon as possible (Fig. 2).

Organ procurement is performed in the order of heart, lungs, small intestine, liver, pancreas, and kidneys. Since both liver and pancreas are procured in more than 90% of the donors, the common hepatic artery (CHA) is divided at 1–1.5 cm from the branch of the celiac artery and splenic artery. The gastroduodenal artery is divided at 5 mm from the branch of the CHA. As a result, the arteries of the pancreatic graft are procured with a Carrel patch containing CEA and SMA. The portal vein is also shared by the liver transplant team and is divided at a position of 5 mm from the upper edge of the pancreas. IVC is cut at the proximal side of the branch of renal veins (Fig. 3). After the procurement of the liver, en bloc procurement of the pancreas and both kidneys are performed. The pancreas is procured with the duodenum, spleen, aorta, and IVC. The proximal and distal sides of the duodenum are separated with an automatic suture device. Separation of pancreas and kidneys is performed on the back table (Fig. 4).

Since more than 80% of the pancreas transplantation is SPK, the pancreas and left kidney are used for SPK. In the case of using blood vessels for reconstruction in recipient operation, both sides' iliac arteries and veins are procured. Blood vessels are shared between the liver and pancreas transplantation team depending on their needs for the recipient operation.

After a closure of the abdominal wound of the donor, the pancreas and kidney are packed and

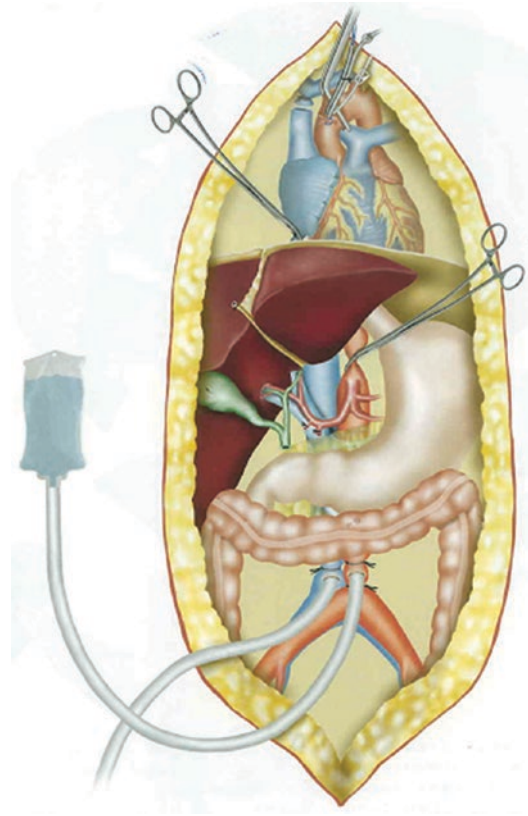


Fig. 2 Cross-clamp after the cannulation into the aorta and vena cava (Japan)

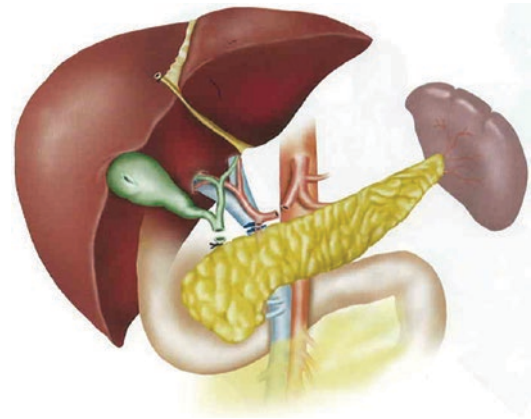


Fig. 3 Procurement of the liver (Japan)

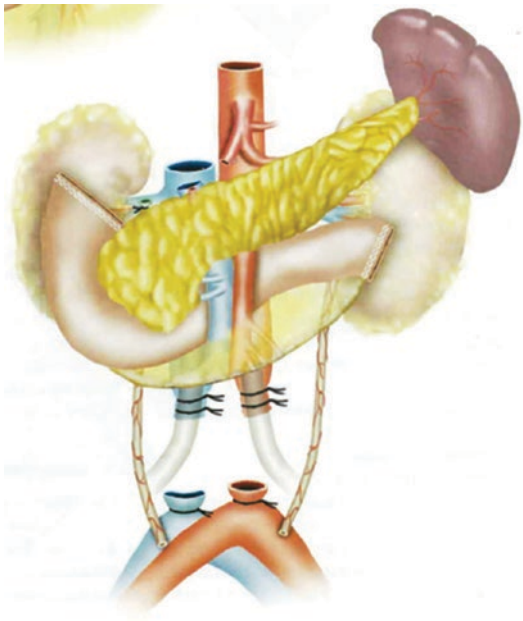


Fig. 4 En bloc procurement of the pancreas and kidney with duodenum and spleen (Japan)

transported to the transplantation center. Both organs are preserved in cold UW solution and placed on ice in a cooler box. Cold ischemic time of the pancreas may be approximately 24 h.

At our facility, we perform kidney transplantation first during the back table operation of the pancreas graft.

The tissues surrounding the pancreas, such as the small intestine, mesenterium, adipose tissue, and spleen, are removed. Treatment is performed in cold UW solution, and all dissections are performed by ligation or vessel sealing system (Ligasure™). For the spleen, it depends on the institution whether it is removed at the back table or during transplantation.

In Japan, >70% of the DBD donors for pancreas transplantation are classified as marginal donors according to the criteria proposed by Kuper et al. [1]. Therefore, in order to secure a good blood flow of the head of the pancreas head and maintain the graft function, I-graft, which was an iliac artery procured from the donor, was placed between the origin of the common hepatic artery and gastroduodenal (GDA) artery (Figs. 5 and 6). However, recently, if there is enough outflow from the GDA by perfusion from SMA on the back table, the reconstruction of blood vessels using I-graft may be omitted. In Japan, an aortic patch (Carrel patch) that includes the celiac artery and superior mesenteric artery is usually used for arterial anastomosis in the recipient operation (Fig. 7), and the cases of using a Y-graft is only 13.5%. Reconstruction of the Y-graft is performed using the iliac artery collected from the donor. If the portal vein of the pancreatic graft is short, the portal vein is extended using the iliac vein harvested from the donor. Recently, there are many cases where portal vein extension is not performed (Figs. 8 and 9).

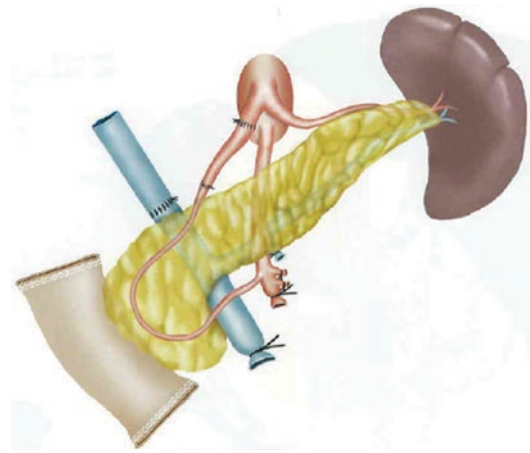
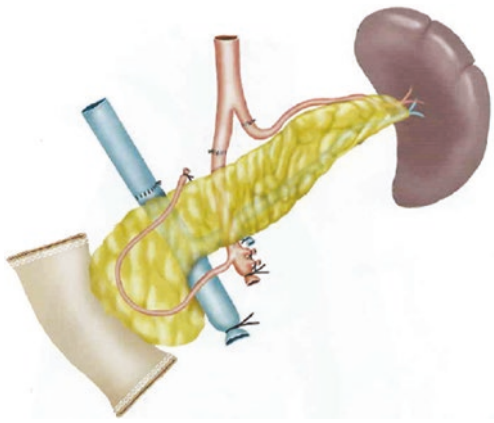


Fig. 5 Arterial reconstruction using I-graft (Japan)

Taiwan

Patients with a positive crossmatch against donor cells are excluded for pancreas transplantation. The pancreas grafts are procured in a "'no-touch" technique en bloc with the duodenum. The spleen is separated from the pancreas before aorta cross-clamping. Histidine-tryptophan-ketoglutarate (HTK) solution, 4000–6000 mL, is used for in situ perfusions via the distal aorta. Back table preparation includes removal of the peripancreatic fat and arterial reconstruction using a donor iliac arterial Y-graft. The gastroduodenal artery stump is remained ligated, and no reconstruction is attempted.



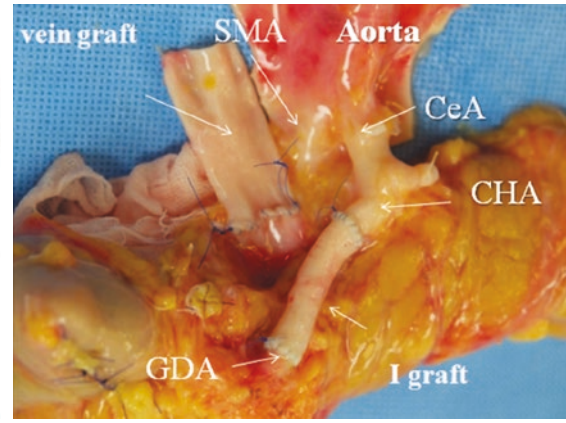


Fig. 6 I-graft and portal vein prolongation (*CeA* celiac artery, *CHA* common hepatic artery, *GDA* gastroduodenal artery, *SMA* superior mesenteric artery) (Japan)

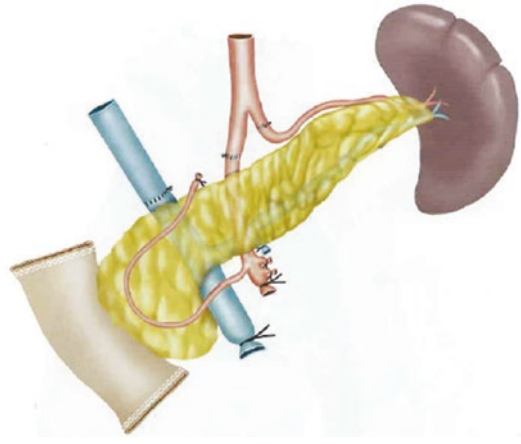


Fig. 7 Arterial reconstruction using Y-graft (Japan)

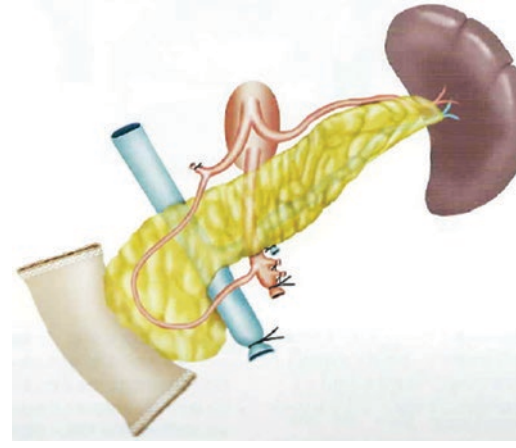


Fig. 9 No reconstruction of the artery by Carrel patch (Japan)

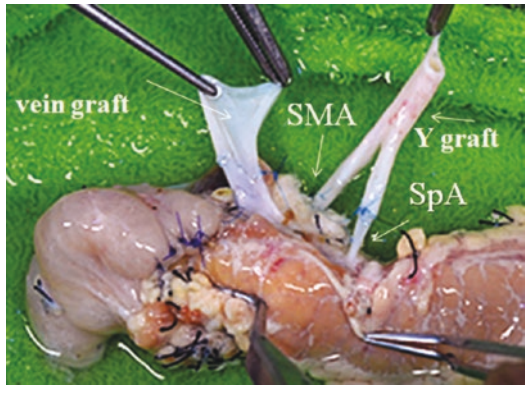


Fig. 8 Y-graft and portal vein prolongation (*SpA* splenic artery, *SMA* superior mesenteric artery) (Japan)

Recipient

General

Since the first pancreas transplant in 1966 [4] a variety of surgical techniques for graft implantation have been reported. In fact, more so than with any other solid organ, the history of pancreas transplantation has predominantly revolved around the development and application of different surgical techniques. The most controversial issues have been the management of exocrine pancreatic secretions (bladder vs. enteric drainage) and the type of

venous drainage (systemic vs. portal vein drainage). According to the International Pancreas Transplant Registry (IPTR), through 1995, more than 90% of all pancreas transplants worldwide were bladder drained [1].

Two main reasons for the widespread use of bladder drained whole organ pancreaticoduodenal transplants are the low complication rate, with no contamination from an enterotomy, and the ability to monitor urinary amylase levels to detect graft rejection [5, 6]. Contrast to enteric drainage, surgical complications with bladder drainage are usually contained to the right or left lower abdominal quadrant: Leaks usually do not result in diffuse peritonitis because no abdominal spillage of enteral contents occurs. Duodenal segment or bladder leaks can frequently be managed conservatively, without surgical repair, by the placement of a foley catheter and percutaneous drain. Urinary amylase measurements have been particularly helpful in solitary pancreas transplants, in which a simultaneously transplanted kidney from the same donor is not available to monitor serum creatinine levels for rejection [7].

However, bladder drainage is associated with unique metabolic and urologic complications. The loss of 1–2 L/day of (alkaline) exocrine pancreatic and duodenal mucosal secretions in the urine results in bicarbonate deficiency and electrolyte derangements, causing chronic (hyperchloremic) metabolic acidosis and dehydration [8].

Urologic complications are common because alkaline pancreatic enzymes are a source of irritation to the transitional epithelium of the bladder and to the lower genitourinary system. Urologic complications include the following: chemical cystitis and urethritis, recurrent hematuria, bladder stones, and recurrent graft pancreatitis from reflux. The high rate of urinary tract infections is a frequent cause of morbidity. More serious but less common complications include severe perineal inflammation and excoriation and, more frequently in men, urethral disruption and strictures [8–11].

In light of the potential complications of bladder drainage and possibly their negative impact on quality of life, interest in enteric drainage resurged in the mid-1990s. Currently, enteric drainage is increasingly used, thanks to improvements in surgical technique, immunosuppressive therapy, radiologic imaging and interventional procedures, and antimicrobial prophylaxis [12–17].

Portal vein drainage creates a more physiologic state of insulin metabolism [18]. While in systemic drainage, peripheral hyperinsulinemia has been associated with atherosclerosis and portal hypoinsulinemia with lipoprotein abnormalities [19–22]. Yet no convincing evidence exists today that systemic vein drainage places pancreas recipients at a disadvantage by increasing their risk of vascular disease [23, 24] or at a high risk of immunologic rejection [25–27]. The pancreas is placed intraabdominal, preferably on the right side of the pelvis, for two reasons: the iliac vessels are more superficial than on the left side and, therefore, dissection is easier on the right side, and the natural position of the right iliac vessels (vein lateral to the artery) does not require vascular realignment or possible ligation and division of the internal iliac artery, although on the left side it might. Currently, inferior vena cava can be a recipient site for venous anastomosis site with the advantage of easy exposure and high outflow venous system of IVC compared with the iliac vein limiting the postoperative venous thrombosis.

When the donor portal vein is used for anastomosis, the head of the pancreas is in a cephalad position in the mid-abdomen. The vast majority of pancreas grafts with portal vein drainage are placed so that the donor portal vein connects to the recipient proximal superior mesenteric vein (SMV) or to the SMV's main feeding vessel. A hole in the small bowel mesentery is made so that the arterial Y-graft traverses the shortest distance to the arterial inflow (most commonly, the right common iliac artery). This distance may be as long as 6 cm.

Korea

Midline laparotomy was performed in the recipient. In the pelvic space, the iliac vein and artery were mobilized to avoid the tension of graft vessel anastomosis. The graft portal vein was anasto-

mosed end-to-side to the recipient's external iliac vein or distal IVC, which is preferred in use currently. The superior mesenteric and splenic arteries reconstructed by donor iliac arterial Y-graft were anastomosed to the recipient's common iliac or external iliac artery. Drainage of the exocrine pancreatic secretions was performed either by bladder or by enteric drainage.

In the case of bladder drainage, the pancreas graft duodenum was placed in a caudal position on the right side of the pelvis with an arterial anastomosis to the iliac artery and venous anastomosis to the iliac vein. The pancreas graft duodenum was then anastomosed to the urinary bladder using two-layer side-to-side hand-sewn sutures.

In the case of enteric drainage, the head of the pancreas graft was placed in a caudal position. Vascular anastomosis of graft portal vein is created to external iliac vein or distal IVC, and pancreas arterial Y-graft to external or common iliac artery. The pancreas graft duodenum was anastomosed to jejunum or ileum by the side to side fashion or Roux en Y limb of jejunum by the end to side fashion.

In SPK, a kidney transplant is performed in the left pelvic site initially, then a pancreas transplant in the right pelvis. The graft distal duodenum is shorted at the level of the junction between the second and third portion of the duodenum by GIA stapler. After meticulous hemostasis, JP drainage is inserted around the graft pancreas, followed by abdominal wall closure [2] (Fig. 10).

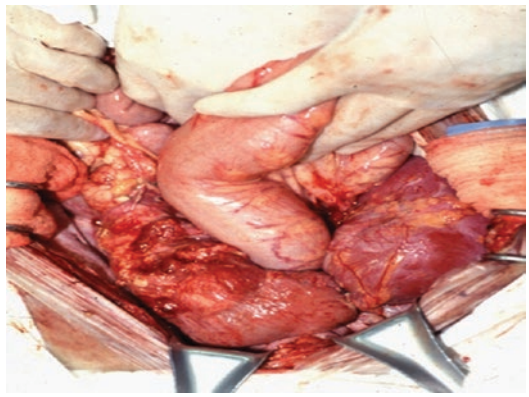


Fig. 10 Simultaneous kidney and pancreas transplantation with bladder drainage (AMC)

Japan

In the case of SPK, it depends on the facility whether to perform a pancreas transplant or a kidney transplant first. The pancreas is transplanted into the right iliac fossa in the abdominal cavity or retroperitoneal space. The external iliac artery and the external iliac vein are sufficiently isolated, and the internal iliac vein is cut if necessary to mobilize the external iliac vein. Venous anastomosis is performed with a running suture between the portal vein of the pancreas graft and the external iliac or common iliac vein of the recipient. The most important point is how to prevent venous thrombosis, and this anastomosis requires the most attention. The points are to secure a sufficient anastomotic opening without any twisting. We usually use 5-0 monofilament nonabsorbable threads for venous anastomosis. Subsequently, an arterial anastomosis between the Carrel patch (or Y-graft) and the external or common iliac artery of the recipient is performed with a running suture using a 5-0 monofilament nonabsorbable thread. In our institution, transposition of iliac artery and vein are frequently performed for the prevention of pressure of graft's artery to graft's vein. After the arteriovenous anastomosis is complete, the blood flow in the pancreas graft is resumed by releasing the vascular clamp. After resuming the blood flow in the pancreas graft, the bleeding from the pancreas graft should be carefully stopped because we use 200 units/h of heparin intraoperatively to prevent venous thrombosis. Also, the pancreas graft is warmed with warm saline. Intestinal drainage or bladder drainage is used for pancreatic juice drainage, but in most recent cases, intestinal drainage is preferred. Overall, 87.7% is intestinal drainage in Japan. The anastomosis between the graft's duodenum and small intestine is performed by the side to side anastomosis or a Roux-Y anastomosis, and we use a 4-0 monofilament absorbent thread (Fig. 11). After confirming hemostasis, two Penrose drains are inserted into the abdominal space near the pancreas graft and connected to J-VAC® closed drainage system. The wound is closed in three layers suture technique.

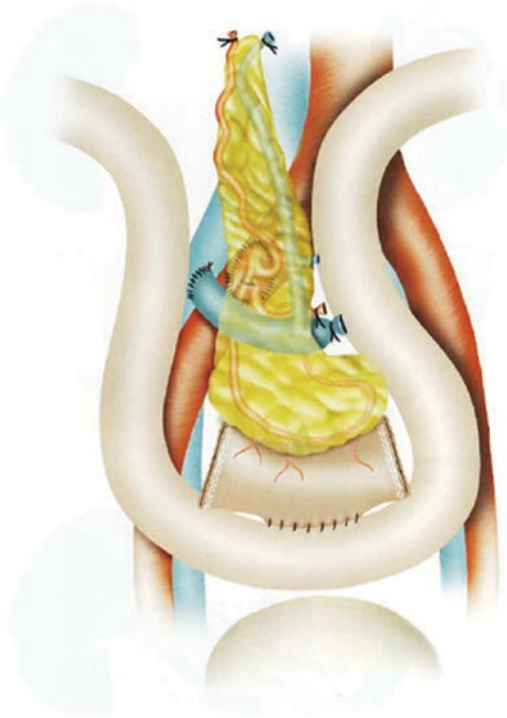


Fig. 11 Technique of pancreas transplantation using enteric drainage (Japan)

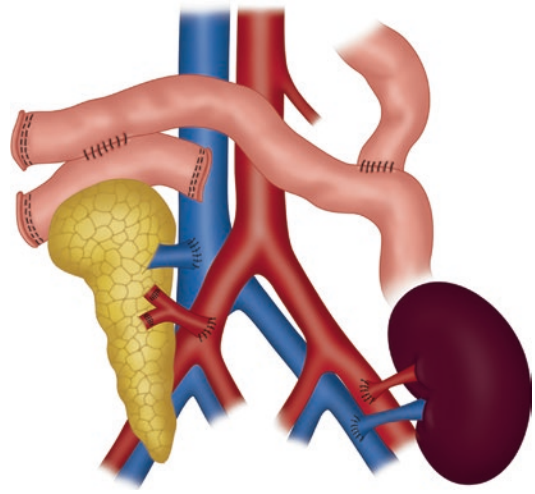


Fig. 12 Pancreas and kidney transplantation for simultaneous pancreas-kidney (SPK) or pancreas-after-kidney (PAK) transplantation. The pancreas graft portal vein is anastomosed to distal inferior vena cava, a systemic venous drainage, and graft duodenum is anastomosed to a roux-y limb of jejunum, an enteric drainage. Retroperitoneally, the pancreas graft is usually placed on the right side. The kidney is placed in the left, opposite, side (Taiwan)

Taiwan

Pancreas transplantation in Taiwan can be categorized mainly into simultaneous pancreas-kidney (SPK) transplantation, pancreas-after-kidney (PAK) transplantation, pancreas-before-kidney (PBK) transplantation (Fig. 4), and pancreas-after-liver (PAL) transplantation (Figs. 12–15). Ideally, a combined kidney and pancreas transplantation should be recommended for patients with severe diabetes and end-stage renal disease. Therefore, SPK is the most common type of pancreas transplantation, accounting for 79% of procedures in the USA in 2016 [2]. Both organs are usually procured from a single deceased organ donor. PAK transplantation is offered to diabetic patients who have already undergone a kidney transplantation. PTA is offered to candidates without end-stage renal disease but with frequent, acute, and potentially life-threatening complications of diabetes such as ketoacidosis, hypoglycemia unawareness, and incapacitating problems with insulin therapy. For this group, pancreas transplantation

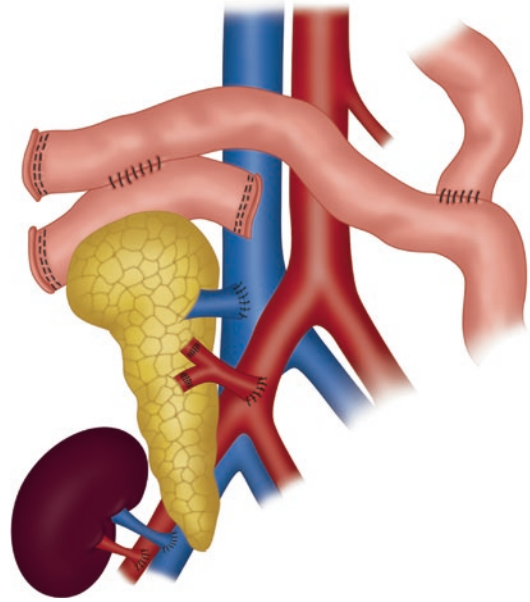


Fig. 13 Ipsilateral placement of pancreas and kidney grafts for simultaneous pancreas-kidney (SPK) or pancreas-after-kidney (PAK) transplantation. The pancreas graft portal vein is anastomosed to distal inferior vena cava, a systemic venous drainage, and graft duodenum is anastomosed to a roux-y limb of jejunum, an enteric drainage. Retroperitoneally, the pancreas graft is usually placed on the right side. The kidney is also placed on the right side (Taiwan)

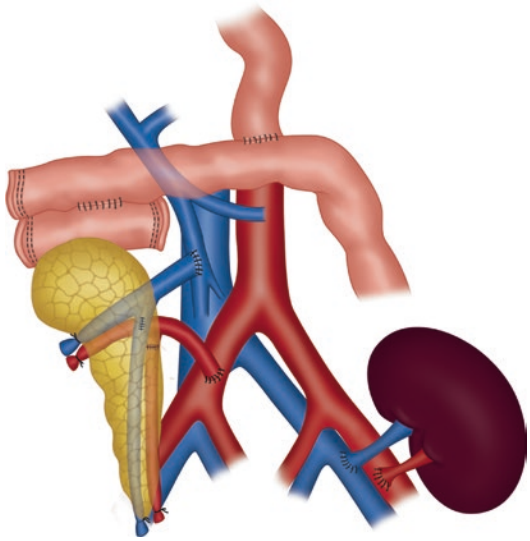


Fig. 14 Pancreas and kidney transplantation for simultaneous pancreas-kidney (SPK) or pancreas-after-kidney (PAK) transplantation. The pancreas graft portal vein is anastomosed to a big tributary of the superior mesenteric vein, a portal venous drainage, and graft duodenum is anastomosed to a roux-y limb of jejunum, an enteric drainage. Retroperitoneally, the pancreas graft is usually placed on the right side. The kidney is placed in the left contralateral, side (Taiwan)

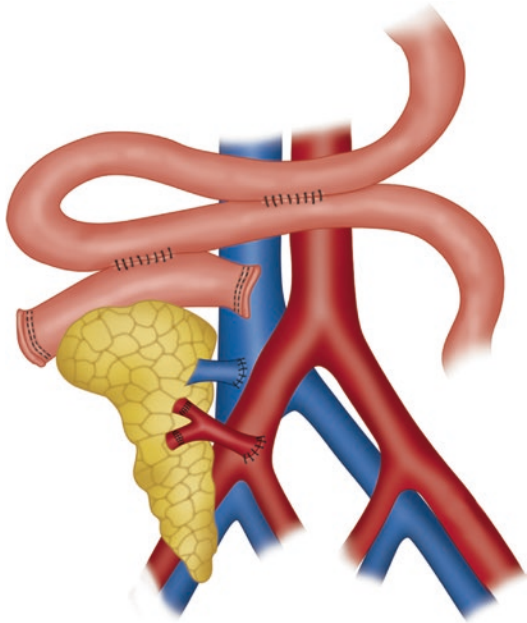


Fig. 15 Solitary pancreas transplantation for pancreas transplant alone (PTA), pancreas-before-kidney (PBK) or pancreas-after-liver (PAL). The pancreas graft portal vein is anastomosed to distal inferior vena cava, a systemic venous drainage, and graft duodenum is anastomosed to a roux-y limb of jejunum, enteric drainage (Taiwan)

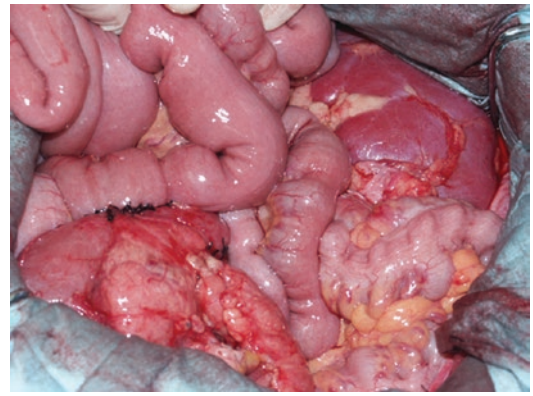


Fig. 16 The first simultaneous pancreas-kidney (SPK) transplantation was performed at Taipei Veterans General Hospital on September 19 of 2003. The pancreas graft was placed in the right side. The kidney was placed on the left, opposite side (Taiwan)

would be life-saving but must be weighed against the untoward risks of life-long immunosuppression [28]. The first simultaneous pancreas-kidney (SPK) transplantation was performed at Taipei Veterans General Hospital on September 19 of 2003 (Fig. 16). In Taiwan, it is very competitive for a uremic patient to have a decreased kidney graft because there are always more than 7000 uremic patients waiting for kidney transplantation [3]. Moreover, the waiting lists for pancreas and kidney transplantation are separate. PTA (48%, 73/151) is the most common type of pancreas transplantation, followed by SPK (24%, 36/151) transplantation, PBK (16%, 24/151), PAK (11%, 17/151), and PAL (1%, 1/151).

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Peri- and Postoperative Management (General Care, Immunosuppressant, Graft Monitoring, Etc.)

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Recipient

General

At the Time of Admission

If on preoperative admission, the significant unexpected disease is identified at the level of the iliac arteries, the patient may require repair (bypass, angioplasty) during the transplant procedure, or the transplant should be deferred until all lesions have been corrected [1].

As with arterial evaluation, a complete history of venous catheterizations and anomalies should also be obtained to avoid undue delays intraoperatively with central venous catheter placement.

In uremic candidates, the need for hemodialysis must be determined prior to transplantation. In this context, knowledge of dialysis status and preoperative fluid management is vital. Special attention is given to recipient potassium and fluid overload. Adequate pretransplant hemodialysis not only simplifies perioperative management but also reduces the risk of hyperkalemia during surgery. The duration of pretransplant hemodialysis should be discussed by the transplant surgeon and nephrologist to minimize the surgical risk as well as minimize graft cold ischemic time so as not to compromise graft function [2].

If the patient is on peritoneal dialysis, peritonitis should be ruled out by gram stain examination.

Another important area of evaluation is glucose control, and close monitoring of blood sugar is mandatory.

One-third to one-half the usual dose of insulin is recommended while the patient is NPO.

This period usually ranges from a minimum of 3–5 h due to the time required by the histocompatibility laboratory to complete the crossmatch.

The preoperative orders should be complete and the results of all admission tests reviewed. Ample time is available for a preoperative shower with Hibiclens or betadine. A rectal enema should be given early to ensure evacuation of fecal content. Dialog with the patient regarding the expected risks and benefits of the surgical procedure must take place and conclude with the signing of consent.

Intraoperative Care

Successful intraoperative management depends on cooperation and teamwork between the surgeons, anesthesiologists, and nursing staff involved.

A nasogastric tube and bladder catheter should be placed immediately.

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Pulmonary artery catheters and arterial lines are most commonly used in recipients with compromised cardiovascular status.

Prior to the incision, appropriate antibiotics and immunosuppressants are administered per protocol. Fluids are administered to maintain a CVP in the 12–15 mmHg range. Most centers prefer colloid to minimize fluid overload.

Blood glucose is monitored hourly and usually controlled with an insulin drip; blood glucose levels should be maintained at 110–150 mg/dL. In nonuremic, PAK or pancreas transplant alone (PTA) recipients, 30 U/kg of IV heparin is recommended by some centers to prevent pancreatic vascular thrombosis and is given just prior to reperfusion of the pancreas [3, 4]. Simultaneous pancreas and kidney recipients are rarely heparinized at the time of revascularization. Before revascularization, diuretics are frequently given to promote early kidney graft function in SPK recipients and reduce pancreas graft swelling.

Upon completion of the procedure, the abdomen is copiously irrigated with antimicrobial solutions (e.g., containing bacitracin and amphotericin). Closed-suction drains are rarely placed.

At the time of organ reperfusion, bleeding from the allograft may be problematic, especially from the pancreas. Adequate volume status is imperative at this time point. Aggressive use of blood products may be required, so adequate communication and preparation by the anesthesiology and nursing staff must ensure that immediate infusion can begin if necessary.

Immediate Postop

Pancreas transplantation is a life-altering procedure that, given its long-term goals, is actually lifesaving. To achieve success in stabilizing the often deadly secondary complications of diabetes, the prolonged function of a pancreatic allograft depends on a smooth, uncomplicated postoperative course.

Many pitfalls can confront the transplant team and recipient in the early postoperative period. However, by carefully monitoring every aspect of the recovery phase, most of the dangers can be avoided. In this phase of recovery, three major processes are evolving: The recipient is undergoing the physiological response to surgical trauma, the transplanted organs are in a varying degree of reperfusion injury/recovery (including reperfusion pancreatitis), and the recipient is now immunosuppressed.

During the postanesthesia care unit or intensive care unit, hemodynamic and ventilatory assessment is paramount during recovery. The first 24–48 h posttransplant are the most crucial. The goal is to support the patient's body systems in maintaining a steady state during a period when fluid shifts and medical management are most difficult. Judicious use of blood products is a necessary component, maintaining a Hgb > 10 mg/dL [5]. For pancreas recipients with an underlying coagulopathy or liver dysfunction, fresh frozen plasma may be needed. Rarely, desmopressin acetate (DDAVP) is required to correct platelet dysfunction resulting from uremia. In extreme cases, cryoprecipitate may be needed for consumptive coagulopathies resulting from hemorrhage or disseminated intravascular coagulation [4, 5]. Obviously, blood pressure control is closely related to fluid and electrolyte management. Both hypo- and hypertension must be avoided. Hypotension increases the risk of arterial graft thrombosis, especially in the immediate postoperative period. Further, a low-flow state may enhance thrombus formation (either arterial or venous) at the site of a fresh anastomosis and thus increase the risk of graft loss. Prolonged hypertension, if severe enough, can also induce cerebral vascular events or increase cardiac demand, resulting in ischemia and infarction. Maintaining a systolic pressure between 120 and 160 mmHg for the first 24 h safely maintains graft perfusion while minimizing the risk of a serious adverse event. The use of renal-dose dopamine remains controversial. For those whose blood pressure is extremely difficult to control, an α-1-antagonist may also be part of the regimen. If necessary, IV labetalol or metoprolol on scheduled dosing is safe until oral beta-blockers are tolerated. Similarly, sublingual or transcutaneous clonidine can be used. IV nitroglycerin or nitroprusside may be necessary for refractory hypertension. Calcium channel blockers can also be started early [6–8]. However, the choice of agent and dose must be carefully selected and monitored due to potential side effects. For example, verapamil interacts with calcineurin

inhibitors and may increase serum levels. Angiotensin-converting enzyme inhibitors are usually withheld in the early postoperative period. However, ACE inhibitors may have a role in blood pressure management once stable graft function is obtained [9]. Commonly, pancreas recipients with the secondary complication of insulin-dependent diabetes mellitus have pronounced autonomic neuropathy, which can produce labile blood pressures, especially upon standing. If orthostatic hypotension remains problematic, fludrocortisone or mineral corticoids may be warranted. In long-standing DM patient, coronary and peripheral vascular compliance is compromised. Therefore, individual recipients may have a narrower "window" of optimal volume status compared to nondiabetic, nonrenal failure patients. In most cases, a CVP between 8 and 14 mmHg is adequate. The maintenance solution commonly used following pancreas transplantation is 1/2NS with 10 mEq/HCO_3. We prefer to avoid dextrose in the immediate postoperative period. By tradition, bicarbonate replacement has been especially important for recipients with bladder drainage of pancreatic exocrine secretions. We prefer to avoid dextrose in the immediate postoperative period. A dextrose infusion may unnecessarily prolong the use of an insulin drip. When in use, an insulin drip should be infused at a rate to keep the blood sugar less than 150 mg/dL. Aggressive use of insulin (blood sugars <100 mg/dL) early on in the postoperative period is not recommended due to the risk of over-administration [10]. Maintenance fluids are usually infused at an In = Out rate once hemodynamic stability is obtained. I=O infusion is usually maintained for the first 24 h, incorporating the above guidelines with CVP monitoring. Because of this approach, dextrose is not added in the maintenance or replacement fluids unless the blood glucose level drops below 100 mg/dL [1]. In kidney and pancreas transplant patients where the creatinine plateaus early or in situations of a concerning cardiac history, replacement is adjusted to ½ cc/cc output. After the first 24 h, most patients are converted to a straight rate of IV fluid ranging from 75 to 150 cc/h depending on the recipient's size and volume status. Pancreas after kidney and PTA recipients usually do not have large fluid requirements and in general are more stable with respect to volume status in the uncomplicated postoperative course. However, even enteric-drained SPK recipients have an acidosis that requires bicarbonate replacement in the immediate postoperative period. By tradition, bicarbonate replacement has been especially important for recipients with bladder drainage of pancreatic exocrine secretions. Bladder-drained recipients usually require long-term, oral bicarbonate supplementation. When delayed graft function occurs following SPK transplantation potassium, calcium, and phosphorus balance may become problematic. Early dialysis may be necessary for hyperkalemia. For patients who are hypokalemic, potassium is administered on a supplemental basis. Ionized calcium levels should be followed to maintain an appropriate calcium state. Further, magnesium levels should be maintained above 2 mg/dL according to current cardiac recommendations. Early stabilization of potassium, calcium, and magnesium will minimize cardiac irritability and help reduce risks for a cardiac event. Although many SPK recipients may have had problems with hyperphosphatemia while on dialysis, hypophosphatemia usually ensues with good renal function.

In an inherently immunocompromised diabetic patient, prophylactic coverage against micro-organisms is paramount during the perioperative period. Retrospective studies had demonstrated that pancreas recipients are at high risk for losing a second pancreatic allograft to the same infectious agent when their first graft was lost to infection [11–14]. Broad-spectrum agents covering Gram-negative, Gram-positive, and anaerobic bacteria are recommended. Various single agents or combinations are available and should be given over the first 24–48 h posttransplant. Recipients with positive urine cultures (from preoperative specimens) or positive intraoperative duodenal stump cultures should have antibiotic coverage for 3–7 days [1]. Due to the duodenal anastomosis in pancreas transplantation and the potential contamination of the operative field with small-bowel contents, many centers also recommend antifungal prophylaxis with fluconazole [15] (Table 1). Cytomegalovirus (CMV) prophylaxis is recommended for any positive combination of a donor-recipient pair. However, when antilymphocyte therapy is utilized, CMV

Table 1 Recommendation s for perioperative antibiotics by organ transplant type

Organ type		IDSA/ASHP/SIS/ SHEA guidelines	An alternative approach[b]	Intraoperative redosing	Postoperative dosing	PCN-allergic	Duration postoperative
Renal		Single first-generation cephalosporin (eg. œfazolin)	Cefazdin 2 g IV	Every 4 h	Cefazdin 2 g q8h	Vancomycin[c] or dindamycin 900 mg IV plus gentamicin 5 mg/ kg IV	≤24 h
Pancreas, pancreas-kidney		Single first-generation cephalosporin (eg. œfazolin)	Ampicillin-subactam 3 g IV plus fluconazole 400 mg IV	Every 2 h (fluconazole not redozed)	Amplicillin-subactam 1.5 g q6h	Vancomycin[c] or clindamycin 900 mg IV and gentamicin 5 mg/kg IV and fluconazole 400 mg IV	Anfibacterial ≤48 h, Antifungal × 1 dose, unless high risk in which case ≤14 days
Liver		Third-generation cephalosporin plus ampicillin or pip eracillin-tazobactam alone	Ampicillin-subactam 3 g IV ± fluconazole 400 mg IV × 1	Every 2 h (fluconazole not redosed)	Ampicillin-subactam 1.5 g q6h	Levofbxacin[a] 750 mg IV plus vancomycin[c] ± fluconazole 400 mg IV × 1	Anfbacterial ≤24 h Antifungal × 1 dose
Intestinal/ mulivisceral		None given	Vancomycin[c] plus œfepime 2 g IV plus metronidazole 500 mg IV plus fluconazole 400 mg IV or vancomycin[c] plus piperacillin-tazobactam 4.5 g IV plus fluconazole 400 mg IV	Every 4 h (fluconazole not redosed)	Cefepime 2 g q8h, metronidazole 500 mg q8h, fluconazole 400 mg q24h, piperacillin-tazobactam 4.5 g q6h, Vancomycin per weight/ GFR[c]	Vancomycin[c] plus levofloxacin[a] 750 mg IV plus metronidazole 500 mg IV	≤72 h; if infected mesh or fistulas, then extend to 7 days
Heart	With prior VAD	Single first-generation cephalosporin (eg, œfazolin)	Vancomycin[c] plus either ceftriaxone 1 g IV or cefepime 2 g IV	Every 4 h	Vancomycin per weight/ GFR[c], œftriaxone 1 g q24h, œfepime 2 g q8h	Vancomycin[c] plus levofloxacin 750 mg IV q24h	≤48 h
	Without prior VAD	Single first-generation cephalosporin (eg, œfazolin)	Vancomycin[c] plus cefazolin 2 g IV	Every 4 h	Cefazolin 1 g q8h, Vancomycin per weight/ GFR[c]	Vancomycin[c] plus levofloxacin 750 mg IV q24h	≤48 h
Lung		Single first-generation cephalosporin (eg, œfazolin)	Vancomycin[c] plus œftriaxone 1 g IV or cefepime 2 g IV	Every 4 h	Cefepime 2 g q8h, Vancomycin per weight/ GFR[c]	Vancomycin[c] plus levofloxacin 750 mg IV q24h	≤72 h

GFR glomerular flration rate, *IV* intravenous, *q* every

[a]With abdominal orgen transplarts, any fluoroquinolone may be used in PON-alergic patients

[b]All dosing regimens should be modified based on the patient's renal and liver function

[c]Vancomydin doses should be calculated based on the patient's weight and renel function

prophylaxis is almost always administered. Gancyclovir and, more recently, valganciclovir are at present the antiviral agents of choice in pancreas transplantation and can first be initiated intravenously or per nasogastric tube in the immediate postoperative period, and then orally when the patients intolerant to gancyclovir may tolerate valacyclovir, which provides adequate prophylaxis against CMV infection in renal only transplantation. Most centers begin sulfamethoxazole/trimethoprim immediately postoperatively and continue long-term prophylaxis against *Pneumocystis carinii* and noncardiac infections [16].

Any missing immunizations should be done. Hepatitis B vaccine should be given to candidates who are surface antibody negative. Pneumococcal vaccine should be given to everyone unless it was received within the last 5 years. Keep in mind, however, that vaccinations have reduced efficacy in patients with kidney failure. Also, live vaccines should be avoided in immunosuppressed individuals (e.g., in a previous kidney transplant recipient who is now being evaluated for a pancreas transplant) [1, 17].

There is currently no consensus on the optimal strategy for the prevention and management of thrombosis [18]. Color Doppler ultrasonography (US) at 24 & 72 h after grafting [19] is performed, however, misinterpretation of thrombosis is CT (retrospective analysis) also reported. Misinterpretation of initial US findings by a second radiologist [20]is reported. A severe thrombosed graft is only salvageable within a short time of initial thrombosis formation, highlighting the importance of close postoperative monitoring [21]. Postoperative pancreatic allograft thrombosis monitoring and management algorithm were reported in which a new CT grading system was suggested, and use of therapeutic anticoagulation was decided according to the severity of the thrombosis [18].

*C*ontroversy remains regarding the necessity for early postoperative anticoagulation, in particular in uremic SPK recipients. The rationale for the use of anticoagulation is to avoid early graft thrombosis, which usually results in graft pancreatectomy. Thus, it is better to re-explore the recipient for bleeding (which has little impact on graft function) than for thrombosis (which causes graft loss) [1]. Considering the high thrombosis rate in PT and its related graft loss, postop use of anticoagulants has a rationale. Low-dose heparin showed a trend toward a protective benefit for early graft loss resulting from thrombosis [22]. The incidences of graft thrombosis reported in the literature range from 5.5% to 27% [22–26]. Causes of vascular thrombosis in PT are the pancreas inherently low microvascular flow state, technical failure, early acute rejection and other multifactors like hypercoagulable state associated with dyslipidemia [19, 27]. Pathogenesis of vein thrombosis can be explained by Virchow's triad [1].

The risk factors for thrombosis have to be considered, such as those of donor, recipient, and others, but acute rejection and pancreatitis were important factors [18]. Prophylactic use of anticoagulants was reported in all the cases, but the dose of anticoagulants depends on the type of PT, such as PTA or segment living PT, and the presence of thrombosis [23]. Indication for IV heparin included all PTA and pre-emptive SPK, history of thrombophilia, or clotting disorder in the recipient, CIT (>15 h), extended donor arteria, or history of pancreas graft thrombosis [27].

Anticoagulants therapy is indicated in some centers only when signs of venous thrombosis are observed [28]. Most centers advocate low-dose IV (partial thromboplastin time [PTT] no greater than 1.5× normal) or subcutaneous (SQ) heparin for nonuremic PTA and PAK recipients After segmental pancreas transplantation from a living-related donor, initial systemic heparinization followed by coumadin therapy (for up to 6 months) is recommended.

Low-dose aspirin is then overlapped for 2 days prior to cessation of heparin and continued long-term upon hospital discharge. If an IV heparin drip is used postoperatively, a delay of approximately 4 h after surgery may be necessary to determine hemodynamic stability. Frequent monitoring of coagulation parameters is required to avoid overcoagulation. Early use is recommended within 1 day postoperative period, because early thrombosis occurs within 6 weeks,

and usually within 24 h of transplantation [21]. There is no strict rule for the duration of use of anticoagulants, but a few months is recommended [20, 23].

There is currently no consensus on the optimal strategy for the prevention and management of vascular thrombosis. Arterial signal abnormalities, such as absence or reversal of diastolic flow in US require urgent operative intervention [20]. Percutaneous thrombectomy or operation is suggested in thrombosis >50% of the lumen or >2/3 of the length [24]. Interventions at salvaging the graft may be pharmacological, surgical, or by use of percutaneous interventional radiology. Noncomplex thrombosis (i.e., partial or those isolated to the SV) can be managed with systemic anticoagulation [21, 26]. If thrombosis is diagnosed early enough, surgical salvage may lead to a successful graft rescue rate as high as 67% [26]. However, rescue rate as high as 75% is reported by percutaneous interventional radiologic procedures [26]. Partial thrombosis required therapeutic heparin anticoagulation, but complete vascular graft thrombosis required graft removal in 7/61 [29]; therefore a preventative approach is more desirable [17].

Early graft function (pancreas or kidney) can be monitored by various means. Most centers adopt a protocol that combines laboratory as well as imaging studies to obtain a level of certainty with regard to adequate organ function. Declines in serum blood urea nitrogen, creatinine, amylase, and lipase levels, along with normal blood sugar levels, are all required to assess good graft function in SPK [26, 27]. Some centers routinely obtain sonograms or nuclear scintigraphy on all recipients. Ultrasonography is usually the first mode of imaging utilized to evaluate organ dysfunction, as indicated by an unexpected laboratory value or physical finding [30]. Ultrasonography can determine vascular abnormalities, ductal, or ureteral obstruction, and the presence of periorgan fluid collections. The addition of a renal nuclear study is helpful for renal evaluation. However, nuclear scintigraphy is not as useful for the evaluation of the pancreas. As portal-enteric drainage of the pancreas becomes more popular, imaging of the pancreas likewise has become more difficult, given the medical and deep position of the allograft. Computerized axial tomography scan imaging of a portal drained pancreas can be helpful in determining peripancreatic fluid collections, pancreatic necrosis, and possibly duodenal obstruction or leak [31]. The role of magnetic resonance imaging/angiography as well as positron emission tomography scanning remains to be determined. Creatinine clearance and urine protein, C-peptide levels, and HbAlc can be periodically obtained to assess long-term graft function. For some pancreas transplant recipients, blood sugar levels never fully normalize despite what is believed to be adequate insulin and C-peptide levels. A few hypotheses attempt to explain the cause of persistent hyperglycemia or glucose intolerance following pancreas transplantation. First, the diabetogenic effects of steroids and calcineurin inhibitors(especially tacrolimus) are thought to play a significant role [32]. Second, some recipients have developed insulin resistance and are confronted with a situation no different from type 2 (adult-onset) diabetes mellitus. Third, for portal-enteric-drained pancreas recipients, the hepatic "first pass" of insulin may offset the hyperinsulinemic effects of systemically venous-drained pancreases. In other words, systemic venous drainage possibly counteracts the diabetogenic effects of immunosuppression or overrides the receptor defect occurring with insulin resistance. Thus, recipients with portal drained pancreases may have a tendency to ward slightly higher glucose levels. Only a few cases of recurrent insulitis resulting in pancreatic graft failure have been described. For pancreas recipients with bladder-drained exocrine secretions, urinary amylase levels can be monitored. An analysis of a 12- or 24-h urine collection in which urinary amylase levels have declined 50% or more from baseline is suggestive of rejection or pancreatitis [33, 34]. Finally, biopsies are warranted either percutaneously via the US or computed tomography (CT) guidance or transcystoscopically, assisted by US guidance [35]. Serum amylase and lipase levels provide additional means for following pancreas function, especially for enteric drained grafts. However, these markers lack the sensitivity and specificity of urinary amylase. Serum human anodal trypsino-

gen (HAT) has been shown to complement serum amylase and lipase levels in the determination of graft dysfunction [36]. But, few laboratories are equipped to monitor this factor. In the immediate postoperative period, serum amylase and lipase levels may be significantly elevated despite good glucose control and endocrine function. These early elevations usually result from reperfusion injury and resolve spontaneously. Some centers use somatostatin analogs to minimize the pancreatic inflammatory response. Use of this agent is in general reserved for the intraoperative findings of restrictive pancreatic edema, subcapsular hematoma, or profound duodenal edema. Early rejection during the initial hospitalization appears to be decreasing in frequency as immunosuppressive regimens evolve. The sentinel sign of rejection in SPK recipients still remains a rise in serum creatinine. A percutaneous renal biopsy with US guidance is warranted.

In some SPK recipients, serum amylase or lipase levels may rise while creatinine levels remain stable. In such situations, a transplant renal biopsy is still warranted, especially if an enteric-portal drained pancreas is present [37]. It has been shown, however, that in an SPK recipient, one organ may have independent rejection while the other organ remains rejection free. For PTA and PAK recipients, the ability to follow rejection is somewhat more difficult. Further, if serum or urinary amylase levels are suggestive of rejection, the option of a transcystoscopic, transduodenal biopsy is still available should the pancreas not be approachable via US or CT.

Patient hemodynamics usually stabilizes by the close of the first 48 h while graft function steadily improves [1]. Following this phase of recovery, the recipient can be transferred to the transplant ward for less intense nursing care and monitoring. The nasogastric tube placed intraoperatively can usually be removed when signs of bowel function have returned. Given the high incidence of autonomic neuropathy in this patient population, many recipients alternate between constipation and diarrhea during the early postoperative period. With enteric drainage, upper gastrointestinal bleeding may occur as bowel function returns. Such hemorrhage usually results from the duodenojejunal anastomosis and should be self-limited. However, transfusion may be required; only rarely is surgical intervention required. Hemorrhage from the duodenojejunostomy can be avoided by the diligent preparation of the enterotomies with completion of the anastomosis in a hemostatic, two-layer, hand-sewn fashion. The timing of Foley catheter removal varies according to surgeon preference, usually within 1–3 weeks posttransplant. The recipients with thin bladder walls or tenuous anastomosis will probably benefit from longer decompression of the bladder. Similarly, recipients with known neurogenic bladders may need to wait until they are capable of self-catheterization prior to Foley removal. Patients with extremely small bladders may require a short period of "bladder training" prior to catheter removal. Typical protocols call for clamping for half-hour periods, steadily increasing to no more than 4 h. The clamp is released as soon as the patient experiences a sensation of fullness or suprapubic pain. The training process may take 3–5 days and possibly more. A low-pressure cystogram prior to catheter removal can be performed to determine the presence of a bladder leak in some cases [38]. The patient should be encouraged to be out of bed and ambulate no later than postoperative day 3. Poor wound healing secondary to long-standing diabetes and immunosuppression is always a concern in this patient population. For a noninfected wound, skin staples remain for 2–3 weeks prior to removal. In most cases, oral intake can begin by postoperative day 4 or 5 and advance as tolerated. Most centers now boast that pancreas transplant recipients are discharged by the end of the first week-a vast change from a decade ago, when hospitalizations of a month or more were common. The patient should initially obtain laboratory studies three times a week. If the patient lives a significant distance from the transplant center, temporary local lodging is recommended for about 2 weeks before returning home. In the development of hematuria in the bladder-drained pancreas, initiation of continuous bladder irrigation through a three-way Foley catheter. The most common cause of hematuria may resolve with increased bicarbonate sup-

plementation. Enteric conversion may be required for refractory irritation.

Type 1 diabetes recurrence (T1DR) is traditionally considered very rare in immunosuppressed recipients of pancreas grafts from organ donors, representing the majority of recipients, and immunological graft failures are ascribed to chronic rejection. George et al. have been performing simultaneous pancreas-kidney (SPK) transplants for over 25 years and find that 6–8% of our recipients develop T1DR, with symptoms usually becoming manifest on extended follow-up. T1DR is typically characterized by (1) variable degree of insulitis and loss of insulin staining, on pancreas transplant biopsy (with most often absent), minimal to moderate and rarely severe pancreas, and/or kidney transplant rejection; (2) the conversion of T1D-associated autoantibodies (to the autoantigens GAD65, IA-2, and ZnT8), preceding hyperglycemia by a variable length of time; and (3) the presence of autoreactive T cells in the peripheral blood, pancreas transplant, and/or peripancreatic transplant lymph nodes. There is no therapeutic regimen that so far had controlled the progression of islet autoimmunity, even when additional immunosuppression was added to the ongoing chronic regimens [39–41].

The most critical period to obtain adequate immunosuppressive levels occurs within the first 24–48 h. Most centers give the first doses of immunosuppression within the few hours just prior to the transplant and then continue intraoperatively. Quadruple immunosuppression is typically utilized for induction therapy, consisting of an anti-T-cell agent (first administered intraoperatively), a calcineurin inhibitor, an antimetabolite, and steroids. Tacrolimus has become the calcineurin inhibitor of choice. Mycophenolate mofetil (MMF) has virtually replaced azathioprine as the antimetabolite agent of choice. While most centers use antilymphocyte preparations (antithymocyte globulin [ATG], OKT3, or thymoglobulin), others have adopted the use of synthetically structured, chimeric-antibody preparations designed to block interleukin-2 (IL-2) receptor (daclizumab, basiliximab) [42–44]. The term “induction therapy” is used to describe antilymphocyte antibodies that are parenterally administered for a short course immediately posttransplant. The rationale for using induction immunotherapeutics pertains to the agents’ potent anti-T-cell immunosuppressive properties. In this context, induction therapy is used in conjunction with maintenance agents for the purpose of minimizing the risks of early rejection episodes, often with aims to accelerate renal allograft function. ATGAM, Zenepax, and Simulect have been approved by the US Food and Drug Administration (FDA). In addition, OKT3 and thymoglobulin are used for induction therapy and are effective for the treatment of acute allograft rejection. Campath is an FDA-approved agent has been described for induction in kidney transplantation and used in pancreas transplant as well. Most centers agree that early levels of tacrolimus should be between 10 and 15 ng/mL with antibody induction. Mycophenolate mofetil can be administered either IV or orally and titrated to 1.5–3 g/day (in two divided doses) depending on gastrointestinal tolerance. Calcineurin inhibitors should be reduced dramatically or held when ATN or delayed graft function (DGF) has occurred. High doses of steroids are administered intravenously during the first few days perioperatively and are usually tapered to 20–30 mg/day by the end of the first 7–10 days. By 6 months, most recipients should have their prednisone tapered to 5 mg or less. Because pancreas transplantation is regarded to be life-enhancing rather than lifesaving, over immunosuppression should be avoided. Solid organ transplantation would not have become the treatment of choice for patients with end-stage organ failure without the concurrent development of potent immunosuppressive drugs as a maintenance treatment. In the late 1970s, the discovery of the calcineurin inhibitor, CSA by Borel et al. [45], propelled solid organ transplantation into a new era and marked the beginning of increasingly successful extrarenal, including pancreas transplantation. By the early 1980s, it was recognized that the combination of cyclosporine, azathioprine, and steroids resulted in the best graft outcome. Currently, triple-drug immunosuppression (now with Tacrolimus and MMF) has

remained the gold standard for maintenance therapy in pancreas transplantation. In the late 1990s, in selected pancreas recipient categories, triple immunosuppression for maintenance therapy was sometimes abandoned by steroid withdrawal or avoidance. The principles of maintenance therapy for pancreas recipients are the same as for other solid organ recipients. But, because of the high immunogenicity of (especially solitary) pancreas transplants, the amount of immunosuppression required is more than for kidney, liver, or heart transplants [1].

Early rejection during the initial hospitalization appears to be decreasing in frequency as immunosuppressive regimens evolve [46].

In most cases of pancreas graft rejection, clinical symptoms are subtle or nonexistent. Only 5–20% of patients with pancreas graft rejection have clinical symptoms [1]. Fever as a clinical symptom of rejection was common in the azathioprine era, but now, because calcineurin inhibitors are used for maintenance therapy, fever is uncommon. Even in the presence of clinical symptoms, the diagnosis of rejection, if a biopsy is not obtained, is usually a composite decision based on clinical and laboratory criteria.

Rejection markers can be determined in the serum or urine. For bladder-drained transplants, urine amylase has been the most widely used rejection marker. For enteric-drained transplants, a combination of serum amylase/lipase has been used. With the successful development of safe, percutaneous biopsy techniques in the early 1990s, it is increasingly used as a definitive diagnostic tool.

It appears that based on uni- and multivariate analyses of US IPTR/UNOS and single center data, SPK transplants can be done with little regard for HLA matching. However, in the PTA and PAK categories, HLA matching has remained an important outcome factor.

Acute pancreas rejection episodes are usually treated with a 7- to 14-day course of mono- or polyclonal antibody therapy [47].

In the immunologically more favorable SPK category, pancreas rejection episodes graded as minimal or mild can be reversed with steroid boluses, recycling of the steroid taper, or increases in calcineurin or target of rapamycin inhibitor dosages. Antibody therapy is frequently reserved for moderate or severe rejection episodes in SPK recipients [48].

Korea

During the postanesthesia care unit or intensive care unit, hemodynamic and ventilatory assessment are crucial during recovery, especially during the first 24–48 h posttransplant. Judicious use of blood products is a necessary component, maintaining a Hgb > 10 mg/dL. For pancreas recipients with an underlying coagulopathy or liver dysfunction, fresh frozen plasma may be needed.

Postoperative hypotension increases the risk of arterial graft thrombosis, especially in the immediate postoperative period. Prolonged hypertension, if severe enough, can also induce cerebral vascular events or increase cardiac demand, resulting in ischemia and infarction. Maintaining a systolic pressure between 120 and 160 mmHg for the first 24 h safely maintains graft perfusion while minimizing the risk of a serious adverse event. If necessary, IV labetalol or nicardipine is used. However, the choice of agent and dose must be carefully selected and monitored due to side effects. In most cases, a CVP between 8 and 14 mmHg is adequate. The maintenance solution commonly used following pancreas transplantation is ½ NS. Bicarbonate replacement has been especially important for recipients with bladder drainage of pancreatic exocrine secretions. We try to avoid dextrose in the immediate postoperative period. Early dialysis may be necessary for hyperkalemia. For patients who are hypokalemic, potassium is administered on a supplemental basis. Ionized calcium levels should be followed to maintain an appropriate calcium state. Further, magnesium levels should be maintained above 2 mg/dL. During the first postoperative week, intravenous insulin was administered continuously unless blood glucose levels were maintained at less than 200 mg/dL. Blood glucose levels were measured every 3 h to determine the rate of insu-

lin infusion (UI/h). Therefore, the cumulative insulin dose was determined by summing up the amount of insulin infused. Subsequently, blood glucose levels of greater than 200 mg/dL were treated with subcutaneous exogenous insulin.

Bacterial and fungal prophylaxis consisted of ampicillin/sulbactam plus fluconazole for 1 week after transplantation, and oral sulfamethoxazole-trimethoprim was administered for 6 months to prevent *Pneumocystis jirovecii* pneumonia infection. CMV monitoring was performed on a weekly basis using CMV DNA assay during the early postoperative period. CMV prophylaxis (valganciclovir) was administered for 6 months only if CMV-negative recipients received CMV-positive transplants.

As mentioned in the previous section of the indication and selection section of the recipient, prophylaxis of voriconazole (200 mg BID/day) for 3 months for the prevention of fatal scedosporiosis occurrence in the nearly drowned donors is a routine practice [49, 50].

Anticoagulation therapy was administered both during and after surgery. In SPK patients just prior to reperfusion, heparin (50–70 U/kg) was IV infused and then administered subcutaneously every 8 h, whereas the PTA and PAK patients were administered continuous intravenous heparin (400–1000 U/h). Activated partial thromboplastin time (aPTT) was checked every 6 h, after which they were administered oral warfarin for 3 months. The target level of aPTT and prothrombin time (international normalized ratio) was ×1.5 to 2 of the upper reference range. We previously published the article in which CT angiography is a safe and efficient process for monitoring vascular patency after pancreas transplantation [51] (Fig. 1, Table 2). If a thrombosis was detected using a CT angiography, heparin was administered intravenously at a dose twice the normal upper level of aPTT, with monitoring of graft patency using CT angiography accordingly. In living donor pancreas transplants, anticoagulation therapy is mandatory both during and after surgery. Continuous intravenous heparin (400–1000 U/h) was administered, and the activated partial thromboplastin time (aPTT) was monitored every 6 h, after which oral warfarin was administered for 3–6 months. The target level of aPTT and prothrombin time (international normalized ratio) was ×1.5 to 2, the upper reference range (Fig. 2).

Before 1999, OKT3 was used for induction and tacrolimus/cyclosporine, mycophenolate mofetil, and steroids for maintenance. From 1999 to 2004, basiliximab was used for induction, and maintenance with tacrolimus, mycophenolate mofetil, and low-dose prednisolone. From 2004, rabbit antithymocyte globulin (thymoglobulin) was used for induction, and tacrolimus and mycophenolate mofetil, coupled with the early withdrawal (within 1 week) of steroids, especially in SPK, for maintenance (Fig. 3).

Total ATG dose was 4.5–5.0 mg/kg regardless of the type of transplant. The first dose (1.5 mg/kg) was intraoperatively administered and followed by 1 mg/kg ATG on postoperative days 1, 2, 4, and 6. Patients received acetaminophen or diphenhydramine prior to infusion, thus reducing the chance of an adverse reaction to ATG. All patients received 500 mg methylprednisolone intraoperatively, which was subsequently tapered, and most of the SPK patients were weaned from steroids within 1 week after transplantation. A target tacrolimus level of 9–11 ng/L was achieved within 7 days in 90% of patients.

In cases of bladder-drained exocrine secretion, urine amylase levels were monitored to evaluate graft function. In some cases, intravenous insulin or oral hypoglycemic agents were used to maintain the glucose level at <200 mg/dL during the early postoperative period. Graft failure was defined as the time at which the reuse of exogenous insulin was required.

In enteric-drained patients, serum amylase and lipase can be a biomarker for graft rejection ahead of glucose elevation, low C-peptide or elevated HbA1C. In SPK serum creatinine can be a surrogate marker of rejection for the pancreas as well as kidney.

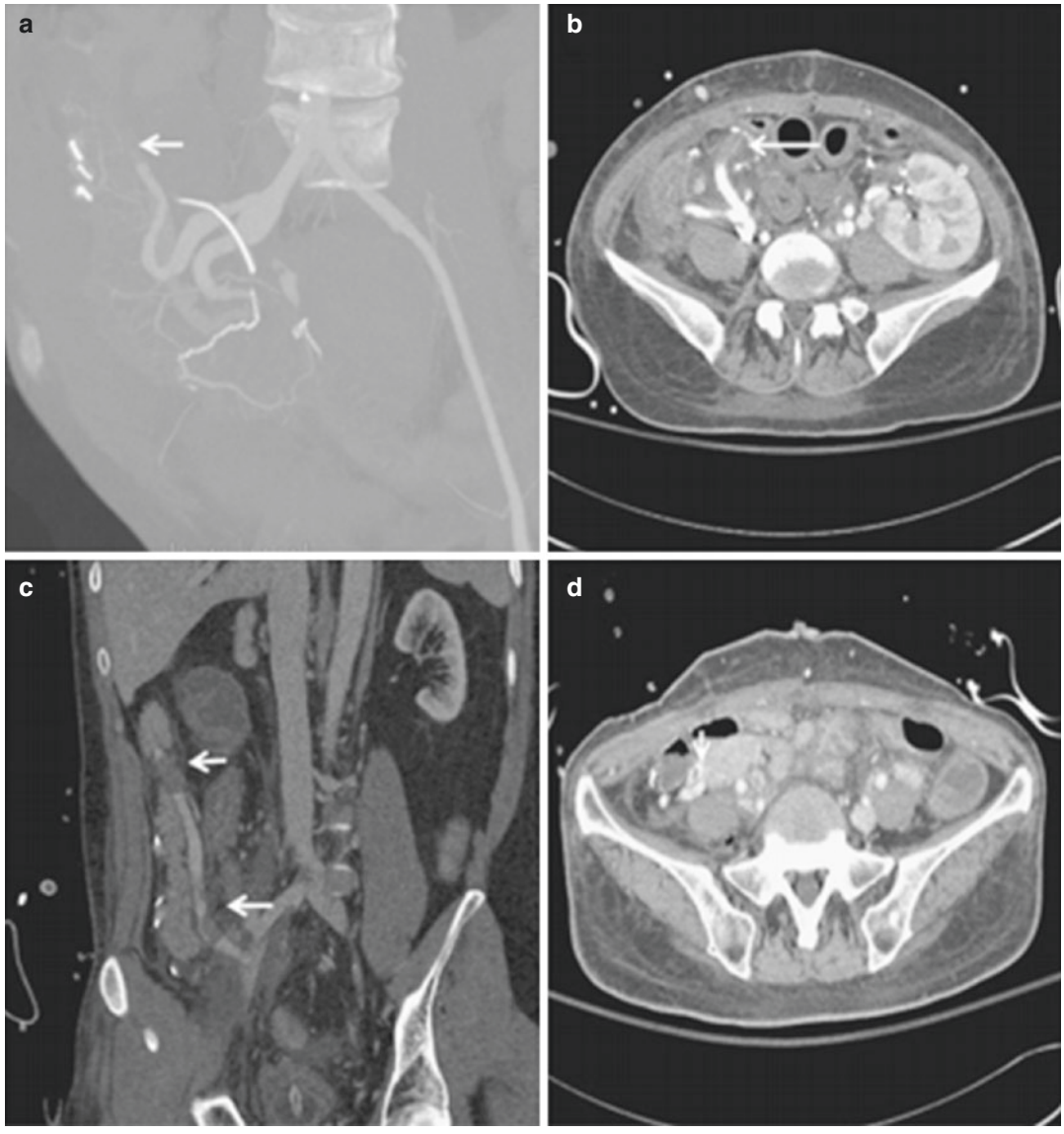

Fig. 1 Computed tomography images of partial thrombi. Images of thrombi at various locations and of various extents. (**a**) Thrombus at the distal splenic artery. (**b**) Thrombus at the superior mesenteric artery. (**c**) Multifocal thrombus at the splenic vein. (**d**) Partial splenic vein thrombus

Japan

Since PT is an emergency operation, it is necessary to efficiently proceed with preoperative treatment while performing various examinations. The patient has fasted after admission, and peripheral venous route is secured. The blood glucose level is adjusted by continuous intravenous glucose administration or artificial pancreas so that the blood glucose level is 100–200 mg/dL. The patient is given a laxative and enema as a bowel preparation. The patient is administered sedatives if mental anxiety is strong.

In principle, we do not place an epidural catheter in consideration of dialysis and decreased coagulation. A nerve block such as a TAP block should be considered for the management of analgesia.

Table 2 Demographics of Group A and B patients

	Demographics	Group A (n = 51)	Group B (n = 68)	
		Doppler	CT Angiography	P
Donor	Age, year	27.6 ± 10.2	33.4 ± 11.5	NS
	Sex (M:F)	41:10	41:27	0.03
	BMI, kg/m^2	21.5 ± 3.5	21.2 ± 3.7	NS
	CIT, min	434 ± 145	389 ± 206	NS
	CAD:living	50:1	57:11	0.02
	Cause of brain death (trauma:nontrauma)	27:23	15:42	0.006
Recipient	Age, year	31.3 ± 9.9	34.7 ± 9.4	NS
	Sex (M:F)	32:19	31:37	NS
	BMI, kg/m^2	20.3 ± 4.5	20.9 ± 5.1	NS
	Duration of DM, year	13.0 ± 6.0	15.9 ± 8.0	NS
	Insulin requirement, U/day	29.3 ± 21.2	29.0 ± 16	NS
	Exocrine drainage (bladder:enteric)	35:16	32:36	0.03

BMI body mass index, *CAD* cadaver, *CIT* cold ischemia time, *CT* computed tomography, *DM* diabetes mellitus, *F* female, *M* male, *NS* not significant

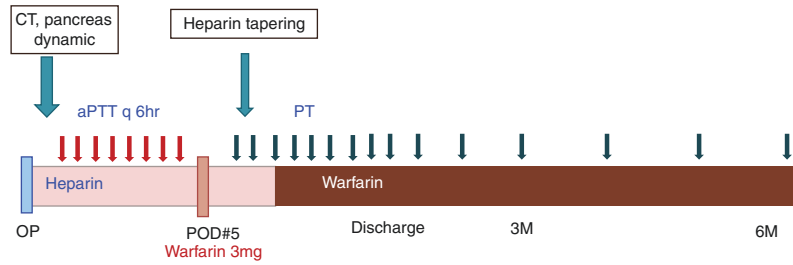

Fig. 2 Anticoagulants in pancreas transplantation in AMC

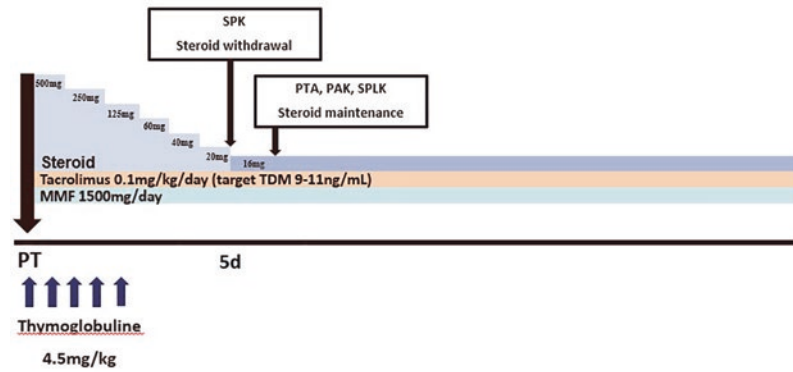

Fig. 3 Immunosuppressant in pancreas transplantation in AMC

In addition to the usual general anesthetic monitoring (ECG, non-invasive blood pressure, transcutaneous arterial blood oxygen saturation, and partial pressure of end-expiratory carbon dioxide), we check and monitor arterial pressure, cardiac output and central venous pressure, muscle relaxation monitoring, and transesophageal echocardiography if necessary.

As a central venous route, a triple-lumen catheter is inserted through the right or left internal jugular vein. This catheter can be used if the postoperative hemodialysis treatment is required. Prophylactic administration of antibiotics is performed before a start of the operation. As an intraoperative infusion fluid, No. 1 solution or saline solution is mainly used. In case that they

do not contain a buffer, bicarbonate is added to compensate a buffer effect. The total volume of infusion fluid should be limited to approximately 5% of the patient's preoperative weight at the end of the operation. Blood transfusion should be performed with a hematocrit value of 20–25% as a guide.

To avoid hypoglycemia and ketone production, the blood glucose level is measured every hour. Continuous administration of glucose at a dose of 2.5–5 g/h is performed. Insulin administration is done by continuous infusion or an artificial pancreas, and the target level of blood glucose is 80–150 mg/dL.

Anesthesia Management for Kidney Graft

In SPK, the kidney transplantation is performed before and after the pancreas transplantation. In most cases, a kidney transplant is performed before a pancreas transplant. Prior to reperfusion of blood flow in the kidney graft, 0.02 μg/kg/h of hANP and 0.01–0.2 μg/kg/h of noradrenaline should be administered, and 3–5 μg/kg/min of dopamine or 0.01–0.02 μg/kg/min of PGE1should be considered to administrate in cases of hypotension with bradycardia. CVP should be maintained at 5–10 mmHg. Since the blood flow of the kidney graft depends on perfusion pressure, hypotension should be avoided before reperfusion.

After blood flow resumption in pancreas graft, significant volumes of fluid and blood transfusions are needed to address the sweating from the surface of the pancreas graft, the little bleeding from surrounding tissues, and the decrease in intravascular volume with fluid transfer to the third space. The administration of the fluid should be based on colloidal fluids and blood products. To provide adequate intravascular volume and good blood flow to the transplanted pancreas, the target level of a systolic blood pressure is 120–140 mmHg, and a CVP is approximately 12–14 mmHg.

The patient should be admitted to the ICU for a few days after transplantation and then transferred to a general ward. During the stay in ICU, ECG, arterial pressure, and transcutaneous arterial oxygen saturation are monitored continuously. Vital signs, including blood pressure, body temperature, urine output, CVP, etc., are measured every hour. Infusion is administered via central and peripheral venous routes. Since circulatory dynamics is often unstable in the early postoperative period, the volume of fluid is needed to be adjusted. Calculation of the fluid and blood balance every hour is necessary until the general condition is stabilized. Body weight is measured 1–2 times daily. To maintain enough blood flow to the graft, the systolic blood pressure should be controlled to approximately 140 mmHg using noradrenaline or antihypertensive agents. For the detection of the bleeding from both grafts, the volume and properties of the drains should be carefully observed. Also, the amylase level in the drainage fluid of the drain is placed around the pancreas graft in the abdominal cavity to detect of leakage of the intestinal anastomosis. Urine volume is measured every hour. The urinary catheter is usually removed at 1 week after transplantation. The patient is placed on bed rest for 2 days. The gastric tube is removed on the next day, and oral intake with water starts on the second day. Oral intake with meal starts on the fifth to seventh day. Early in the postoperative period, the patient should undergo rehabilitation depending on the postoperative status.

Blood glucose levels are measured every hour to assess the graft function during the ICU stay. Since insulin secretion is usually observed immediately after transplantation, the blood glucose becomes normal even without insulin treatment. In case that hyperglycemia persists, insulin replacement should be considered. Alternatively, insulin is administered continuously using an artificial pancreas to fix blood glucose levels at 100–150 mg/dL in the early postoperative period.

Various tests to be measured during the ICU stay are listed below.

1. General Examination: Chest and abdominal X-ray, blood count, liver function, renal function, electrolytes, arterial blood gas, lactate, coagulability, urine stability, urine sediment, etc.

2. Pancreas graft function: C-peptide levels in serum and urine, blood glucose, HbA1c (every week), glycoalbumin (every week).
3. Kidney graft function: Serum creatinine, serum cystatin C, BUN. Urine protein.
4. Blood concentration of immunosuppressive agents.
5. Diagnostic imaging: Ultrasonography of both the pancreas and kidney grafts. CT scan, etc.
6. Urinalysis: Urine amylase, urine pH in case of SPK using bladder drainage.
7. Pancreatic fluid examination (during placement of the ductal catheter): The volume of pancreatic fluid, pH, amylase, lipase, etc.
8. Examination of the exudate from the drain: Volume of the exudate, amylase level.

Medications

1. Antibiotics: Second-generation cephem antibiotics is administered immediately before surgery as prophylaxis for SSI. Postoperative antibiotics is administered continuously for several days.
2. Inhibition of gastric acid secretion: To prevent gastric acid secretion and gastric ulcers caused by postoperative stress, etc., dissolve 20 mg of omeprazole sodium injection in 20 mL of saline once or twice a day. 10 mg of vonoprazan or esomeprazole is given intravenously and transit to oral agents at a dose of 20 mg when oral intake starts
3. Peristaltic agents: The patient with a long-term diabetic history shows an autonomic disorder and poor bowel movement. Peristaltic agents, including dinoprost, are frequently needed.
4. Proteolytic enzyme inhibitors: Ischemia and reperfusion injury of the pancreas graft may result in so-called acute pancreatitis. Gabexate mesilate or nafamostat mesylate is administered by continuous intravenous infusion of 40 mg/day for 7 days, and 100,000 units of urinastatin is given intravenously for 3 days. 300–600 mg of camostat mesylate is given on day 8. We continue to give camostat mesylate at least 1 year after transplantation.

Intravenous administration of heparin (200 U/h) is started intraoperatively and 5000–10,000 units are given daily for 10 days after transplantation. Heparin dose is adjusted for ACT of 180 s. Subsequently, 100 mg of biaspyrin or 30 mg of edoxaban is administered orally until 1 year after transplantation.

Venous thrombosis of the graft is the most important early complication after pancreas transplantation. Although the frequency of thrombosis is 5.5% for SPK and 7.6% for PAK/PTA in national data, thrombosis is the main cause of early pancreas graft failure, and diagnosis and treatment are clinically important issues for pancreas transplantation. Thrombi are usually confirmed by Doppler ultrasonography and enhanced CT, but at Fujita Medical University Hospital, a contrast-enhanced ultrasonography(CEUS) is used (Fig. 4). CEUS uses Sonazoid as a contrast medium, and it can be performed immediately after transplantation because it can be performed at the bedside and there is no renal dysfunction. Compared to Doppler ultrasonography, the blood flow itself is visible, and it is easier to detect thrombi, so we perform it every other day for 1 week after PT. If blood flow in the pancreas is good, even if thrombi are found in the splenic vein or SMV,

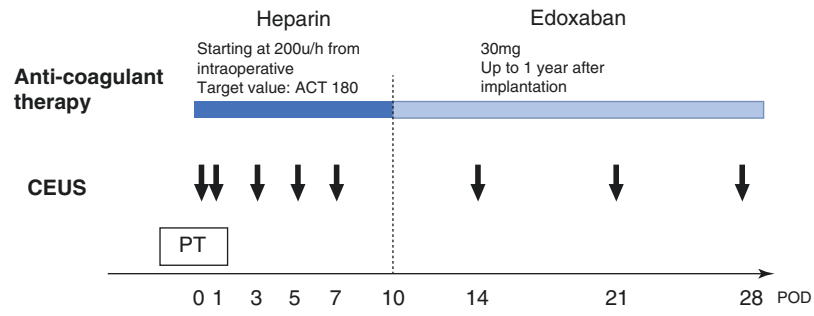

Fig. 4 Protocol of anticoagulant therapy after pancreas transplantation (Department of Organ Transplant Surgery, Fujita Health Univ. Hospital)

we only increase the amount of heparin and carefully monitor the course. Although thrombosis is usually common within 1 week after transplantation, it may happen after 10 days. In addition, since delta TP calculated by CEUS is a factor that predicts pancreatic endocrine function at 1 year after transplantation, maintenance of blood flow at an early stage after transplantation may also be important for long-term graft survival.

Thrombectomy is performed by an intervention radiologist or open surgery for cases in which blood flow in the parenchyma of the pancreas has decreased, blood flow has disappeared, and thrombi have grown near the anastomotic site. Even if thrombus removal was successful and pancreatic function was maintained, it was found that the survival rate of thrombus-treated cases was significantly lower than that of non-thrombus cases (Table 3).

The immunosuppressive protocol for pancreas transplantation is almost the same as that for kidney transplantation. Namely, a quadruple therapy using calcineurin inhibitors (cyclosporine, tacrolimus), mycophenolate mofetil, steroid as maintenance immunotherapy, and basiliximab or thymoglobulin as an induction therapy is the standard immunosuppressive protocol in Japan. Table 4 shows the immunosuppressive protocol for pancreas transplantation in Japan.

Figure 5 shows the immunosuppressive protocol for deceased donor pancreas transplantation at Fujita Medical University. At our institution, basiliximab is used for SPK and thymoglobulin is used for PAK and PTA as induction therapy

Since pancreas graft's rejection initially impairs the conduit epithelium, vascular endothelium, and glandular cells of exocrine glands, monitoring of pancreatic exocrine function may be an early indicator. Later, when blood glucose levels rise, and endocrine function is impaired, it is often in the late stages of advanced fibrosis and thrombus formation. In the case of SPK, a kidney biopsy may be performed as an indicator of the

Table 3 Comparison of pancreas graft survival rates depending on whether or not a graft's thrombus was developed (JPITA, 2000.4–2018.12)

Pancreas graft survival	1 year	3 years	5 years
Graft's thrombus (recovered by treatment)	71.4%	71.4%	35.7%
Graft's thrombus	91.6%	85.4%	81.8%

Table 4 Immunosuppressive therapy after pancreas transplantation in Japan (JPITA, 2000.4–2019.12), $n = 410$

	n	Induction therapy			
		No	Yes		
Tac-based	405	19	386	Anti-IL-2	293
				ALG	2
				ATG	85
				ATG+anti-IL-2	6
CsA-based	5	1	4	Anti-IL-2	2
				ALG	1
				ATG	1
	410	20	390	Anti-IL-2	295
				ALG	3
				ATG	86
				ATG+anti-IL-2	6

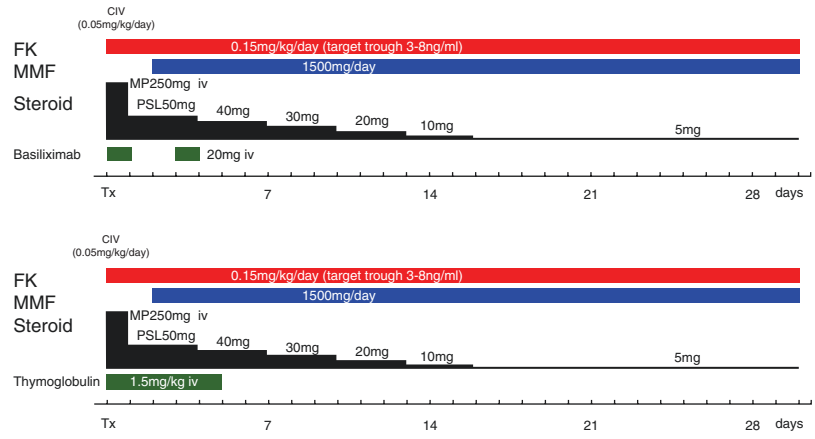

Fig. 5 Immunosuppressive protocol for deceased donor pancreas transplantation (Department of Organ Transplant Surgery, Fujita Health University Hospital)

pancreas graft's rejection, because both kidney and pancreas from the same donor are rejected at the same time with the frequency of 60–70%.

Rejection is diagnosed by comprehensively judging the following findings.

Clinical diagnosis: Graft tenderness, fever, etc.

As a laboratory diagnosis, serum amylase and lipase, plasma pancreatic secretory trypsin inhibitor (PSTI), phospholipase A2, C-reactive protein, etc., are evaluated. Blood glucose, serum insulin (IRI), serum C-peptide, urine amylase and lipase, urine PH, urine cytology etc.

And urine C-peptide is evaluated.

As a diagnosis by imaging techniques, in echography (including Doppler) vascular resistance increases during rejection. CEUS, as mentioned above, shows the decreased blood flow in the parenchyma of the pancreas graft and may show *to and fro* pattern.

A plain abdominal CT may show a markedly enlarged and heterogeneous pancreatic parenchyma in case of severe rejection. Fluid collection around the pancreas graft may also be detected. These findings are, however, similar to graft pancreatitis and infection, and there are no CT findings specific to rejection.

Biopsy is the most useful tool to confirm rejection. An ultrasound or CT-guided needle biopsy is performed, but if there is a bowel between the abdominal wall and the transplanted pancreas, laparoscopic or open pancreas biopsy is recommended. Cystoscopic pancreas biopsies can also be performed in cases of bladder drainage. The Banff classification is used for the histopathological findings of rejection.

In SPK patients, the kidney graft biopsy is essential for the diagnosis of rejection of pancreas graft.

For the diagnosis of antibody-associated rejection in patients with a history of transfusion, pregnancy, or repeated transplantation, donor-specific assay like flow cytometry crossmatch (FCXM) or Flow PRA (flowcyte panel reactive action), CDC (compliment-dependent cytotoxicity) test, or solid-phase immunoassays (Luminex method) are studied. Donor-specific antibodies (DSA) and non-donor-specific antibodies (NDSAs) are used to infer the type and amount of antibodies.

Rejection of pancreas graft is treated by the following method as in kidney transplantation.

1. Steroid pulse therapy: Generally, pulse therapy with methylprednisolone (MP) is used at a dose of 0.5–1.0 g/day for 3 days
2. Anti-human thymic cell rabbit immunoglobulin (ATG, thymoglobulin): 1.5 mg/kg/day is administered intravenously for 7 days for steroid-resistant cellular rejection.
3. Rituximab: 200–500 mg of rituximab is given.
4. IVIG: If antibody-mediated rejection is suspected, 0.5 g/kg/day of IVIG two or three times in combination with plasma exchange.

Chronic rejection has come to be used synonymously with pancreatic parenchymal fibrosis, which is difficult to treat, although it can be divided into three stages depending on the degree. The idea that the presence of minute amounts of antibodies may contribute to chronic rejection has been proposed, and plasma exchange, rituximab, intravenous IVIG, and increased MMF doses may be used. Dietary therapies such as fat restriction and antiplatelet therapy may also be used symptomatically.

As a post-discharge management, patients should measure body weight, body temperature, urine volume, and blood pressure and record daily at home at the early stage of discharge from the hospital. Patients should visit the hospital once every 2 weeks. When the patient's condition becomes stable, the patient visits the hospital once a month.

In addition to the general examination, the following items are examined.

1. Blood count and chemistry, including liver function, kidney function, electrolytes, coagulation, and urinalysis
2. Blood glucose level
3. Serum amylase and lipase levels
4. Serum C-peptide level
5. Hemoglobin A1c level
6. Blood concentrations of immunosuppressive agents

Pancreas graft function is assessed by a diabetologist before discharge from the hospital at 3 months after transplantation and every year after 1 year after transplantation. In addition, evaluation for diabetic complications and screening of malignancy should be performed every year.

Pancreatic endocrine functions are evaluated by following examinations.

1. 75 g oral glucose tolerance test: Blood glucose, insulin, C-peptide are measured before and at 30, 60, 90, 120, and 180 min.
2. Glucagon stimulation test: C-peptide is measured before and after the loading of glucagon.
3. Monitoring of daily blood glucose fluctuations.
4. Continuous glucose monitoring for several days

Concerning diabetic complications, retinopathy should be evaluated by an ophthalmologist every year. Neuropathy is evaluated by a neurologist by R-R interval coefficient of variation for electrocardiogram, electromyography, oscillatory threshold testing. As a cardiovascular test, echocardiography should be performed every year. When cardiac dysfunction is observed, myocardial scintigraphy or coronary catheterization is recommended. To evaluate the peripheral artery, arm-ankle blood pressure ratio (ABI), cardiac-to-carotid pulse wave velocity (hcPWV), arm-ankle pulse wave velocity (baPWV) should be measured.

Screening for malignant tumors should be performed every year, using measuring tumor markers, chest and abdominal CT, upper and lower gastrointestinal endoscopy, mammography, etc.

Taiwan

Proper planning and care increase the success of pancreas transplants. Moreover, an efficient teamwork would pave the right way to a successful pancreas transplant. The following orders usually work well for pancreas transplants at Taipei Veterans General Hospital (Table 5).

Preoperative orders for PT are NPO except for medication for 8 h before operation and check laboratory blood data: CBC, platelet, DC, PT, APTT, C-peptide, amylase/lipase, biochemical check-up panel, HbA1c, and CXR, EKG.

Colon preparation by E-vac immediate after admission & Flagyl po and Hibiscrub shower (skin preparation) before going to operation room (OR). Immunosuppressants are recommended with myfortic 4# po, tacrolimus 5 mg (1 mg × 5#) po after admission, and set up CVP for thymoglobulin IV 1 h before going to OR with the dose of 1–1.5 mg/kg/day for 12 h via central line using iv pump (need premedication!). Premedication for thymoglobulin are scanol po 1 h before thymoglobulin, Allermin 1 amp iv 30 min, and methylprednisolone (Solu Medrol) 20 mg iv. 30 min before thymoglobulin.

Pantaloc 1 amp, ciproxin 400 mg, and mycamin 50 mg iv. 1–2 h before going to OR.

Intraoperative orders are methylprednisolone (Solu Medrol) 1000 mg at OR (given before SPK procedure), Amikin 1 vials and Bacide for bladder irrigation (in 200 c.c. N/S), Lasix 80 mg and 500 c.c. Mannitol just after renal reperfusion. Amphotericin-B 50 mg in 200 c.c. N/S for peritoneal and wound irrigation, and gentamicin 80 mg 1 vial in 200 c.c. N/S for peritoneal and wound irrigation.

Postoperative orders are: Send patient to ICU isolation room care, NPO except for medication.

Monitor vital signs q 15 min till stable, then ICU routine, and monitor urine output q1h × 3 days.

Check blood sugar by one-touch q30m. and then q2h for 24 h, then qid.

Keep CVP level above 8–12 cmH_2O.

Check daily: CBC, FBS, Amylase/Lipase, C-peptide, BUN/Creat, Na/K, FK506 serum level, BIW (W1 and W4): SMA, Mg, PT, APTT IV. Fluids are D5/0.5S vol. by vol. if urine amount <500 c.c./h, L/R 1/2 vol. by vol. If urine amount = 500–1000 c.c./h, and D5/1/2S 1/2 vol. by vol. If urine amount = 1000–1500 c.c./h especially in SPK.

Actrapid 8 u iv. prn. if BS > 200, and recheck BS in 1 h.

Table 5 Orders for Pancreas Transplant

Preoperative Orders for SPK (Taiwan)
- NPO except for medication for 8 h before operation
- Inform ICU to keep an ICU bed available for SPK patients after operation
- On CVP line for thymoglobulin ivd. before operation
- Key in recipient operation schedule
- Check Lab. Blood Data: CBC, platelet, DC, PT, APTT, C-peptide, amylase/lipase, Biochemical check-up panel, HbA1c
- Prepare two units of PRBC (leukocyte-poor)
- CXR, EKG
- Colon preparation by E-vac immediate after admission & Flagyl 2# po st. and tid if possible
- Hibiscrub shower (skin preparation) before to operation room (OR)
- Sign permit for IV PCA (no epidural PCA)
- Myfortic 4# po st. after admission
- Tacrolimus 5 mg (1 mg × 5#) po st. after admission
- Set up CVP for Thymoglobulin IVD 1 h before sent to OR
- Thymoglobulin mg (1–1.5 mg/kg/day) ivd for 12 h st. via central line using iv pump (need premedication!)

Premedication for Thymoglobulin:
- Scanol 1# po st. 1 h before Thymoglobulin
- Allermin 1 amp iv st. 30 min. before Thymoglobulin
- Methylprednisolone (Solu Medrol) 20 mg iv. st. 30 min before Thymoglobulin
- Pantaloc 1 amp iv. st. 1–2 h before sent to OR
- Ciproxin 400 mg iv. st. 1–2 h before sent to OR
- Mycamine 50 mg iv. st. 1–2 h before sent to OR

Intraoperative Orders
- Methylprednisolone (Solu-medrol) 1000 mg iv. to OR (given before SPK procedure)
- Amikin 1 vials and Bacide 2# with patient to OR for UB irrigation (in 200 c.c. N/S)
- Lasix 80 mg and 500 c.c. mannitol with patient to OR for ivd after Kidney Tx
- Albumin 2 vials to OR, and to be given after off-clamp for pancreas graft
- Amphotericin-B 50 mg with patient to OR (in 200 c.c. N/S for peritoneal and wound irrigation)
- Gentamicin 80 mg 1 vial with patient to OR (in 200 c.c. N/S for peritoneal and wound irrigation)

Postoperative Orders for SPK
- Send patient to ICU isolation room care
- NPO except medication
- NG free & decompression prn (clamp 2 h after oral medication)
- Monitor vital signs q 15 min till stable, then ICU routine
- Monitor urine output q1h × 3 days
- Check blood sugar by one-touch q30m. and then q2h for 24 h, then qid
- I & O, and body weight, qd
- Check CVP value q4h × 3 days
- Keep CVP level above 8–12 cmH_2O
- On IV PCA pain control care
- Morphine 5–10 mg im. or iv. prn q4h if severe pain
- On J-P drain × 2 care
- Check data:
- Daily: CBC, FBS, Amylase/Lipase, C-peptide, BUN/Creat, Na/K, FK506 serum level
- BIW (W1 and W4): SMA, Mg, PT, APTT
- IV. Fluid as following:
- D5/0.5S vol. by vol. if urine amount <500 c.c./h
- L/R 1/2 vol. by vol. if urine amount = 500–1000 c.c./h
- D5/1/2S 1/2 vol. by vol. if urine amount = 1000–1500 .c./h
- Actrapid 8 u iv. prn. if BS > 200, and recheck BS in 1 h

Solu-medrol (methylprednisolone) 250 mg iv. on POD 1 and 2, then 30 mg iv. POD 3 and 4
- Prednisolone 20 mg po qd from POD 5, then tapering gradually within 6 months.
- Myfortic 4# po q12h (9 AM–9 PM) (no food 1 h before and after MMF)
- Tacrolimus (FK506) 5 mg po. q12h (9 AM–9 PM), with therapeutic serum trough level of FK-5-6 at 10 ± 2 ng/mL during the first year.
- Thymoglobulin mg (1–1.5 mg/kg/day) ivd for 12 h st. via central line using iv pump (need premedication!)

Premedication for Thymoglobulin:
- Scanol 1# po st. 1 h before Thymoglobulin
- Allermin 1 amp iv st. 30 min. before Thymoglobulin
- Solu-medrol (methylprednisolone) as standing order 30 min. before Thymoglobulin
- Pantaloc 1 amp iv. q6h × 7 days, then Pantaloc 1# po qd
- Ciproxin 400mg iv. (or other third-generation cephalosporin drug) q12h × 7 days
- Mycamine 50 mg iv. qd × 7 days

Gancyclovir 50–300 mg iv. qd (adjusted with renal function)
- Valcyte 1# po qd after DC Gancyclovir × 100–200 days
- Nystatin 1# in 20 c.c. water gurgling and po. qid × 6 months
- Bactrim (TMP/Sulfa 160/800 mg) 1 tab. po. qd from POD 3 for 1 year
- Bokey 1# po. qd from POD 3 for life long unless contraindicated
- Albumin 2 vials iv. bid × 3 days

Postoperative immunosuppressants are Solu Medrol (methylprednisolone) 250 mg iv. on POD 1 and 2, then 30 mg iv. POD 3 and 4, and prednisolone 20 mg po qd from POD 5, then tapering gradually within 6 months.

Myfortic 4# po q12h (9 AM–9 PM) (no food 1 h before and after MMF), and tacrolimus (FK506) 5 mg po. q12h (9 AM–9 PM), with therapeutic serum trough level of FK-5-6 at 10 ± 2 ng/mL during the first year are maintained.

Thymoglobulin (1–1.5 mg/kg/day) ivd for 12 h st. via central line using iv pump (need premedication!) Pantoloc, Ciproxin (or other third-generation cephalosporin drug), Mycamine, for 7 days, gancyclovir 50–300 mg iv. qd (adjusted with renal function), Valcyte po after gancyclovir × 100–200 days, nystatin gurgling and po. qid × 6 months, Bactrim (TMP/Sulfa 160/800 mg) 1 tab. po. qd from POD 3 for 1 year, Bokey 1# po. qd from POD 3 for life long unless contraindicated, and albumin 2 vials iv. bid × 3 days.

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Outcome

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Global

From December 16, 1966, to December 31, 2019, more than 60,000 pancreas transplants have been reported to the IPTR, including 34,133 from the USA and 27,119 from outside the USA (Fig. 1) [1].

However, the number of primary pancreas transplants from deceased donors declined from 6046 from 2001 to 2005, to 5214 from 2006 to 2010, and to 5159 from 2011 to 2016 [2]. The average number of transplants declined, therefore, from approximately 1200 down to 860 primary transplants per year. Relatively more SPK than solitary transplants were performed over time. From 2011 to 2016, 84% of all pancreas transplants in the diabetic population were SPK. Although the number of PTA remained relatively stable, a drop of 70% in PAK was noted (Fig. 2). Most recipients had type 1 diabetics, but the number of recipients with type 2 diabetes increased significantly in SPK but declined in PTA over time (Fig. 3). The age distribution changed in all three categories over time. There was a trend to accept older recipients, especially for solitary transplants. From 2011 to 2016, a significant age difference between solitary and SPK recipients was found; SPK recipients, on average, were younger. The two oldest patients at the time of transplant were each 71 years of age; one received an SPK and the other a PAK (Fig. 4).

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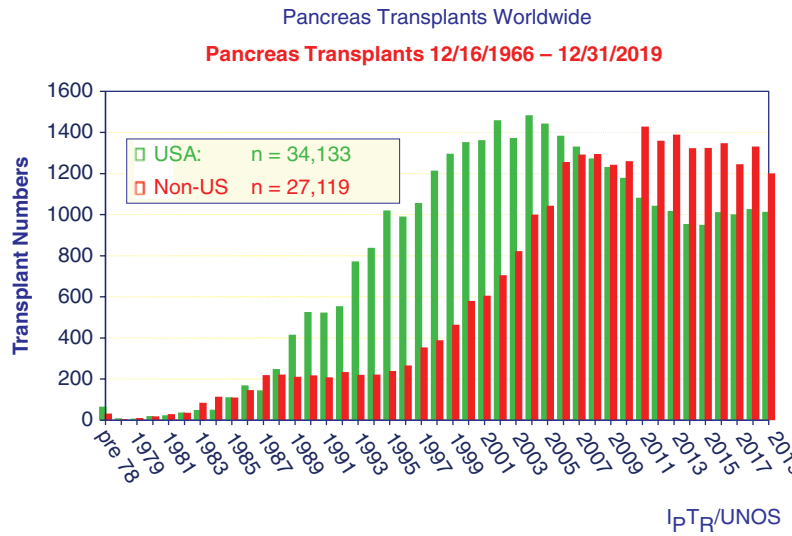


Fig. 1 The registry data of global pancreas transplantation

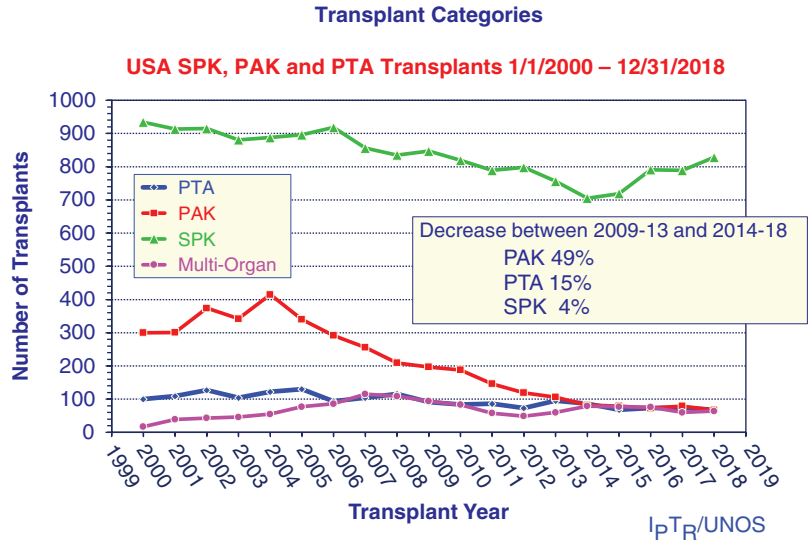


Fig. 2 US pancreas transplants according to the operation categories

The rate of male recipients remained significantly higher in uremic SPK and posturemic PAK compared with PTA, in which most were female recipients (Fig. 5).

Over time, the bodyweight of the recipients followed the national trend: the number of overweight or obese recipients increased significantly. From 2011 to 2016, 50% or more of the recipients were overweight or obese at the time of transplant.

The rate of sensitized recipients increased in all three categories over time. From 2011 to 2016, this accounted for 15–22% of all recipients (Table 1).

The wait time between listing and transplant remained stable for PTA, with a median of 144 days from 2011 to 2016. The time on the waitlist decreased for SPK from a median of 536 days from 2001 to 2005 to 495 days from 2006 to 2010. No further decline was noted from the years 2006–2010 to the years 2011–s2016 for SPK. In contrast, the wait time in PAK increased significantly from 183 days from 2001 to 2005 to up to 366 days from 2011 to 2016.

Over the analyzed time, the donor factors changed significantly. A significant trend to younger donors was detected in all three categories. From 2011 to 2016, the median donor age for solitary transplants was 21 years, for SPK, it was 23 years. Only 25% of donors were older

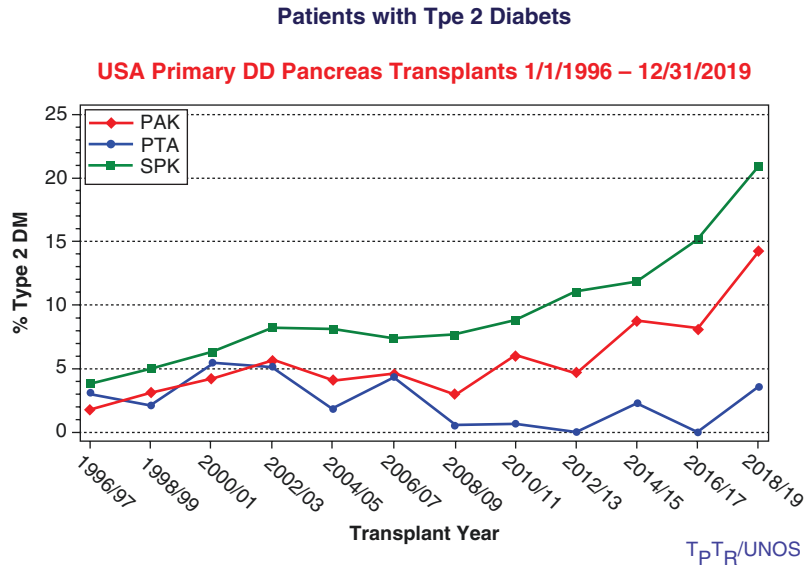


Fig. 3 Type 2 DM in primary pancreas transplantation in the USA

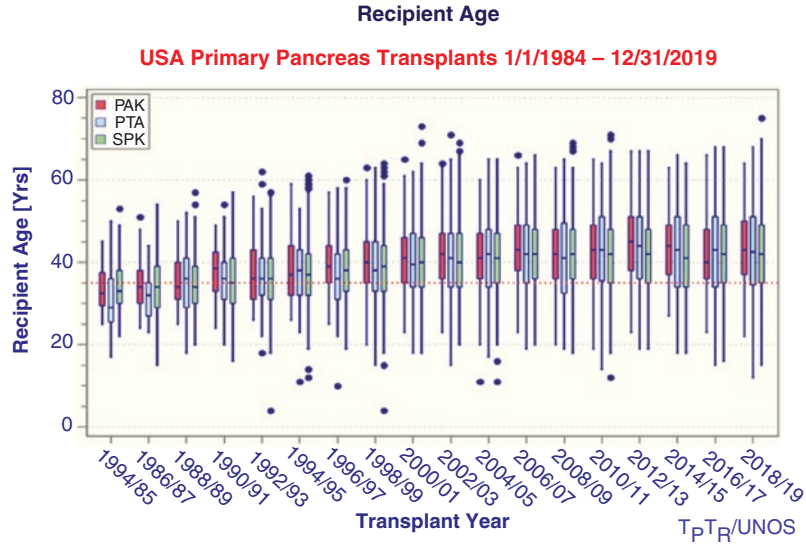


Fig. 4 Recipient age in primary pancreas transplantation in the USA

than 29 years of age during this time, but older donors were still used. The oldest SPK donor was 72 years of age, and the oldest solitary pancreas donor was 58 years old. Most pancreas donors were white, but over time the number of black and Hispanic donors increased significantly in all three categories. For most pancreas donors, the cause of death was related to traumatic accidents. The rate remained stable in solitary transplants but increased significantly in SPK over time. More than three-quarters of donors had trauma reported as the cause of death. Donation after circulatory death (DCD) donors are only very rarely used in pancreas transplantation and make up less than 3% of all transplants. The number of DCD donors is higher for SPK but very low in solitary transplants. Male donors were used significantly more frequently than female donors. This was because the rate of accidental death was significantly higher in male donors.

The importance of HLA antigen matching decreased over time. From 2011 to 2016, 57% of all SPK had a five or six antigen mismatch, and the same trend was seen in PAK. Historically, in PTA, more emphasis was put on matching, but

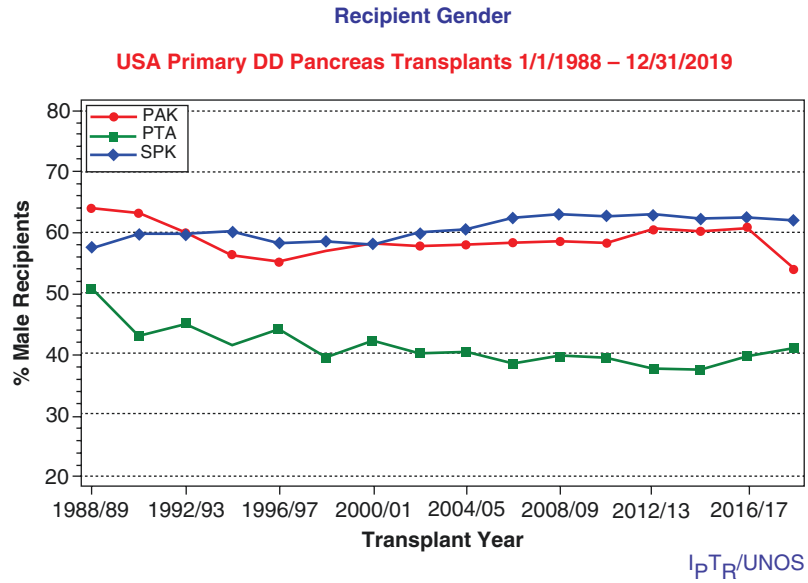


Fig. 5 Recipient gender in primary pancreas transplantation in the USA

the trend was also to less emphasis on matching. From 2011 to 2016, 48% of all PTA were performed with a five or six antigen mismatch (Table 2).

With the overall decline in the number of transplants, the distribution of transplants performed by low-volume, medium-volume, or high-volume centers changed in all three categories (Table 3). Fewer transplants were performed at high-volume centers over time. This was because the centers that were high-volume, in the beginning, became medium-volume centers. PTA was the transplant type that was mostly performed at high-volume centers, and only very few PTA were reported from low-volume centers.

With the drop in transplant numbers, the preservation time in all three categories decreased significantly.

From 2011 to 2016, the reported preservation time in greater than 50% of transplants was less than 12 h. This trend to shorter preservation times was transplanted highly significant, especially in SPK.

The use of bladder drainage for the management of the pancreatic duct decreased significantly in all three categories and was used in less than 10% of all transplants from 2011 to 2016. In most transplants, enteric drainage was used, and duct injection was only occasionally chosen. In enteric-drained transplants, systemic venous drainage was the most common, whereas drainage into the portal vein declined, especially in solitary transplants (Table 3).

Over time, more and more induction therapy was used in all three categories. The trend for using depleting antibody therapy increased significantly and made up greater than 80% of all cases from 2011 to 2016. Fewer and fewer non-depleting antibodies were used, and the combination of depleting and non-depleting antibodies became less common over time.

Most maintenance immunosuppressive protocols were based on tacrolimus in combination with MMF. From 2011 to 2016, greater than 90% of this combination was used in SPK and PAK; only in PTA was the rate lower. The promise of the sirolimus-based protocol has not been kept, and the rate declined in all three categories over time. The overall use of steroid-free maintenance protocols increased in all three categories from 20% to 32% over time. The steroid-free protocol was most frequently used in combination with tacrolimus and MMF. All other drug combinations with CsA and AZA were used less and less over time and make up only a very small percentage of protocols (Table 3).

Table 1 Transplant recipient characteristics for primary deceased donor pancreas transplants performed from 2001 to 2005, 2006 to 2010, and 2011 to 2016

	SPK				PAK				PTA			
	2001–2005	2006–2009	2011–2016	*P*	2001–2005	2006–2009	2011–2016	*P*	2001–2005	2006–2009	2011–2016	*P*
# Primary Tx (%)	4192 (69)	4009 (77)	4342 (84)	—	1321 (22)	770 (15)	399 (8)	—	533 (9)	435 (8)	418 (8)	—
Diabetes												
Type1	3870 (92)	3699 (92)	3838 (88)	<.0001	1255 (95)	740 (96)	371 (93)	.07	508 (95)	426 (98)	412 (99)	.006
Type2	322 (8)	310 (8)	504 (12)		66 (5)	30 (4)	28 (7)		25 (5)	9 (2)	6 (1)	
Recipient age (years)												
<18	2 (0)	0 (0)	1 (0)	<.0001	1 (0)	0 (0)	0 (0)	.0002	2 (0)	2 (0)	0 (0)	.011
18–29	332 (8)	302 (8)	72 (5)		72 (5)	42 (5)	24 (6)		64 (12)	61 (14)	45 (11)	
30–44	2490 (59)	2166 (54)	779 (59)		779 (59)	384 (50)	203 (51)		276 (52)	203 (47)	171 (41)	
45–59	1325 (32)	1484 (37)	458 (35)		458 (35)	324 (42)	160 (40)		175 (33)	153 (35)	180 (43)	
>60	43 (1)	57 (1)	11 (1)		11 (1)	20 (3)	12 (3)		16 (3)	16 (4)	22 (5)	
Gender												
Male	2588 (62)	2517 (63)	2719 (63)	.57	782 (59)	452 (59)	245 (61)	.66	206 (39)	178 (41)	158 (38)	.62
Race												
White	3165 (76)	2841 (71)	2582 (59)	<.0001	1111 (84)	647 (84)	288 (72)	<.0001	509 (96)	409 (94)	381 (92)	.07
Black	601 (14)	673 (17)	995 (23)		108 (8)	57 (7)	47 (12)		8 (2)	17 (4)	17 (4)	
Hispanic	343 (8)	392 (10)	594 (14)		83 (6)	59 (8)	52 (13)		12 (2)	8 (2)	18 (4)	
Asian	45 (1)	52 (1)	102 (2)		8 (1)	5 (1)	3 (1)		1 (0)	0 (0)	1 (0)	
Multiracial or Other	38 (1)	51 (1)	69 (2)		11 (1)	2 (0)	9 (2)		3 (0)	1 (0)	1 (0)	
Body mass index												
<18.5 (underweight)	100 (2)	75 (2)	75 (2)	<.0001	37 (3)	11 (1)	12 (3)	.02	13 (2)	8 (2)	5 (1)	.03
18.5–24.9 (normal)	2233 (54)	1989 (500)	2098 (480)		654 (50)	349 (46)	173 (43)		251 (48)	203 (48)	162 (39)	
25–29.9 (overweight)	1349 (33)	1427 (36)	1663 (38)		446 (34)	300 (39)	148 (37)		199 (38)	157 (37)	179 (43)	
>30 (obese)	456 (11)	510 (13)	506 (12)		166 (13)	104 (14)	66 (17)		63 (12)	57 (13)	72 (17)	
Missing	54	8	0		18	6	0		7	10	0	
Recent PRA%												
0–19	3544 (94)	3567 (91)	3687 (85)	<.0001	1149 (96)	672 (90)	322 (81)	<.0001	437 (91)	328 (78)	328 (78)	<.0001
>20	208 (6)	364 (9)	469 (15)		52 (4)	74 (10)	77 (19)		52 (12)	90 (22)	90 (22)	
Missing	440	78	0		120	24	0		7	0	0	

(continued)

Table 1 (continued)

	SPK				PAK				PTA			
	2001–2005	2006–2009	2011–2016	*P*	2001–2005	2006–2009	2011–2016	*P*	2001–2005	2006–2009	2011–2016	*P*
Blood group												
A	1628 (39)	1451 (36)	1541 (35)	.06	525 (40)	310 (40)	168 (42)	.42	220 (41)	200 (46)	171 (41)	.31
B	486 (12)	497 (12)	536 (12)		171 (13)	78 (10)	47 (12)		54 (10)	36 (10)	47 (11)	
AB	171 (4)	179 (4)	186 (4)		61 (4)	29 (4)	15 (4)		19 (4)	21 (5)	12 (3)	
O	1907 (45)	1882 (47)	2079 (48)		564 (43)	353 (46)	169 (42)		240 (45)	178 (41)	188 (45)	
Time to Tx (days)												
0–30	350 (8)	373 (9)	424 (10)	<.0001	166 (13)	62 (8)	30 (7)	<.0001	94 (18)	76 (18)	71 (17)	.32
30–180	1139 (27)	1279 (32)	1413 (33)		482 (36)	219 (28)	82 (21)		241 (45)	191 (44)	165 (40)	
180–360	957 (23)	920 (23)	919 (21)		293 (22)	181 (24)	83 (21)		93 (17)	93 (22)	93 (22)	
≥360	1746 (42)	1437 (36)	1586 (36)		380 (29)	308 (40)	204 (51)		105 (20)	89 (21)	89 (21)	

Abbreviations: # number, *PRA* panel reactivity assay, *Tx* transplant

Table 2 Donor characteristics for primary deceased donor pancreas transplants performed from 2001 to 2005, 2006 to 2010, and 2011 to 2016

	SPK				PAK				PTA			
	2001–2005	2006–2009	2011–2016	*P*	2001–2005	2006–2009	2011–2016	*P*	2001–2005	2006–2009	2011–2016	*P*
# Primary Tx (%)	4192 (69)	4009 (77)	4342 (84)	—	1321 (22)	770 (15)	399 (8)	—	533 (9)	435 (8)	418 (8)	—
Donor age (years)												
<15	425 (10)	377 (9)	452 (10)	<.0001	167 (19)	70 (9)	62 (9)	<.0001	64 (12)	45 (10)	64 (15)	.0007
16–30	2407 (57)	2544 (63)	2961 (68)		793 (60)	533 (69)	270 (68)		313 (59)	287 (66)	282 (68)	
31–45	1078 (26)	918 (23)	837 (19)		300 (23)	142 (18)	63 (16)		124 (23)	82 (19)	62 (15)	
>45	282 (8)	170 (4)	92 (2)		61 (5)	25 (3)	4 (1)		32 (6)	21 (5)	10 (2)	
Donor gender												
Male	2864 (68)	2747 (69)	3040 (70)	.18	915 (69)	534 (69)	294 (74)	.21	345 (65)	293 (67)	274 (66)	.68
Donor race												
White	2958 (71)	2540 (63)	2671 (62)	<.0001	969 (73)	495 (64)	239 (60)	<.0001	394 (74)	300 (69)	275 (66)	.01
Black	573 (14)	750 (19)	852 (20)		145 (11)	124 (16)	74 (18)		54 (10)	64 (15)	75 (18)	
Hispanic	559 (13)	596 (15)	609 (14)		171 (13)	130 (17)	66 (12)		66 (12)	62 (14)	56 (13)	
Asian	62 (1)	75 (2)	94 (2)		19 (1)	15 (2)	11 (3)		6 (1)	4 (1)	8 (2)	
Multiracial or other	40 (1)	48 (1)	116 (3)		17 (1)	6 (1)	9 (2)		13 (2)	5 (1)	4 (0)	
Donor cause of death												
Trauma	3139 (76)	3078 (78)	3410 (80)	<.0001	1001 (77)	589 (78)	301 (78)	.64	392 (75)	319 (75)	308 (76)	.25
CCV	976 (24)	845 (21)	856 (20)		295 (23)	166 (22)	86 (22)		126 (24)	106 (25)	89 (22)	
CNS tumor	27 (0)	22 (1)	9 (0)		7 (1)	1 (0)	1 (0)		7 (1)	1 (0)	7 (2)	
Missing	2	4	4		18	8	8		8	9	16	
DCD donor	55 (1)	129 (3)	113 (3)	<.0001	7 (1)	8 (1)	1 (0)	.21	10 (2)	12 (3)	13 (3)	.45
Donor body mass index												
<18.5 (underweight)	264 (6)	233 (6)	281 (6)	.07	81 (6)	34 (4)	27 (7)	.0007	37 (7)	26 (6)	39 (9)	.002
18.5–24.9 (normal)	2411 (58)	2301 (57)	2492 (58)		752 (57)	430 (56)	243 (61)		243 (61)	254 (59)	255 (61)	
25–29.9 (overweight)	1168 (28)	1169 (29)	1277 (29)		382 (29)	261 (34)	113 (28)		113 (28)	129 (30)	111 (27)	
>30 (obese)	347 (8)	302 (8)	288 (7)		106 (8)	45 (6)	16 (4)		16 (4)	25 (6)	12 (3)	
Missing	14	15	260		0	0	0		0	1	1	
HLA A, B, DR MM												
0	77 (2)	27 (1)	16 (0)	<.0001	19 (1)	4 (1)	1 (0)	<.0001	8 (2)	4 (1)	4 (1)	<.0001
1	55 (1)	13 (0)	23 (1)		33 (3)	14 (2)	5 (1)		26 (5)	9 (2)	6 (1)	
2	133 (3)	134 (3)	128 (3)		102 (8)	22 (3)	20 (5)		56 (11)	22 (5)	30 (7)	

(continued)

Table 2 (continued)

	SPK				PAK				PTA			
	2001–2005	2006–2009	2011–2016	*P*	2001–2005	2006–2009	2011–2016	*P*	2001–2005	2006–2009	2011–2016	*P*
3	556 (13)	481 (13)	520 (12)		235 (18)	121 (16)	54 (14)		125 (23)	70 (16)	72 (17)	
4	1071 (26)	1001 (25)	1170 (27)		361 (27)	198 (26)	105 (26)		112 (21)	113 (26)	104 (25)	
5	1457 (35)	1443 (36)	1527 (35)		360 (27)	267 (35)	147 (37)		131 (25)	136 (31)	120 (29)	
6	841 (20)	910 (23)	958 (22)		209 (16)	144 (19)	67 (17)		75 (14)	81 (19)	82 (19)	
Rec/Dnr CMV status												
−/−	886 (23)	778 (21)	833 (20)	<.0001	257 (21)	137 (19)	66 (15)	.27	119 (24)	114 (28)	94 (23)	.04
−/+	1176 (30)	1199 (32)	1168 (27)		309 (26)	211 (29)	101 (26)		153 (30)	109 (26)	148 (36)	
+/−	738 (19)	666 (18)	864 (20)		259 (22)	144 (20)	92 (24)		106 (21)	87 (21)	63 (15)	
+/+	1115 (28)	1148 (30)	1393 (33)		377 (31)	233 (32)	199 (33)		127 (25)	101 (25)	105 (26)	
Missing	227	218	84		119	45	11		28	8	8	

Table 3 Transplant characteristics for primary deceased donor pancreas transplants performed from 2001 to 2005, 2006 to 2010, and 2011 to 2016

	SPK				PAK				PTA			
Transplant year	2001–2005	2006–2009	2011–2016	*P*	2001–2005	2006–2009	2011–2016	*P*	2001–2005	2006–2009	2011–2016	*P*
# Primary Tx (%)	4192 (69)	4009 (77)	4342 (84)	—	1321 (22)	770 (15)	399 (8)	—	533 (9)	435 (8)	418 (8)	—
Tx center volume												
Low	239 (6)	215 (5)	274 (6)	<.0001	63 (5)	84 (11)	49 (12)	<.0001	10 (2)	7 (2)	22 (5)	<.0001
Medium	858 (20)	985 (25)	1030 (24)		329 (25)	193 (25)	114 (29)		49 (9)	84 (19)	58 (14)	
Large	3095 (74)	2809 (70)	2073 (70)		929 (70)	493 (64)	236 (59)		474 (89)	344 (79)	338 (81)	
Preservation time (h)												
0<12	1491 (46)	2009 (65)	2705 (65)	<.0001	382 (37)	376 (54)	227 (59)	<.0001	117 (28)	205 (53)	218 (54)	<.0001
12–23	1636 (50)	1479 (41)	1374 (33)		610 (58)	306 (44)	150 (40)		283 (67)	175 (45)	184 (45)	
>24	132 (4)	102 (3)	76 (2)		51 (5)	12 (2)	2 (1)		25 (6)	7 (2)	4 (1)	
Missing	993	419	187		278	76	20		108	48	12	
Duct management												
Enteric drainage	3464 (85)	3548 (91)	3938 (92)	<.0001	967 (74)	639 (85)	357 (91)	<.0001	346 (66)	337 (79)	376 (91)	<.0001
Bladder drainage	611 (15)	318 (8)	322 (8)		339 (26)	98 (13)	28 (7)		172 (33)	89 (21)	35 (9)	
Duct injection	24 (0)	40 (1)	10 (0)		4 (0)	18 (2)	9 (2)		5 (1)	1 (0)	0 (0)	
Missing	93	103	72		11	15	5		10	8	7	

Outcome

Patient Survival

The outcomes of pancreas transplantation improved significantly over time. Patient survival improved significantly at 1-year (3-year) posttransplant for SPK from 95.2% (91.0%) in 2001–2005 (91.0%), to 97.6% (94.6%) in 2011–2016 (Fig. 6a). Ten-year patient survival reached 71.6% for transplants performed from 2001 to 2005. The improvement was significant from time period to time period ($P < .008$). For PAK, the improvement in patient survival occurred between the periods of 2001–2005 and 2006–2010 (Fig. 6b) and only there a significant improvement in patient survival was detected ($P = .05$). PAK patient survival at 10 years was 64.8% for transplants between 2001 and 2005. PTA patient survival was the highest in the three categories. The improvement in patient survival was noted for transplants between the periods of 2001–2010 and 2011–2016. The increase in PTA survival between the time periods did not reach significance ($P = .11$). PTA patient survival at 10 years reached 72.3% for transplants from 2001 to 2005 (Fig. 6c). According to recent report, patient survival has been improved in all three categories [1] (Figs. 7, 8 and 9).

The distribution of the causes of death changed during the posttransplant time in all three categories. For the first 3 months, posttransplant cardiocerebrovascular events and infections were the main reason for patient death. Overall, in 11% of death, the reason was unknown, and those were most likely also cardiocerebrovascular accidents. During the next 9 months infections and unknown causes remained the main reason for death. For the next 5 years, cardiocerebrovascular events were the main reason, followed by infections. In one-third of all deaths, the reasons were unknown, and these may also have been cardiocerebrovascular events. Malignancies made up for 7% of deaths during this time. The distribution of death causes did not change significantly over the analyzed time periods.

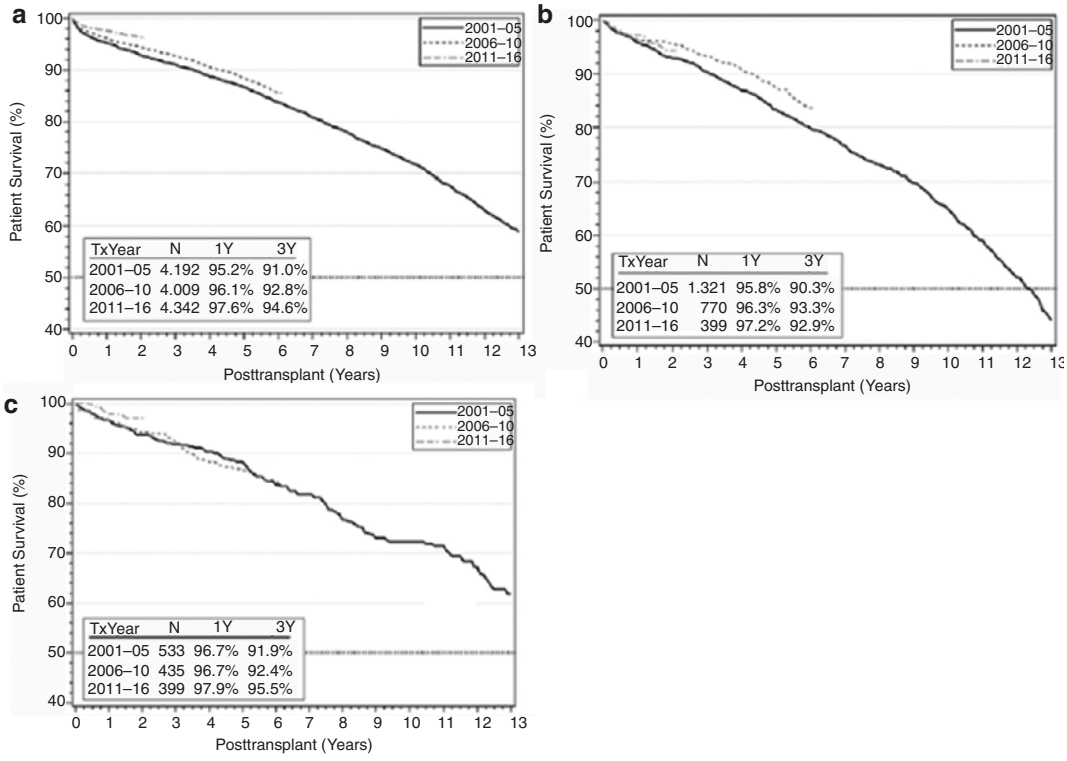


Fig. 6 Patient survival following pancreas transplantation in Asan Medical Center (2001–2016)

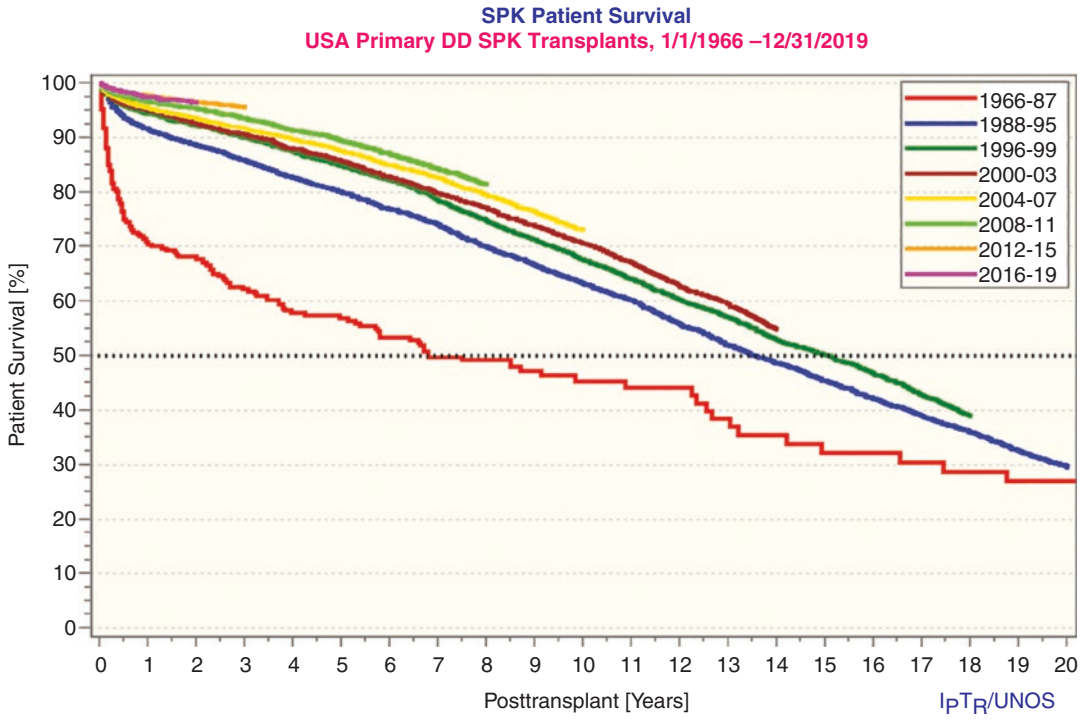


Fig. 7 Patient survival in primary DD SPK transplantation in the USA (1996–2019)

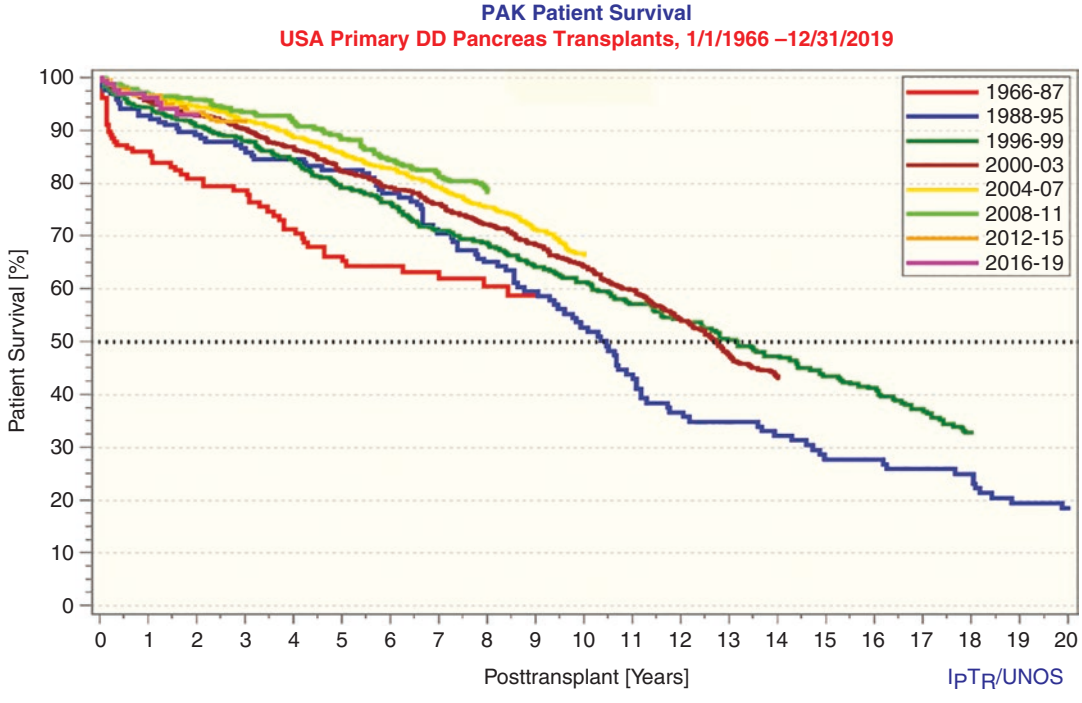


Fig. 8 Patient survival in primary DD PAK transplantation in the USA (1996–2019)

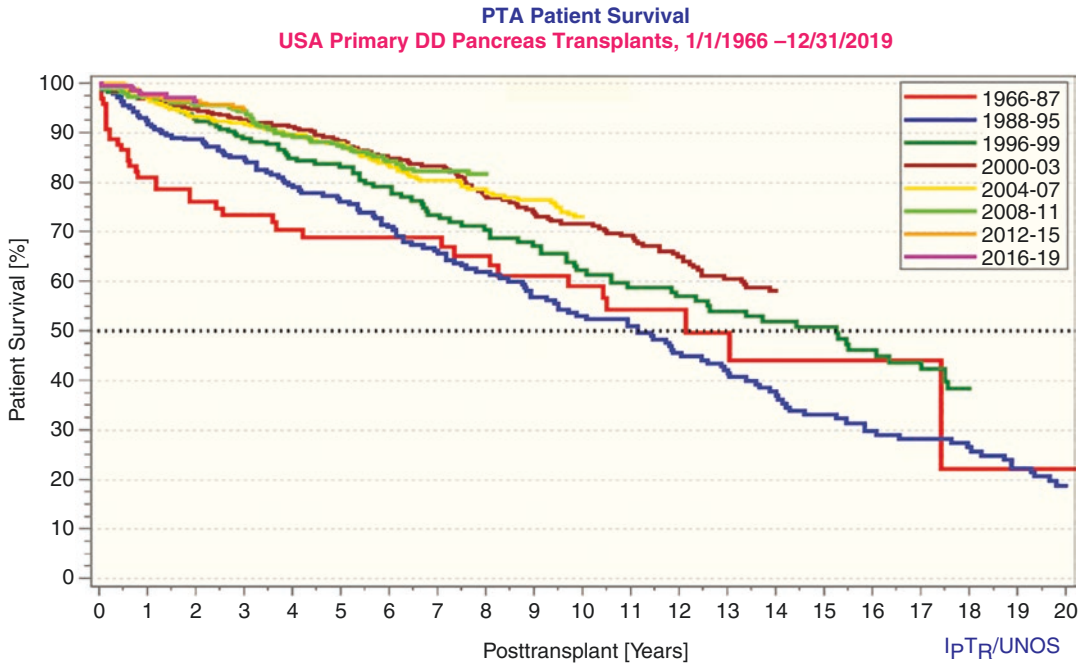


Fig. 9 Patient survival in primary DD PTA transplantation in the USA (1996–2019)

The multivariate risk factor analysis for patient survival after transplantation (Table 4) showed that losing a pancreas and/or a kidney graft represented the highest relative risk to die. Losing a kidney was more life-threatening than losing the pancreas in SPK and in PAK.

Older recipient age at transplant was a risk factor. The relative risk to die increased with growing age in SPK and PAK. In PTA, the relative risk to die was also increased in pancreas transplant recipients younger than the age of 30 years. This is the group of patients with very brittle diabetes who have a high cardiocerebrovascular risk to die. In SPK, being on dialysis pretransplant increased the relative risk to die by 40%. In a separate analysis, it could be shown that the relative risk to die increased by 9% for every year on dialysis.

Having received a previous living donor versus a deceased donor kidney in PAK decreased the relative risk to die. Having a deceased donor kidney raised the relative risk by 46%.

Diabetes type, recipient gender and race, and center volume did not significantly affect patient survival. The significant improvement of patient survival over time could only be verified by the multivariate analyses for SPK but not for the solitary transplants.

Graft Function

SPK pancreas graft function improved over the analyzed time significantly 1-year (3-year) to 89.9% (83.4%) from 2011 to 2016 (Fig. 10a). The improvement in pancreas graft function was significant (P = .001). Ten-year SPK pancreas graft function reached 56.6% for 2001–2005 transplants. SPK kidney graft function improved accordingly (Fig. 10b). As in SPK transplantation, the significant changes happened between the periods of 2006–2010 and 2011–2016 (P = .003). The most critical time for graft loss is the first-year posttransplant. When only the SPK transplants were analyzed that reached the first-year mark with a functioning graft, 3-year pancreas graft function reached greater than 92%, and no difference could be found between the different time periods (P = .17). For SPK kidney graft function with greater than 1-year graft func-

Table 4 Risk factor analysis for patient death after pancreas transplantation performed from 2001 to 2005, 2006 to 2010, and 2011 to 2016

	SPK		PAK		PTA	
	RR (95% CI)	*P*	RR (95% CI)	*P*	RR (95% CI)	*P*
Transplant year						
2001–2005	1.00	.0002	1.00	.31	1.00	.26
2006–2010	0.83 (0.71–0.97)		0.77 (0.54–1.08)		0.96 (0.59–1.58)	
2011–2016	0.68 (0.56–0.81)		0.86 (9.30–1.13)		0.58 (0.30–1.13)	
Recipient age						
18–30	1.01 (0.79–1.28)	<.0001	0.91 (0.49–1.68)	.03	2.05 (1.08–3.91)	.005
31–45	1.00		1.00		1.00	
>45	1.65 (1.42–1.92)		1.46 (1.08–1.98)		2.29 (1.37–3.81)	
Recipient gender						
Female	1.00	.57	1.00	.80	1.00	.67
Male	1.04 (0.90–1.20)		1.04 (0.77–1.40)		1.10 (0.70–1.74)	
Recipient race						
White	1.00	.52	1.00	.13	1.00	.86
Black	0.96 (0.79–1.16)		1.37 (0.87–2.15)		0.61 (0.18–4.40)	
Hispanic	0.83 (0.64–1.07)		0.50 (0.23–1.08)		0.54 (0.17–3.94)	
Other	1.05 (0.71–1.55)		—		—	
Diabetes						
Type 1 DM	0.99 (0.78–1.28)	.98	1.29 (0.63–2.66)	.51	0.44 (0.19–1.03)	.08
Type 2 DM	1.00		1.00		1.00	
PreTx dialysis						
No	1.0	.0001	—	—	—	—
Yes	1.38 (1.17–1.63)		—		—	
Pancreas status						
Function	1.00	<.0001	1.00	<.0001	1.00	<.0001
Failed	2.56 (2.15–3.04)		2.15 (1.51–3.04)		3.65 (2.18–6.11) 1.00	
Kidney status						
Function	1.00	<.0001	1.00	<.0001	—	—
Failed	10.38 (8.63–12.49)		13.48 (8.69–20.90)		—	
Kidney donor type						
Living	—	—	1.00	.03	—	—
Deceased	—		1.46 (1.04–1.90)		—	
Center volume						
Low	1.00	.12	1.00	.79	1.00	.59
Medium	0.75 (0.57–0.99)		0.82 (0.44–1.50)		1.63 (0.54–4.90)	
High	0.80 (0.62–1.03)		0.88 (0.50–1.54)		1.71 (0.61–4.77)	

tion in all three time periods, the outcome at 3 years was 93.5%, and no differences between the time periods were noted ($P = .55$).

Overall, PAK pancreas graft function improved from period to period ($P < .0001$), but only the progress between the periods of 2001–2005 and 2006–2010 reached statistical significance ($P = .01$) for the pairwise comparison (Fig. 10c). If only PAK were analyzed with pancreas graft function at 1 year, no statistical difference for the time periods could be found, but the long-term outcome increased.

PTA pancreas function increased over time ($P = .004$) (Fig. 10d). The significant improvement for the pairwise comparisons was between the periods of 2001–2005 and 2011–2016. The

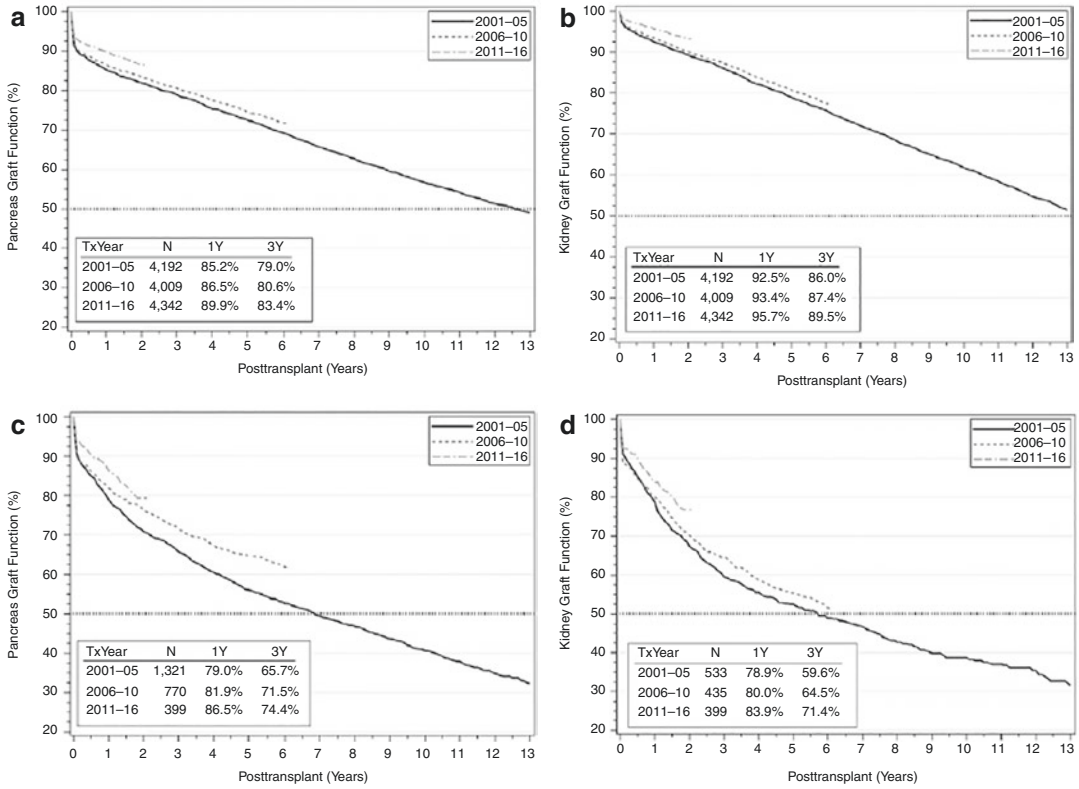


Fig. 10 Graft survival following pancreas transplantation (2001–2016)

improvement remained significant when only PTA transplants with at least 1 year of graft function were analyzed. From 2011 to 2016, 3-year graft function reached 85.1% for those cases. According to a recent report graft function improved in all three categories [1] (Figs. 11, 12 and 13).

In all three categories, technical failures were the main reason for pancreas graft loss during the first 3 months, with greater than 70% of all losses followed by patient death (Fig. 14). During the next 9 months the main reason for graft failure was patient death, especially in PAK and SPK, followed by immunologic losses and infections. In solitary transplants, immunologic pancreas graft losses were significantly higher compared with SPK. After the first year, immunologic graft loss remained the main reason for the failure of SPK and PAK, followed by patient death. In PTA, the main reason remained immunologic graft loss.

In SPK, the main risk factors for graft failure were young age, black race, a body mass index of greater than 30 kg/m^2, older donor age, and longer preservation time. The use of induction therapy and a maintenance protocol based on Tac in combination with MMF decreased the relative risk of graft loss. Higher volume centers had a lower graft loss rate. For SPK, the relative risk for kidney graft loss was significantly lower when the pancreas was enteric-drained and not bladder-drained. The progress could be verified by the model with decreasing risk over time.

For PAK, the younger recipient and older donor ages were the main risk factors for graft loss. Induction therapy and standard maintenance immunosuppression significantly lowered the relative risk. High-volume centers had better outcomes, and the progress over time was confirmed.

For PTA, younger recipient age was the most influential factor, with an increased relative risk of greater than 2.0%. A maintenance protocol that was not based on tacrolimus in combination

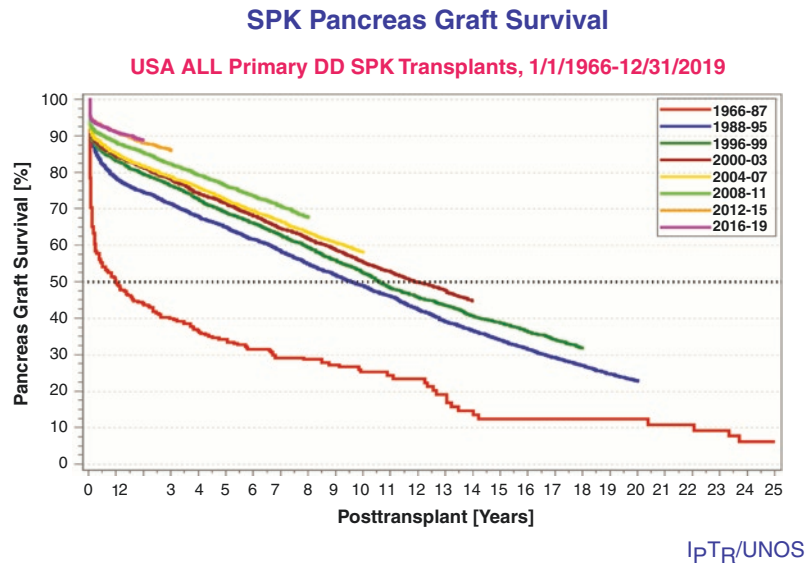


Fig. 11 Graft survival following primary SPK transplantation in the USA (1996–2019)

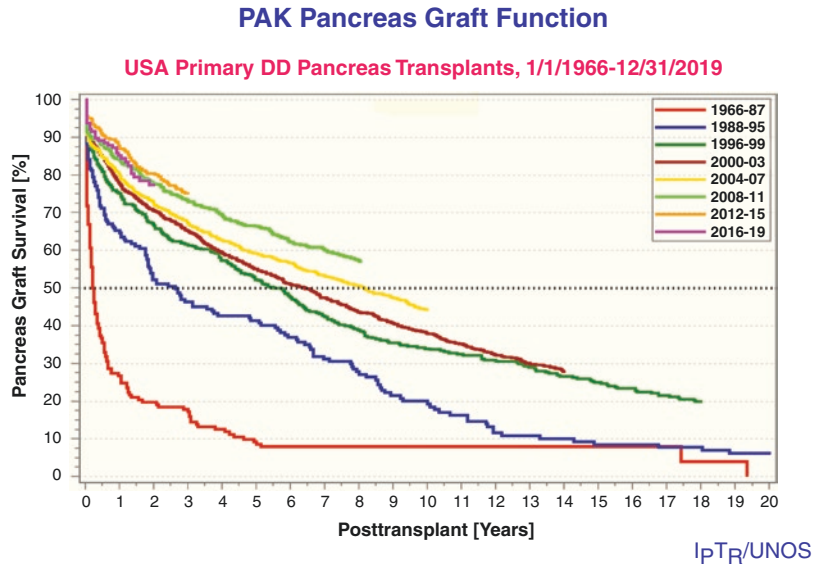


Fig. 12 Graft survival following primary PAK transplantation in the USA (1996–2019)

with MMF, or on sirolimus (SRL), also increased the relative risk of graft failure significantly. No significant improvement over time and no impact of center volume could be detected.

Immunologic Graft Loss

The immunologic graft loss for the SPK pancreas and kidney significantly improved over time for the pancreas (P = .0004) but not for the kidney (P = .45) (Fig. 15). The immunologic loss was initially much lower for the SPK kidney, but, over time, the differences between the two grafts shrunk. Of interest was the constantly ascending slope of the rate of kidney losses. More impressive was the development in PAK (Fig. 15). Here, a highly significant improvement in the reduction of immunologic loss was noted (P < .0001). In PAK, the initial slope of immunologic graft loss was steep, but it slightly leveled off later on. Immunologic pancreas graft loss remained a

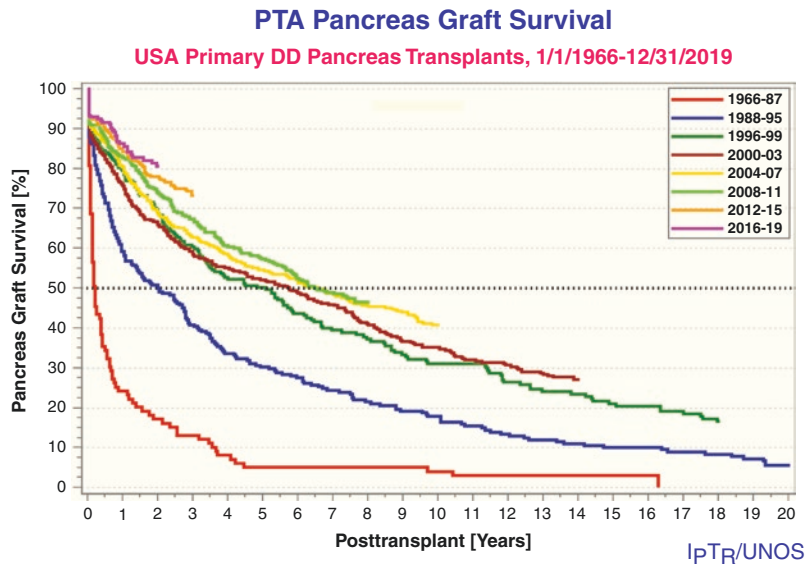


Fig. 13 Graft survival following primary PTA transplantation in the USA (1996–2019)

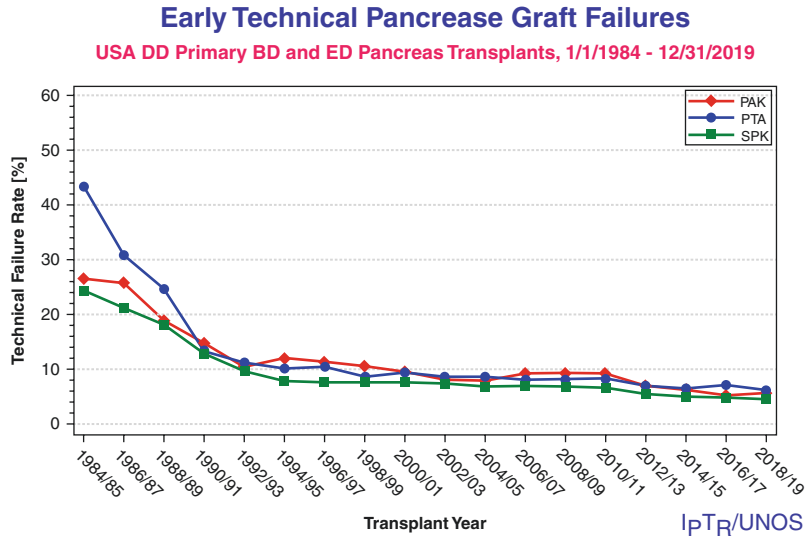


Fig. 14 Early technical graft failures following pancreas transplantation

problem in PTA. A significant reduction of the immunologic loss was found between the periods of 2001–2005 and 2011–2016. As in PAK, the slope was initially steep but then slightly decreased. In all three categories and in the SPK kidney, the relative risk of immunologic graft loss in recipients younger than the age of 30 years was significantly increased.

Male recipients showed a significantly lower relative risk of losing their kidney but not their pancreas graft. For both organs, a treatment of an acute rejection episode during the first-year post-transplant was a significant risk factor, more than doubling the risk of graft loss. Maintenance protocols were important for the pancreas but not for the kidney graft. HLA mismatching and center volume did not significantly affect immunologic loss in SPK. The decline in immunologic losses over time was significant for the pancreas but not for the kidney.

In PAK, a significantly increased risk in recipients with a panel reactive antibody (PRA) level greater than 20% and an HLA-A antigen mismatch could be found. Treatment of an acute

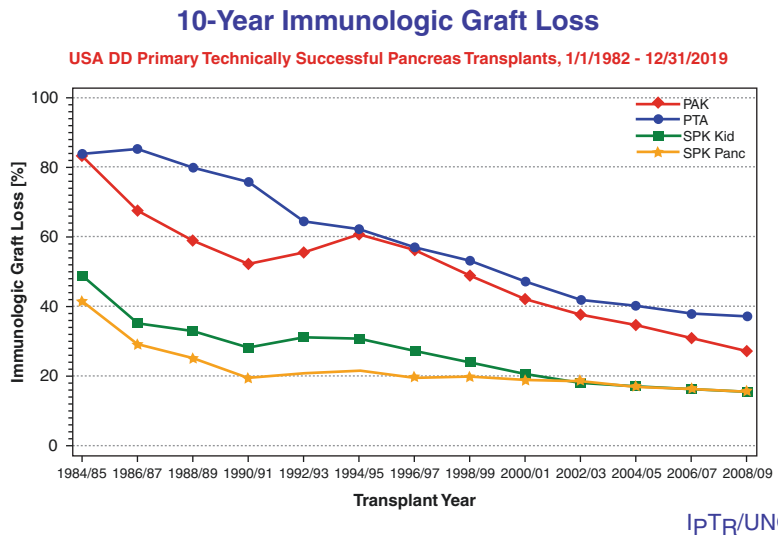


Fig. 15 The chronologic change of immunologic graft loss in pancreas transplant

rejection episode during the first year also increased the relative risk significantly. The overall use of induction therapy could lower the relative risk significantly compared with no induction therapy at all. The decline of immunologic loss overtime was also significant in the multivariate model.

Male recipients showed a significantly lower relative risk for immunologic graft in PTA. Besides the increased risk in younger recipients only treatment of an acute rejection episode during the first year reached significance and more than doubling the relative risk of pancreas loss. The changes in immunologic graft loss were not significant over time.

Comparison of Recent Category Outcomes

Regarding the patient survival for the three transplant categories over the first 3 years for the years from 2011 to 2016, the outcome is not statistically significant between the three categories, but, as expected, the highest patient survival rate could be observed in PTA and the lowest in PAK. The best function could be seen in the SPK kidney; however, when the initial technical problems were eliminated, the SPK kidney and pancreas grafts were almost identical. The outcome of solitary transplants was equal to that of the SPK pancreas during the first 6 months but then dropped. PAK graft function improved over PTA graft function, but the difference was not significant ($P = .67$). The differences in long-term graft function were mainly due to the differences in immunologic graft loss. Although the difference between SPK kidney and pancreas was small, the immunologic graft loss of the solitary grafts was significantly higher. The pairwise comparison of the immunologic graft loss in all three categories was highly significant. The immunologic graft loss in PTA was significantly higher compared with the loss in PAK (Fig. 16). Current analysis of patient and graft kidney graft survival between SPK and living donor kidney alone were compared in which SPK recipients with a functioning pancreas graft had significantly better kidney graft and patient survival than living donor kidney transplant alone [3].

Korea

From 1992 to Dec 2019, 739 patients underwent pancreas transplantation in Korea.

The demographics and clinical characteristics of the two groups are shown in Table 5.

The mean donor age was 28.67 year old, and the male was 64.2%. Causes of the deceased donor were trauma in 235 out of 707 (33.23%), CVA in 132 (18.67%), and others. Pancreas graft

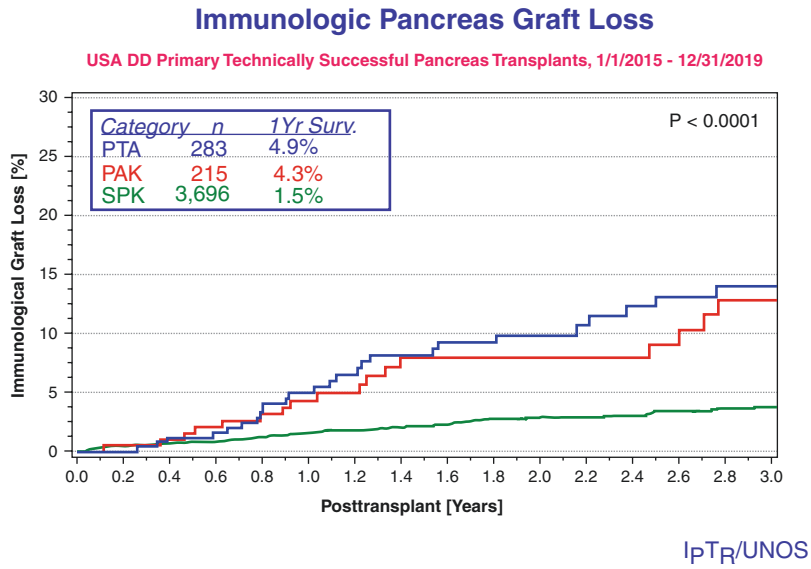


Fig. 16 The immunologic pancreas graft loss according to the operation type

weight was 178.4 g. Cold ischemic time of harvested organ was 375.75 min in the pancreas and 293.87 min in the kidney. The mean age of the patients was 39.0 years old, and the male was 48.4%. BMI was 21.75 kg/m^2. The age of onset of diabetes was 21.8 years old, and the duration diabetes from the onset of diabetes to transplant was 17.1 years. Preoperative insulin requirement was 36.1 u/day, preoperative HbA1C was 8.2%, and preoperative C-peptide was 2.4 ng/ml. HLA DR mismatching was 3.96, and retransplant was 18 (2.5%).

According to the operation type, the number of simultaneous pancreas and kidney transplantation (SPK), pancreas transplant alone(PTA), pancreas-after-kidney transplantation(PAK), and simultaneous deceased pancreas and living donor kidney transplant(SPLK) were 343 (48.5%), 207 (29.3%), 100 (14.1%), and 57 (8.1%) respectively.

Bladder drainage was performed in 251 (35.5%).

Overall patient survivals at 1, 5, 10 years were 96.2%, 93.6%, 90.4% each (Fig. 17). Overall pancreas graft survivals at 1, 5, 10 years were 90.6%, 80.8%, and 75.2% each (Fig. 18). The pancreas graft survivals in SPK, PAK, PTA, and SPLK were 93.6%, 91.6%, 83.7%, and 98.3% respectively at 1 year. Those were 91.0%, 80.2%, 65.9%, and 81.6% at 5 year, and 84.5%, 72.4%, 61.4%, and 81.6% at 10 year respectively which showed the better graft survival in SPK and SPLK in uremic condition compared with PAK or PTA (Fig. 19).

Japan

Herein we show posttransplant outcome after pancreas transplantation (PT) in Japan. A total of 410 PTx were performed for type 1 diabetes from deceased donors in Japan between April 2000 and December 2019 [4]. The PT was performed in 18 approved institutions in Japan, and the clinical data were registered in the Japan Pancreas Transplant Registry of Japan Pancreas and Islet Transplantation Association (JPITA). The following data are based on the extracted data from this registry. Among the 410 PTs, 407 transplantations were from brain-dead donors, and the remaining three were from non-heart-beating donors. Table 6 presents the clinical characteristics of the 410 PTs from deceased donors. The 410 PTs included 344 simultaneous pancreas-kidney transplantation (SPK), 48 pancreas-after-kidney transplantation (PAK), and 18 PT alone (PTA). Notably, 71% of donors (291 out of the 410 cases) satisfied criteria for the marginal donor in expanded donor criteria defined by Kapur et al. Postoperative survival after PT, including overall patient survival and

Table 5 Baseline characteristics

Variables	Overall (n = 707)	SPK (n = 343, 48.5%)	PAK (n = 100, 14.1%)	PTA (n = 207, 29.3%)	SPLK (n = 57, 8.1%)	P-value
Recipient characteristics						
Mean age, years (SD)	38.98 (11.34)	40.44 (9.56)	46.79 (10.52)	32.26 (11.58)	40.91 (8.93)	0.007
Female gender, *n* (%)	365 (51.62)	194 (56.55)	21 (21)	117 (56.52)	33 (57.89)	
Body mass index, kg/m^2 (SD)	21.75 (3.14)	21.61 (3.16)	22.52 (3.01)	21.78 (3.02)	21.12 (3.50)	0.981
Onset of DM, years (SD)	21.79 (10.05)	20.46 (8.57)	27.37 (10.49)	20.77 (11.25)	23.49 (9.25)	<.0001
Duration of DM, years (SD)	17.08 (7.75)	19.86 (6.20)	19.13 (7.02)	11.53 (7.40)	17.56 (7.84)	
Insulin amount in use, IU/day (SD)	36.06 (21.20)	28.75 (19.55)	41.31 (21.21)	44.76 (20.56)	32.75 (17.37)	
HbA1c, % (SD)	8.23 (2.17)	7.69 (1.87)	7.95 (1.33)	9.45 (2.62)	7.41 (1.27)	<0.001
C-peptide, ng/mL (SD)	2.44 (6.22)	4.28 (8.58)	1.31 (2.22)	0.26 (0.57)	2.44 (3.73)	<0.001
Anti-GAD antibody, U/mL (SD)	4.44 (16.38)	3.08 (16.63)	3.09 (13.05)	697 (18.13)	3.61 (12.36)	0.040
Bladder drainage, *n* (%)	251 (35.50)	80 (23.32)	43 (43)	96 (46.37)	32 (56.14)	
HLA-DR mismatch, *n* (SD)	3.96 (1.29)	3.75 (1.25)	4.33 (1.23)	4.07 (1.32)	4.14 (1.32)	0.657
Retransplant, *n* (%)	18 (2.54)	6 (1.74)	6 (6)	5 (2.41)	1 (1.75)	
Donor characteristics						
Mean age, years (SD)	28.67 (10.43)	31.28 (11.15)	27.36 (9.19)	25.80 (9.19)	25.70 (8.20)	<0.001
Female gender, *n* (%)	253 (35.78)	107 (31.19)	35 (35)	90 (43.47)	21 (36.84)	
Body mass index, kg/m^2 (SD)	21.88 (3.30)	22.09 (3.38)	21.91 (2.64)	21.66 (3.45)	21.45 (3.32)	0.125
Cold ischemic time, h (SD)						
Pancreas	375.75 (141.31)	407.31 (147.53)	345.52 (130.32)	331.73 (117.79)	419.96 (151.29)	0.072
Kidney	293.87 (169.31)	333.24 (153.62)	–	–	93.84 (83.10)	0.004
Cause of death						
Trauma, *n* (%)	235 (33.23)	104 (30.32)	32 (32)	74 (35.74)	25 (43.85)	
CVA[8], *n* (%)	132 (18.67)	89 (25.94)	16 (16)	23 (11.11)	4 (7.01)	
Pancreas graft weight, g (SD)	178.40 (45.94)	176.51 (47.54)	184.01 (39.86)	175.77 (45.82)	187.66 (45.19)	0.772

graft survival, was investigated in the 410 cases of PT from deceased donors (Fig. 20). Pancreas graft loss was defined as the return to a serum C-peptide level of <0.3 ng/ml, and kidney graft loss was defined as the reintroduction of dialysis. For the assessment of graft survival, death with a functioning graft (DWFG) was considered graft failure. At 1, 3, 5, and 10 years after PT, the overall patient survival rates were 95.8%, 95.8%, 94.2%, and 88.7%, respectively. Pancreas and kidney graft survival rates of 1, 3, 5, and 10 years after PT were 85.9%, 80.6%, 76.2%, and 67.4%, in pancreas and 93.2%, 92.9%, 90.8%, and 78.2%, in kidney respectively. Pancreas graft survival was also investigated according to the category of PT (Fig. 21). At 1, 3, 5, and 10 years after PT, the pancreas graft survival rates were 87.3%, 85.4%, 83.2%, and 74.6% among the 344 SPK respectively while 85.4%, 67.6%, 52.3%, and 41.8% among the 48 PAK cases. The 1-, 3-, and 5-year pancreas graft survival rates among the 18 PTA cases were 66.7%, 41.6%,

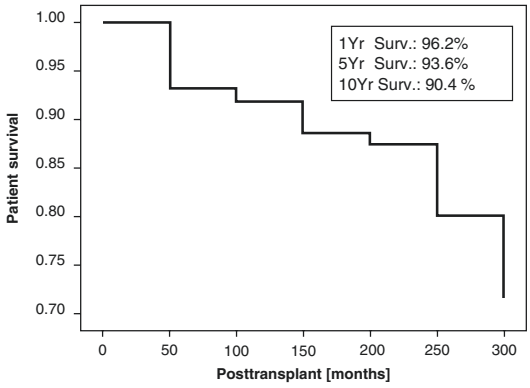


Fig. 17 Patient survival following pancreas transplant in Korea, June 1992–Dec 2020

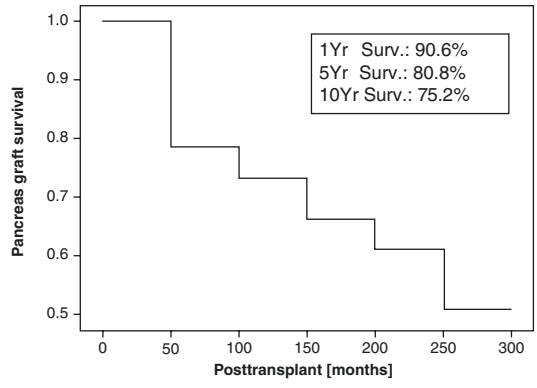
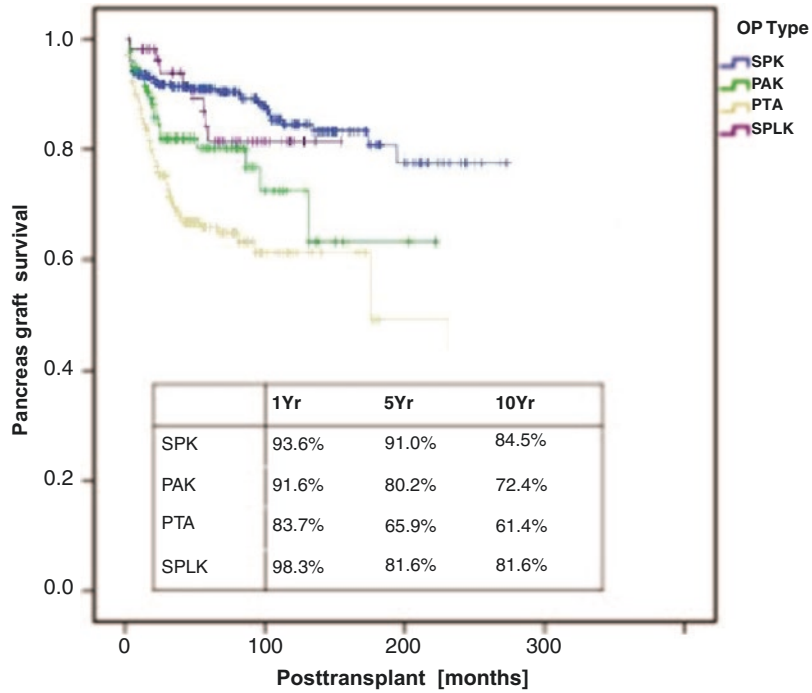


Fig. 18 Pancreas graft survival following pancreas transplant in Korea, June 1992–Dec 2020

Fig. 19 Pancreas graft survival according to operation type in Korea, June 1992–Dec 2020



and 31.2%, respectively. Survival was significantly better in SPK cases as compared to PAK and PTA cases.

Taiwan

The overall rejection rate of pancreas graft was 24.8%, with 18.2% acute and 9.7% chronic rejection**.** Rejection was highest in the PTA group (36.0%), followed by SPK (23.7%), PAK (16.7%), and lowest in PBK (3.6%). There were 56 (33.9%) cases with pancreas graft loss, with the highest graft loss rate in PTA (38.7%), followed by PBK (38.5%), SPK (28.9%), and PAK (25.0%). Rejection was attributed to 53.6% (30/56) of pancreas graft losses. The most common cause for the pancreas graft loss was chronic rejection in PTA (24.0%) and SPK (13.2%), (P = 0.002). However, the majority of pancreas

Table 6 Clinical background characteristics of 410 PTs in Japan

Factor		All cases (n = 410)
Donor-related factors		
Age, years		43 (4–72)
Sex	Male	234 (57%)
	Female	176 (43%)
Height, cm		165 (110–186)
Weight, kg		58.5 (18.5–94.1)
BMI, kg/cm^2		21.8 (11.4–34.3)
Cause of death	CVA	208 (51%)
	Anoxic brain injury	114 (28%)
	Head trauma	78 (19%)
	Heart disease	7 (2%)
	Other	3 (1%)
HbA1c, %		5.4 (4.3–7.7)
Cardiopulmonary arrest	–	220 (54%)
	+	190 (46%)
Cardiopulmonary arrest time, min		36 (2–282)
Hemodynamic stability	–	201 (49%)
	+	209 (51%)
Marginal donor using expanded donor criteria	–	119 (29%)
	+	291 (71%)
HLA mismatch number		3 (0–6)
Recipient-related factors		
Age, years		44 (24–69)
Sex	Male	161 (39%)
	Female	249 (61%)
Height, cm		161 (139–185)
Weight, kg		54 (36–87)
BMI, kg/cm^2		20.9 (14.6–30.5)
HbA1c, %		7.6 (4.8–15.2)
Anti-CMV IgG antibody	–	103 (25%)
	+	295 (72%)
Duration of diabetes, years		28 (2–53)
Duration of dialysis, years		7 (0–29)
Time from registration to PT, days		1395 (6–5740)
PT-related factors		
PT category	SPK	344 (84%)
	PAK	48 (12%)
	PTA	18 (4%)
Transport time, min		227 (0–560)
Ischemic time of pancreas graft, min		718 (271–1381)
Ischemic time of kidney graft, min		611 (196–1357)
Portal vein extension	–	323 (79%)
	+	87 (21%)
Arterial reconstruction	Carrel patch	355 (87%)
	Y graft	55 (13%)
GDA reconstruction	–	191 (47%)
	+	219 (53%)
Duct management	Bladder drainage	52 (10%)
	Enteric drainage	358 (90%)

Data are presented as number of patients (percentage) or median (range)
BMI body mass index, *CMV* cytomegalovirus, *CVA* cerebrovascular accident, *GDA* gastroduodenal artery, *HbA1c* hemoglobin A1c, *HLA* human leukocyte antigen, *PAK* pancreas-after-kidney transplantation, *PTA* pancreas transplantation alone, *PT* pancreas transplantation, *SPK* simultaneous pancreas-kidney transplantation

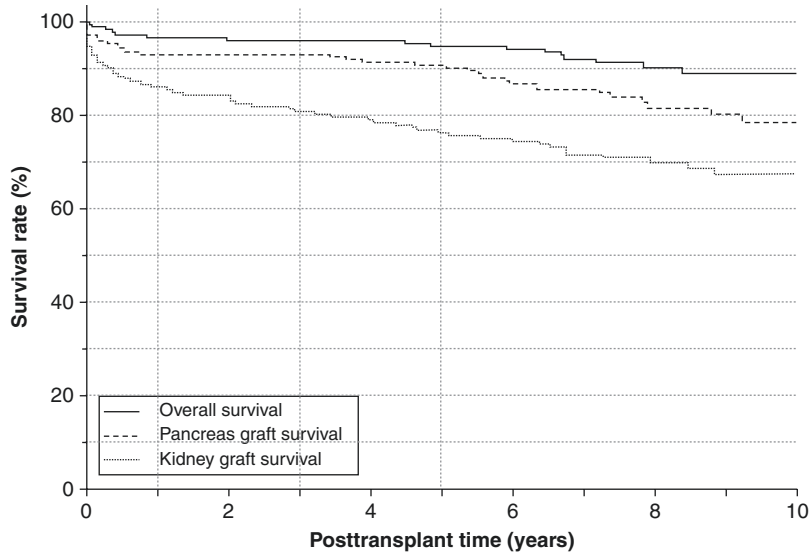


Fig. 20 Overall patient survival and graft survival of deceased donor pancreas transplantation in Japan (Registration Committee of JPITA, 2004–2019)

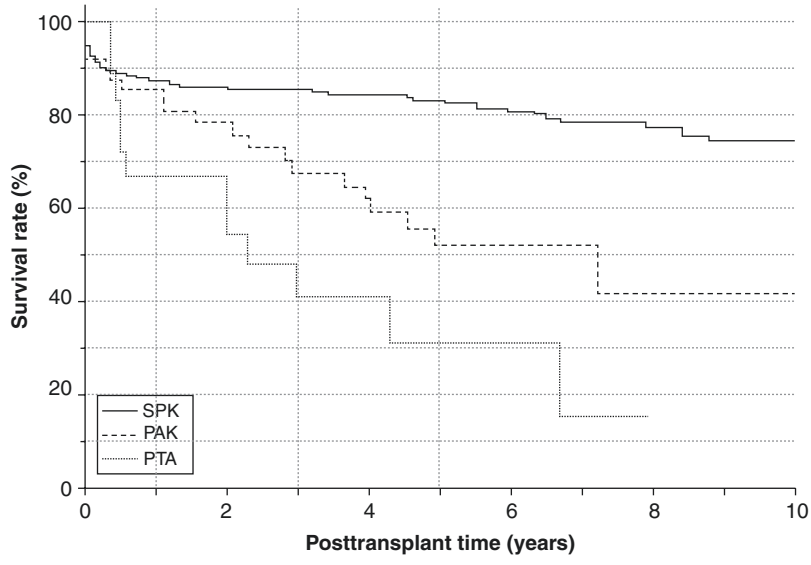


Fig. 21 Pancreas graft survivals depending on the category in Japan (Registration Committee of JPITA, 2004–2019)

graft loss in PBK (32.1%) and PAK (12.5%) were due to patient death with a functioning graft, ($P = 0.001$). Eight (4.8%) of the patients with loss of pancreas graft underwent another successful re-transplant.

The 1-year, 5-year, and 10-year pancreas graft survivals for total patients were 97.4%, 87.2% and 70.4%, respectively (Table 7; Fig. 22). Pancreas graft survival after PTA was the worst among the pancreas transplant subgroups ($P < 0.001$) (Fig. 23). The 1-year, 5-year, and 10-year patient survivals in 156 patients were 96.7%, 91.1% and 91.1%, respectively (Table 8; Fig. 24). Patient survival after PBK was worse than other pancreas transplant subgroups ($P < 0.001$) (Fig. 25). The causes for patient death in the PBK group included three cerebrovascular accidents, two acute myocardial infarction, two sepsis, one hepatic failure due to hepatitis B, and one unknown cause.

Table 7 Pancreas graft survivals after pancreas transplant at Taipei Veterans General Hospital

	Total	SPK	PAK	PTA	PBK	*P*-value
Pancreas graft						
Case number	156	36	19	75	26	<0.001
Median, month	69	119	66	62	39	
Range, month	2–204	5–204	10–173	2–160	3–124	
Mean ± SD, month	76 ± 51	113 ± 53	76 ± 46	67 ± 45	47 ± 38	
1-year survival	97.4%	100%	100%	94.6%	100%	
5-year survival	87.2%	97.0%	100%	76.1%	100%	
10-year survival	70.4%	89.1%	100%	47.5%	100%	

Technique failure was not included; Graft loss due to patient death with functioning graft was considered as death censor

SPK simultaneous pancreas and kidney transplant, *PAK* pancreas-after-kidney transplant, *PTA* pancreas transplant alone, *PBK* pancreas before kidney transplant

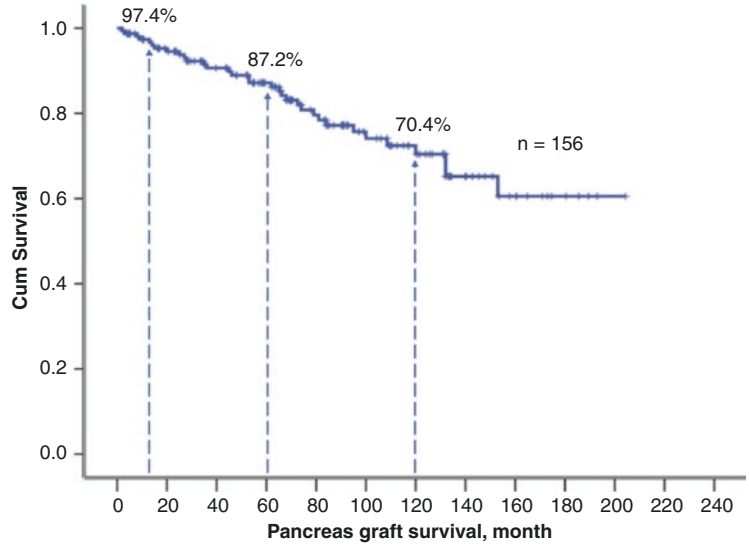


Fig. 22 Pancreas graft survival for overall patients after pancreas transplants. Technique failure was not included. Graft loss due to patient death with functioning graft was considered as death censor

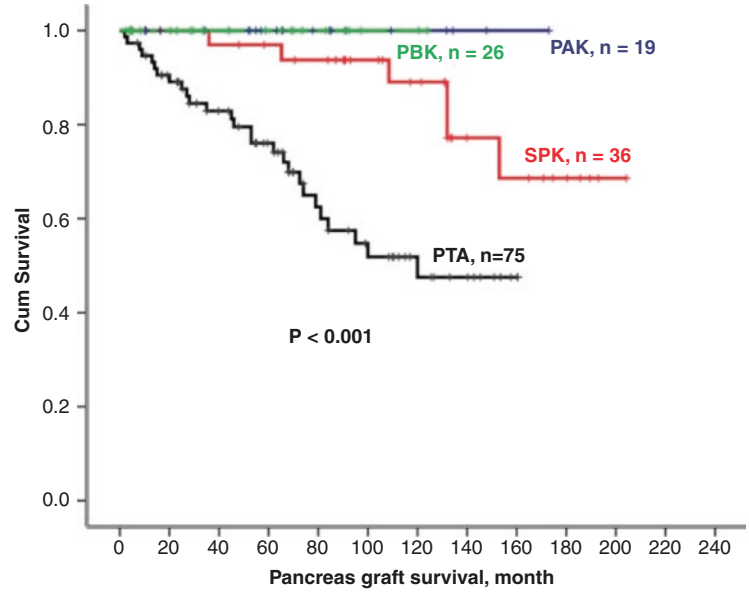


Fig. 23 Pancreas graft survivals after pancreas transplants. *SPK* simultaneous pancreas and kidney transplant, *PAK* pancreas-after-kidney transplant, *PTA* pancreas transplant alone, *PBK* pancreas before kidney transplant. Technique failure was not included. Graft loss due to patient death with functioning graft was considered as death censor

Table 8 Patient survivals after pancreas transplant at Taipei Veterans General Hospital

	Total	SPK	PAK	PTA	PBK	*P*-value
Patient						
Case number	156	36	19	75	26	<0.001
Median, month	69	126	66	84	44	
Range, month	2–204	5–204	10–173	2–160	3–124	
Mean ± SD, month	76 ± 51	114 ± 53	76 ± 46	68± 45	47 ± 38	
1-year survival	96.7%	97.1%	100%	100%	83.8%	
5-year survival	91.1%	94.1%	100%	98.5%	68.3%	
10-year survival	91.1%	94.1%	100%	94.9%	68.3%	

Patients with surgical mortality and technique failure were not included
SPK simultaneous pancreas and kidney transplant, *PAK* pancreas-after-kidney transplant, *PTA* pancreas transplant alone, *PBK* pancreas before kidney transplant

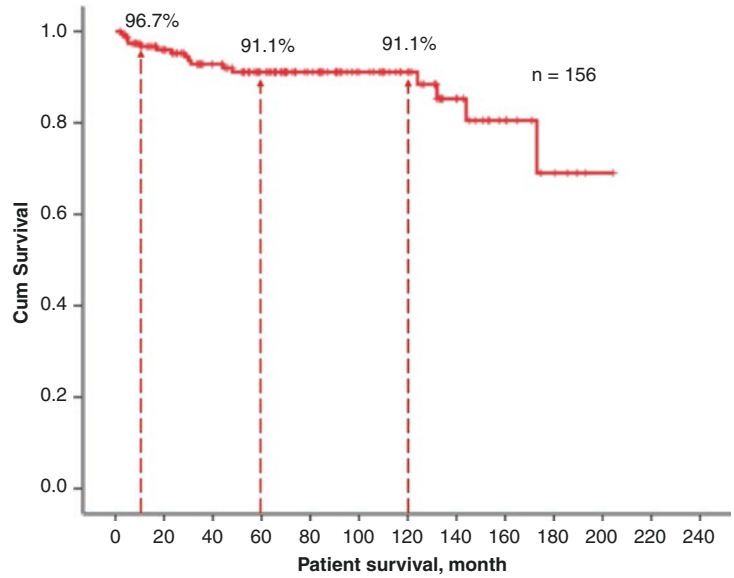


Fig. 24 Patient survival for overall patients after pancreas transplants. Patients with surgical mortality and technique failure were not included

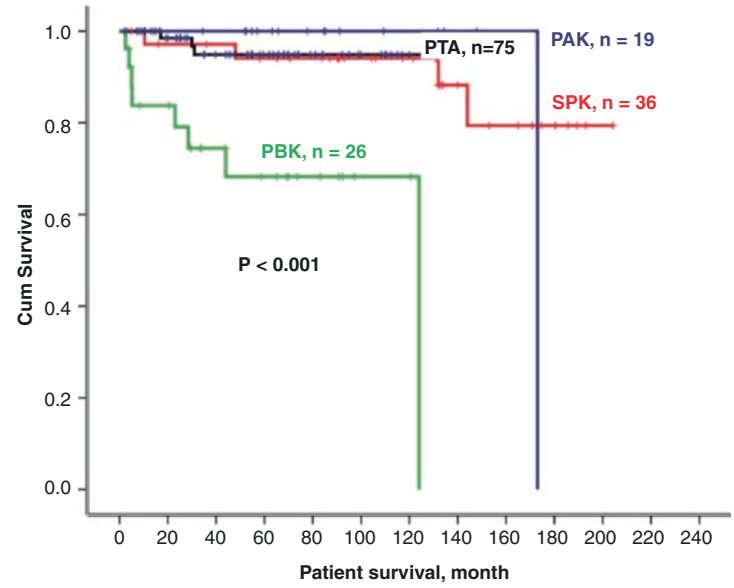


Fig. 25 Patient survivals after pancreas transplants. *SPK* simultaneous pancreas and kidney transplant, *PAK* pancreas-after-kidney transplant, *PTA* pancreas transplant alone, *PBK* pancreas before kidney transplant. Technique failure was not included. Patients with surgical mortality and technique failure were not included

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The Effect of Pancreas Transplant on the Diabetic Complication

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General

Nephropathy

Bohman et al. [1] in 1985 first demonstrated that the development of diabetic glomerulopathy was prevented in recipients of SPK (two patients) and PAK (six patients). Thus, pancreas transplant performed within the first several years after KT appears to halt the progression of diabetic glomerulopathy lesions [2].

It appeared that the total mesangial volume per glomerulus stopped expanding in the pancreas transplant recipients but continued to expand in the untreated patients [3]. Nevertheless, the disappointing conclusion of this study was that diabetic glomerulopathy lesions were not reversed by 5 years of normoglycemia. However, GBM and TBM width, unchanged at 5 years, decreased at 10-year follow-up. Total mesangial and total mesangial matrix volumes per glomerulus were consequently unchanged at 5 years and markedly decreased at 10 years.

Thus, this study provides clear evidence that diabetic glomerular and tubular lesions in humans are reversible [4].

Retinopathy

Most of the studies showed little impact on the progression of retinopathy. However, results pointed to the possibility that the beneficial effects on retinopathy appeared by about 3 years posttransplant, that a transplant is probably more helpful if performed at earlier stages of retinopathy, and that a transplant may have a benefit regarding macular edema [5].

From an ophthalmologic standpoint, it seems almost a certainty that earlier transplants would be of benefit in preventing the development or progression of diabetic retinopathy.

Neuropathy

Polyneuropathy affecting somatic and autonomic nervous systems is a common secondary complication of long-term diabetes mellitus.

Chronic hyperglycemia with its metabolic consequences is considered the most important factor in the development of diabetic neuropathy [6, 7].

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After a successful pancreas transplant, the results of neurological evaluations tended to improve, as indicated by the increase in the mean values of the indices of neuropathy. The motor and sensory nerve conduction indices already showed significant improvement from values at entry in the study after 1 year, and additional improvements were seen at all the intervals tested. On the other hand, the mean autonomic function indices only showed noticeable improvement after 5 years of transplantation [8].

During 10 years of follow-up clearly demonstrated that peripheral nerve function improved in patients who achieved a normoglycemic state after a successful transplant [9]. Improvement was maintained throughout the 10-year follow-up after transplant and was more obvious for somatic than for autonomic nerve functions.

Quality of Life

In addition to the potential favorable effects of pancreas transplant on the secondary complications of diabetes, several studies have shown that the overall quality of life improves after a successful transplant [10–13].

Improvement in quality of life is, at least in part, attributable to the improvement of autonomic and somatic nerve function, which allows for better development of general life activities and adaptation to social stress events [14].

Korea

Retinopathy

Limited data are available regarding the long-term effects of pancreas transplantation on the progression of diabetic retinopathy (DR) and the incidence and associated risk factors for early worsening of DR. Patients who underwent successful pancreas transplantation between January 2007 and October 2015 and were followed for 1 year or longer in Asan Medical Center (AMC) were consecutively enrolled [15]. Variables regarding demographic, systemic, metabolic, and surgical factors were reviewed for each patient. DR progression was defined as (1) development or aggravation of macular edema requiring intravitreal anti-VEGF injections and/or (2) progression of DR severity requiring pan-retinal photocoagulation (PRP) and/or pars planar vitrectomy (PPV) (Table 1). Early worsening was defined as progression within 1 year of post-transplant. Three hundred three eyes of 153 patients were included in the analysis. At the pretransplant ocular evaluation, 221 eyes (72.9%) showed advanced DR with a history of PRP and/or PPV. During a mean follow-up period of 4.2 years, 62 eyes (20.5%) experienced DR progression, and early worsening was noted in 57 eyes (18.8%). DR with recent PRP within pretransplant 1 year and pancreas transplant alone were significant risk fac-

Table 1 Incidence of DR progression after pancreas transplantation during the entire follow-up period according to baseline severity of DR

Baseline severity of DR	Eyes (H)	Progression of DR					
		Overall		Macular edema		PRP/PPV	
		Eyes (N)	Progression rate (%)	Eyes (N)	Progression rate (%)	Eyes (N)	Progression rate (%)
No DR	37	4	10.8	3	8.1	1	2.7
Mild-moderate NPDR	38	14	36.8	10	26.3	8	21.1
Severe MPDR	7	4	57.1	3	42.8	3	42.8
Severe NPDR-PDR s/p PRP							
Overall	154	40	26.0	16	10.4	30	195
≤ 1 year	39	23	59.0	11	28.2	19	48.7
> 1 year	115	17	14.8	5	4.3	12	10.4
PDR s/p PPV	67	0	0	0	0	0	0
Total	303	62	20.5	32	10.6	43	14.2

tors for early worsening. In four of five patients who received a pancreas transplant, the degree of DR remained stable over time after transplantation. Meanwhile, early worsening of DR could occur in patients at risk, particularly within the first post-transplant year. We suggest that physicians should have a high index of suspicion and carefully monitor for early worsening of DR and timely manage possible ocular deterioration (Tables 2 and 3, Fig. 1).

Table 2 Baseline demographic and clinical characteristics: comparison between eyes with early worsening of DR after pancreas transplantation and those without early worsening

	Total eyes (*N* = 153)	Eyes with progression (*N* = 34)	Eyes without progression (*N* = 119)	*P*
Demographics				
Age, years	36.3 ± 10.7	31.8 ± 8.1	37.6 ± 11.1	0.001
Sex, *n* (%)				
Female	88 (57.5)	20	68	0.862
Male	65 (42.5)	14	51	
Type of DM, *n* (%)				
Type 1	121 (79.0)	32	89	0.016
Type 2	32 (21.0)	2	30	
Age at onset of DM, years	20.4 ± 9.1	17.3 ± 7.4	21.3 ± 9.3	0.024
DM duration, years	15.7 ± 7.9	14.8 ± 6.5	15.9 ± 8.3	0.474
Systemic				
BMI, kg/m^2	21.6 ± 2.9	20.3 ± 2.9	21.3 ± 2.8	0.068
HbA1C, %				
Preoperative	8.3 ± 2.0	8.9 ± 2.1	8.1 ± 1.9	0.046
Postoperative 6 M	5.4 ± 0.5	5.2 ± 0.5	5.5 ± 0.5	0.015
Changes 6 M postoperative	2.9 ± 2.1	3.7 ± 2.2	2.6 ± 2.0	0.011
Surgical				
Type of transplantation, *n* (%)				
SPK/SPLK	77 (50.3)	10	67	<0.001
PAK	25 (16.3)	1	24	
PTA	51 (33.3)	23	28	
Drainage, *n* (%)				
Bladder	103 (67.3)	28	75	0.025
Enteric	50 (32.7)	6	44	
Induction regimen, *n* (%)				
ATG	144 (94.1)	31	113	0.322
Basiliximab	9 (5.9)	3	6	
Steroid regimen, *n* (%)				
Withdrawal	139 (90.8)	29	110	0.133
Maintenance	14 (9.2)	5	9	
Ocular				
Baseline severity of DR, *n* (%)				
No DR	21 (13.7)	3	18	<0.001
Mild-moderate NPCR	18 (11.8)	7	11	
Severe NPDR	3 (2.0)	2	1	
Severe NPDR-PDR s/p PRP				
≤ 1 year	21 (11.1)	15	6	
> 1 year	60 (39.2)	7	53	
PDR s/p PPV	30 (22.2)	0	34	
BCVA, logMAR	0.14 ± 0.24	0.11 ± 0.13	0.15 ± 0.26	0.460

Table 3 Univariate and multivariate logistic regression with forward elimination for predicting early worsening of DR after pancreas transplantation

	Overall early worsening (n = 34)		Macular edema (n = 17)		PRP/PPV (n = 24)	
Univariate analysis	OR	P	OR	P	OR	P
Demographics						
Age, years	0.943	0.007	0.907	0.004	0.951	0.037
Male (vs female), n	0.933	0.861	0.528	0.253	1.175	0.718
Type 1 diabetes (vs type 2 diabetes), n	5.273	0.029	—	—	3.255	0.124
Age at onset of DM, years	0.944	0.026	0.931	0.050	0.963	0.178
DM duration, years	0.982	0.471	0.942	0.086	0.974	0.384
Systemic						
BMI, kg/m^2	0.873	0.071	0.774	0.018	0.869	0.104
Presence of anti-GAD, n	2.853	0.026	3.941	0.029	2.185	0.138
HbA1C, %						
Preoperative	1.197	0.051	1.254	0.044	1.179	0.105
Postoperative 6 M	0.318	0.016	0.116	0.002	0.437	0.160
Changes 6 M postoperative	1.247	0.012	1.326	0.009	1.210	0.050
Surgical						
Type of transplantation, n						
SPK/SPLK	1		1		1	
PAK	0.279	0.235	—		0.417	0.424
PTA	5.504	<0.001	9.333	0.001	4.571	0.002
Bladder drainage, n	3.457	0.010	4.091	0.069	2.771	0.078
Induction ATG (vs basiliximab), n	0.550	0.418	1.041	0.971	0.623	0.571
Steroid withdrawal (vs maintenance), n	0.419	0.152	0.688	0.646	0.580	0.437
Ocular						
Baseline seventy of DR, n						
No DR	1		1		1	
Mild-moderate NPDR	3.813	0.090	3.654	0.155	10.000	0.043
Severe NPDR	12.000	0.071	4.750	0.277	10.000	0.049
Severe NPDR-PDR s/p PRP (≤1 year)	14.400	0.001	5.182	0.068	22.500	0.006
Severe NPDR-PDR s/p PRP (>1 year)	1.200	0.789	0.500	0.466	2.642	0.378
PDR s/p PPV	—	—	—	—	—	—
BCVA (log MAR)	1.163	0.592			1.230	1.230
Multivariate analysis						
BMI, kg/m^2			0.770	0.050		
Type of transplantation, n						
SPK	1		1		1	
PKA	0.103	0.079	—		0.273	0.272
PTA	7.727	0.002	7.350	0.013	4.524	0.018
Baseline seventy of DR, n						
No DR	1		1		1	
Mild-moderate NPDR	5.285	0.042	2.625	0.340	12.727	0.027
Severe NPDR	24.049	0.038	7.175	0.197	13.735	0.011
Severe NPDR-PDR s/p PRP (≤1 year)	78.140	<0.001	11.878	0.013	62.057	0.001
Severe NPDR-PDR s/p PRP (≥1 year)	11.630	0.005	1.515	0.703	9.038	0.063
PDR s/p PPV	—	—	—	—	—	—

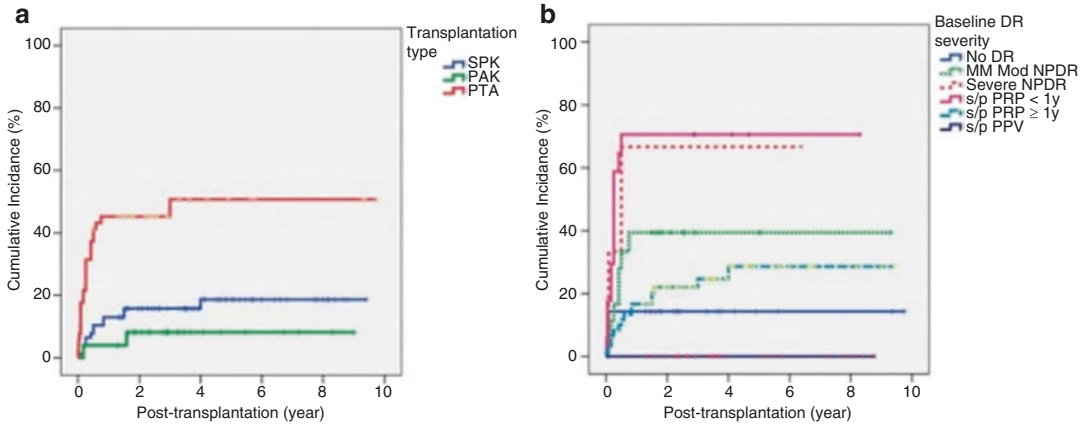


Fig. 1 Kaplan-Meier survival curves illustrating the cumulative incidence of DR progression according to transplantation type (**a**) and baseline DR severity (**b**)

Endocrine Function

Limited data are available regarding the long-term metabolic outcomes of functioning pancreas transplants in patients with type 2 diabetes mellitus (T2DM). To compare the long-term effects of pancreas transplantation in terms of insulin resistance and β cell function, a comparison of metabolic variables was performed between type 1 diabetes mellitus (T1DM) and T2DM patients from 1-month posttransplant to 5 years using generalized, linear-mixed models for repeated measures [16]. Among 217 consecutive patients who underwent pancreas transplantation in AMC between August 2004 and January 2015, 193 patients (151 T1DM and 42 T2DM) were included in this study. Throughout the follow-up period, postoperative hemoglobin A1c did not differ significantly between T1DM and T2DM patients, and the levels were constantly below 6% (42 mmol/mol) until 5 years post-transplant, whereas C-peptide was significantly higher in T2DM ($p = 0.014$). There was no difference in fasting insulin, homeostasis model assessment (HOMA) of insulin resistance, HOMA β cell, or the insulinogenic index between the groups. Furthermore, fasting insulin and HOMA-insulin resistance steadily decreased in both groups during the follow-up period. There was no significant difference in insulin resistance or β-cell function after pancreas transplantation between T1DM and T2DM patients. We demonstrated that pancreas transplantation is capable of sustaining favorable endocrine functions for more than 5 years in T2DM recipients (Figs. 2, 3, and 4).

Nephropathy

Limited data are available regarding optimal selection criteria for pancreas transplant alone (PTA) to minimize the aggravation of diabetic nephropathy. A total of 87 type-1 diabetic patients were evaluated before and after PTA in AMC from January 1999 to December 2015, together with 87 matched non-transplanted type-1 diabetic subjects who were candidates for PTA to compare deterioration of native kidney function (Fig. 5) [17]. A total of 163 patients (79 in the transplanted group and 84 in the non-transplanted group) were finally enrolled after excluding nine patients with an estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 and two patients with moderate proteinuria (≥1.5 g/day). A total of seven recipients (8.9%) had end-stage renal disease post-transplant whereas only one patient (1.2%) developed the end-stage renal disease in the non-transplanted group during their follow-up period (median 12.0, range 6–96 months) ($p = 0.03$). Furthermore, a composite of severe renal dysfunction and end-stage renal disease

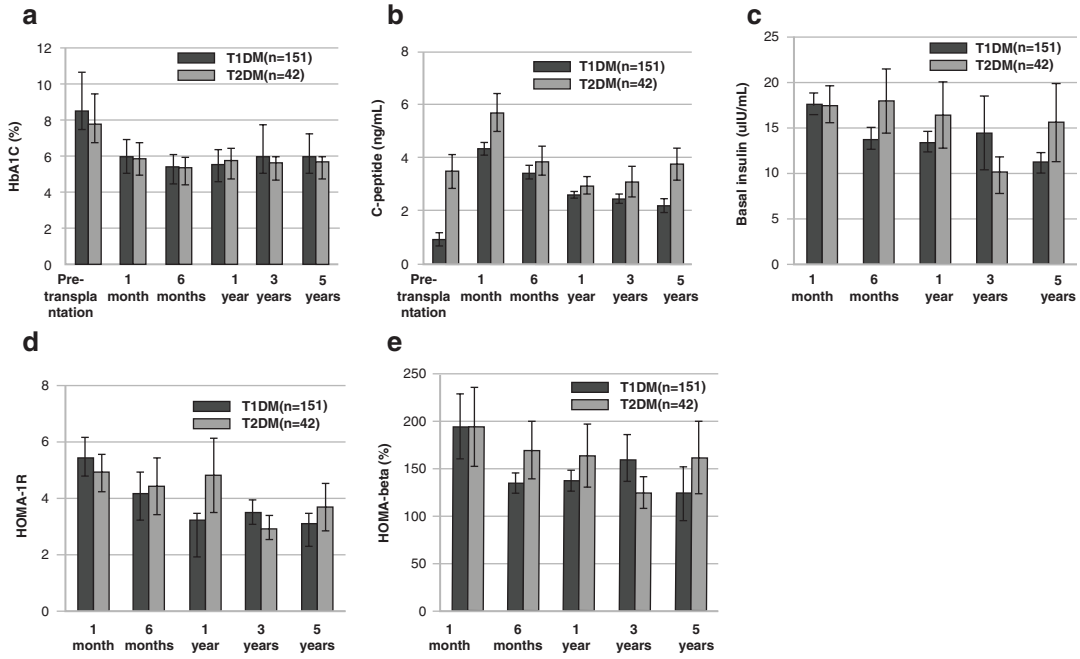


Fig. 2 The mean level of HbA1c (**a**), C-peptide (**b**), basalinsulin (**c**), HOMA-IR (**d**), and HOMA-β (**e**) according to the type of diabetes until postoperative 5 years

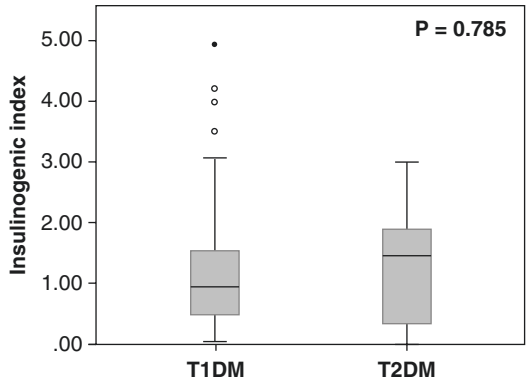


Fig. 3 The Box and Whisker plot for insulinogenic index according to the type of diabetes within 1 month posttransplant

(31.6% vs 2.4%) was significantly higher in the transplanted group ($p < 0.001$) (Figs. 6, 7, and 8). Multivariate Cox regression analysis revealed that a higher level of tacrolimus at 6 months post-transplant (HR = 1.648, CI = 1.140–2.385, $p = 0.008$) was the only significant factor associated with end-stage renal disease (Table 4). There is a considerable risk for deterioration of renal function in PTA recipients post-transplant compared with non-transplant diabetic patients. With rather strict selection criteria such as preoperative proteinuria and estimated glomerular filtration rate, PTA should be considered in diabetic patients to minimize the post-transplant aggravation of diabetic nephropathy.

Diabetic Foot

It is known that successful pancreas transplantation enables patients with diabetes to maintain a normal glucose level without insulin and reduces diabetes-related complications. However, we have little information about foot-specific morbidity in patients who have undergone successful pancreas transplantation. The purpose of this study was to investigate the prevalence and predisposing factors for foot complications after successful pancreas transplantation [18]. This retrospective study included 218 patients (91 males, 127 females) who had undergone pancreas transplantation for diabetes in AMC. The

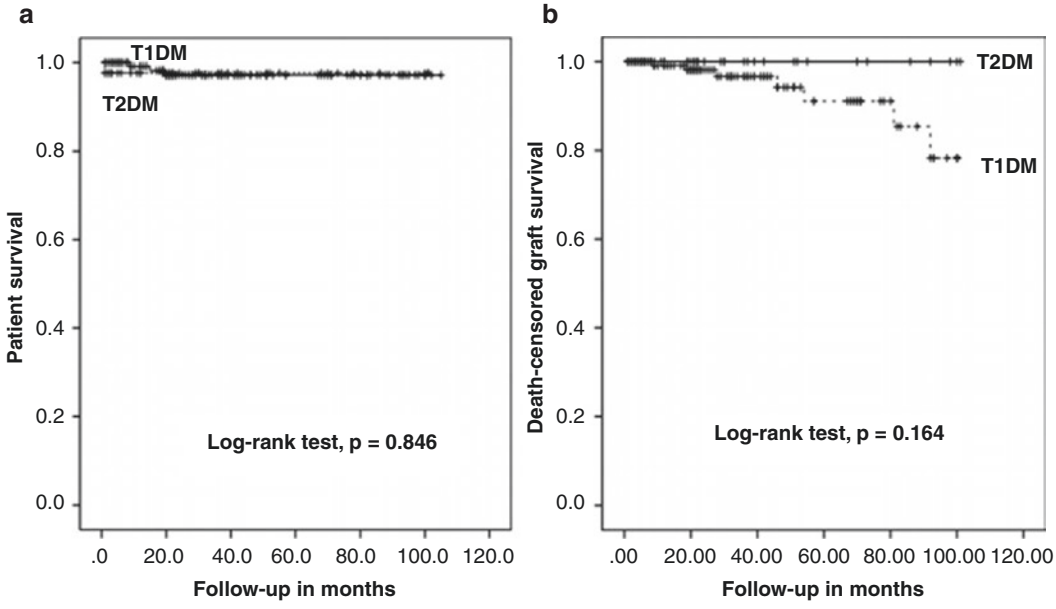


Fig. 4 Kaplan-Meier curves for 10-year patient survival (**a**) and death-censored pancreas graft survival (**b**) according to the type of diabetes

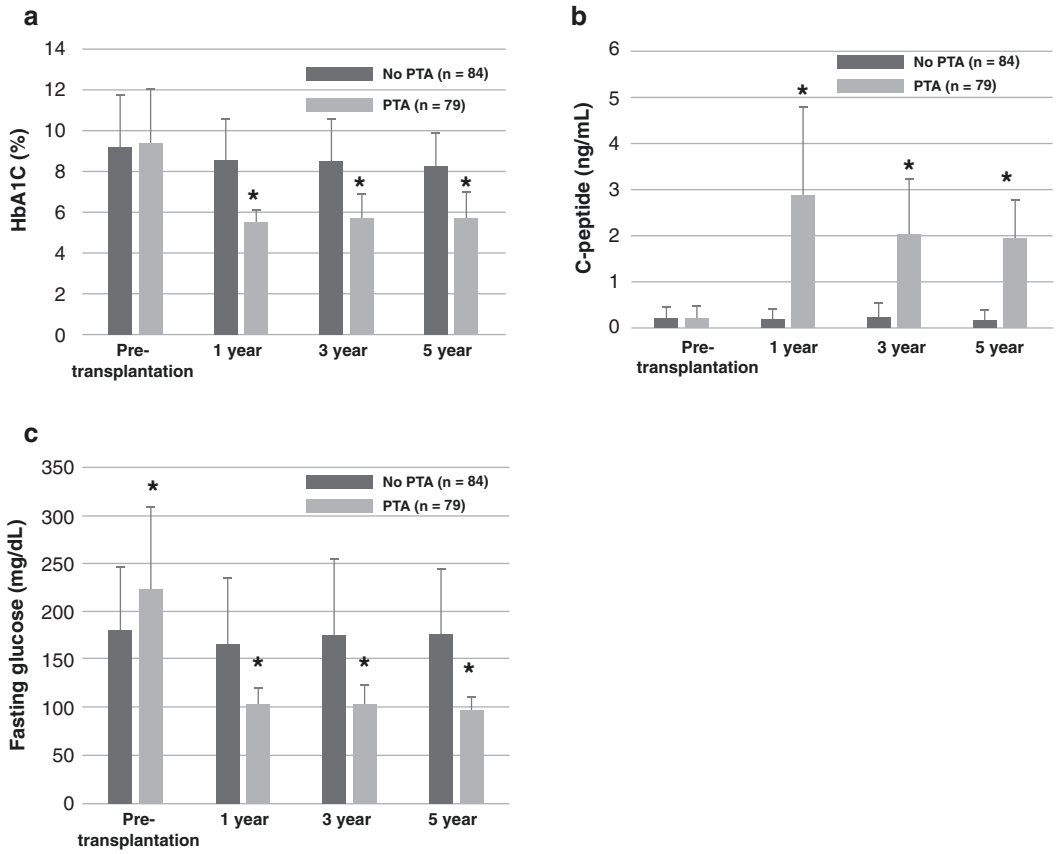


Fig. 5 Comparison of the mean level of HbA1c (**a**), C-peptide (**b**), and fasting glucose (**c**) between nontransplanted type 1 diabetic patients and PTA recipients during the 5-year follow-up period.*$p < 0.001$

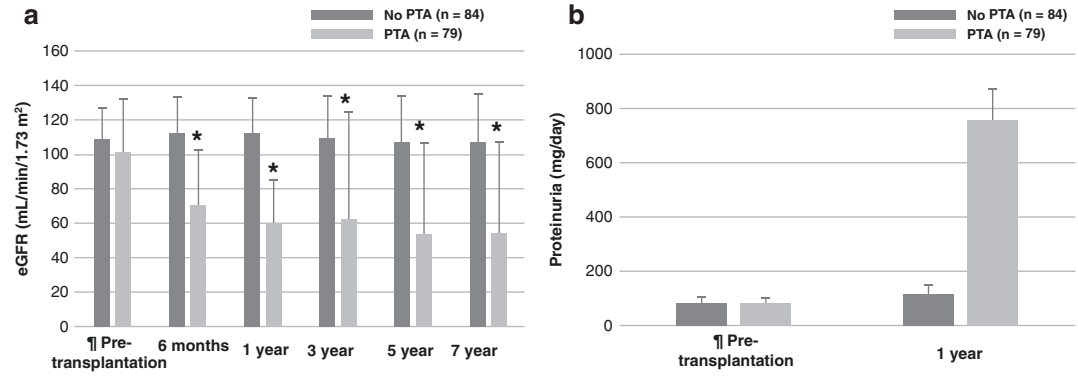


Fig. 6 Comparison of the mean level of eGFR (**a**) and proteinuria for 24 h (**b**) between nontransplanted type 1 diabetic patients and PTA recipients during the follow-up periods. ¶Pre-transplantation for PTA recipients and beginning of observation for nontransplanted patients;*$p < 0.001$

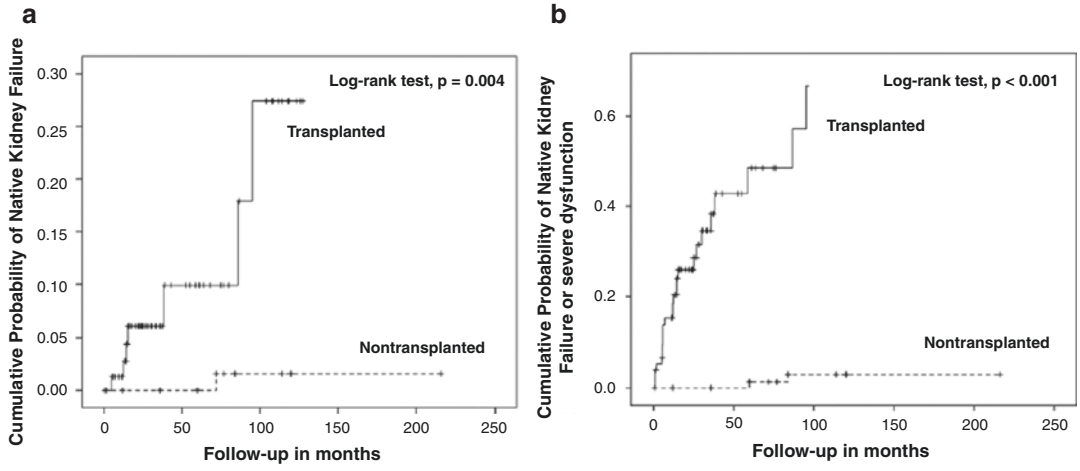


Fig. 7 Cumulative probability of (**a**) native kidney failure and (**b**) a composite outcome of native kidney failure and severe dysfunction

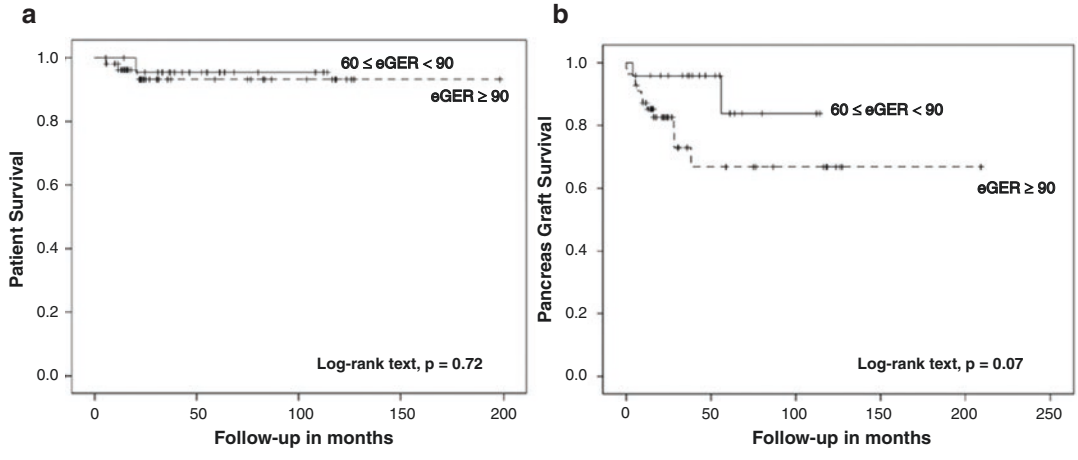


Fig. 8 Kaplan-Meier curves for more than 15-year (**a**) patient survival and (**b**) death-censored pancreas allograft survival according to a preoperative eGFR

Table 4 The risk of end-stage renal disease after pancreas transplant alone and adjusted HR from multivariate cox regression

Variables	HR_{unadj}[a]	HR_{adj}[b]	95% CI[c]	*p*-value
Preoperative proteinuria	1.003	1.002	0.998–1.005	0.308
Preoperative hemoglobin A1c	1.286	1.308	0.948–1.805	0.102
Cyclosporine (vs. Tacrolimus)	9.640	1.029	0.076–13.899	0.983
Trough level of CNI[d] at 6 months post-transplant	1.294	1.368	1.023–1.829	0.034
Readmission due to metabolic acidosis	5.788	5.747	0.639–51.651	0.119

[a]Hazard rate unadjusted
[b]Hazard rate adjusted
[c]Confidence interval
[d]Calcineurin inhibitor

Table 5 Comparison of laboratory results and use of immunosuppression between the complication and the noncomplication groups[a]

	Total	Complication group	Noncomplication group	OR (95% CI)	*P* value
Preoperation					
Fasting glucose level, mg/dL	202.6 ± 117.9	204.2 ± 132.5	201.4 ± 116.6	–1.8 (–54.51)	.946
HbA_{1c}, %	8.1 ± 1.9	7.9 ± 1.3	8.1 ± 1.9	0.2 (–0.7, 1.0)	.690
Creatinine, mg/dL	4.6 ± 4.0	5.7 ± 3.0	4.5 ± 4.0	–1.2 (–2.7, 0.2)	.087
Postoperative, 6 months					
Fasting glucose level, mg/dL	103.6 ± 30.6	101.9 ± 27.7	104.0 ± 31.1	1.9 (–11.7, 15.5)	.784
HbA_{1c},%	5.5 ± 0.6	5.2 ± 0.5	5.5 ± 0.8	0.3 (–0.0, 0.7)	.086
Creatinine, mg/dL	1.4 ± 0.5	1.3 ± 0.7	1.4 ± 0.5	0.1 (–0.2, 0.3)	.650
Postoperative, 1 year					
Fasting glucose level, mg/dL	102.2 ± 35.6	91.1 ± 19.1	103.5 ± 37.0	12.4 (–3.4, 28.1)	.123
HbA_{1c}, %	5.6 ± 0.9	5.3 ± 0.4	5.7 ± 0.9	0.3 (–0.1, 0.7)	.098
Creatinine, mg/dL	1.4 ± 0.8	1.8 ± 1.6	1.4 ± 0.7	–0.4 (–0.8, –0.1)	.020
Postoperative immunosuppression, mg					
Methylprednisolone, cumulative dosage	2681 ± 4611	3370 ± 2980	2617 ± 4783	–766 (–2813, 1281)	.461
Deflazacort [Calcort]	990 ± 2728	812 ± 2082	1021 ± 2808	198 (–1014, 1410)	.747
Fludrocortisone [Florinef]	0.6 ± 5.3	0.5 ± 2.6	0.6 ± 5.6	0.0 (–2.3, 2.4)	.972

[a]Data were analyzed by *t* test

mean age was 40.7 (range, 15–76) years. Diabetes type, transplantation type, body mass index, and diabetes duration before transplantation were confirmed. After pancreas transplantation, the occurrence and duration of foot and ankle complications were assessed. Twenty-two patients (10.1%) had diabetic foot complications. Fifteen patients (6.9%) had diabetic foot ulcers and seven patients (3.2%) had Charcot arthropathy. Three patients had both diabetic foot ulcer and Charcot arthropathy.

Three insufficiency fractures (1.4%) were included. Mean time of complications after transplantation was 18.5 (range 2–77) months. Creatinine level 1 year after surgery was higher in the complication group rather than the noncomplication group (p = .02) (Table 5). Complications of the foot and ankle still

occurred following pancreas transplantation in patients with diabetes.

Japan

Pancreas transplantation restores physiological glycemic control and achieves insulin independency and elimination of hypoglycemic attacks. Simultaneous pancreatic kidney transplantation also achieves dialysis withdrawal and dramatically improves the quality of life. In this chapter, from the data of the patients who underwent pancreas transplantation at Fujita Health University Hospital, changes in blood glucose level and glucose tolerance after pancreas transplantation, evaluation of diabetic neuropathy before and after pancreas transplantation, QOL using SF-36 before and after pancreas transplantation, and the evaluation and changes in bone density after pancreas transplantation are described.

Immediately after the pancreas transplantation, the blood glucose level became normal and insulin independency was achieved in almost all patients. In a glucagon stimulation test performed 1 month after transplantation, good insulin secretory capacity was observed (Fig. 9). The blood glucose level of one SPK case was shown by Continuous Glucose Monitoring (CGM) (Fig. 10). HbA1c decreased from 9.3% to 5.4% at 2 months after PT. The fasting blood C-peptide level, which was less than 0.03 ng/mL before transplantation, increased to 1.71 ng/mL. In addition, the daily blood glucose level remained extremely stable, and no hypoglycemia or hyperglycemia was observed.

After pancreas transplantation, the HbA1c level also stabilized rapidly and remained at 4.8–5.8%

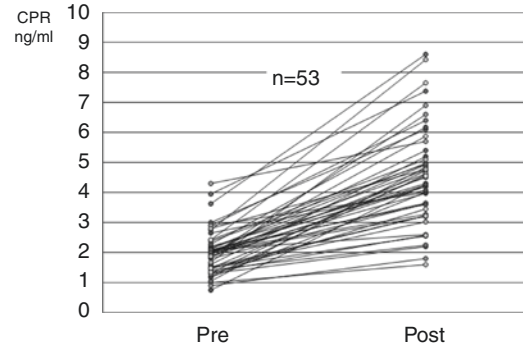


Fig. 9 Glucagon challenge test at 1 month after pancreas transplantation (Post; 6 min after glucagon injection) (Dept. of Endocrinology and Metabolism, Fujita Health University Hospital, 2012.8–2019.12)

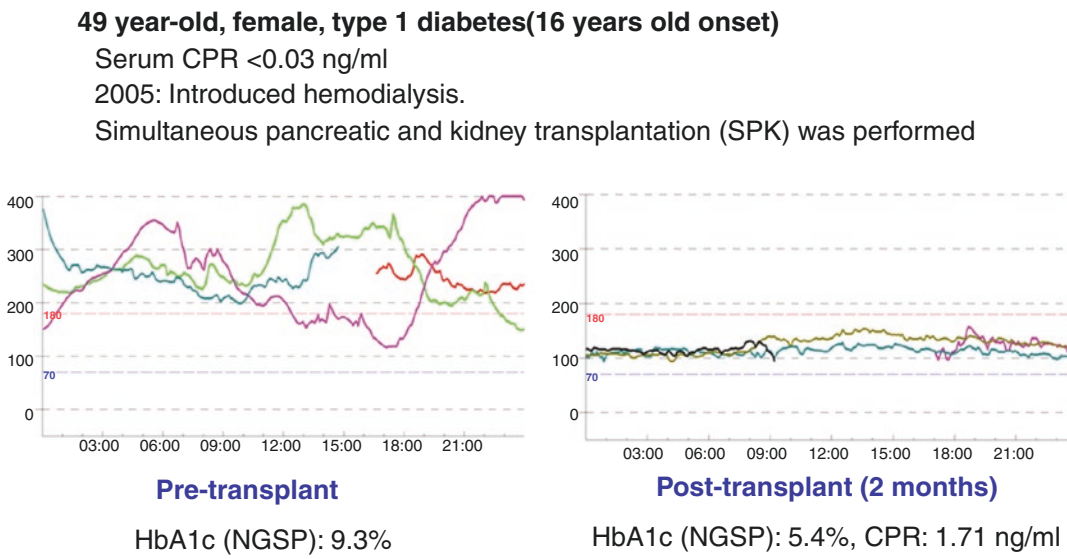


Fig. 10 Pre- and post-transplant CGM of the SPK patient (Dept. of Endocrinology and Metabolism, Fujita Health University Hospital)

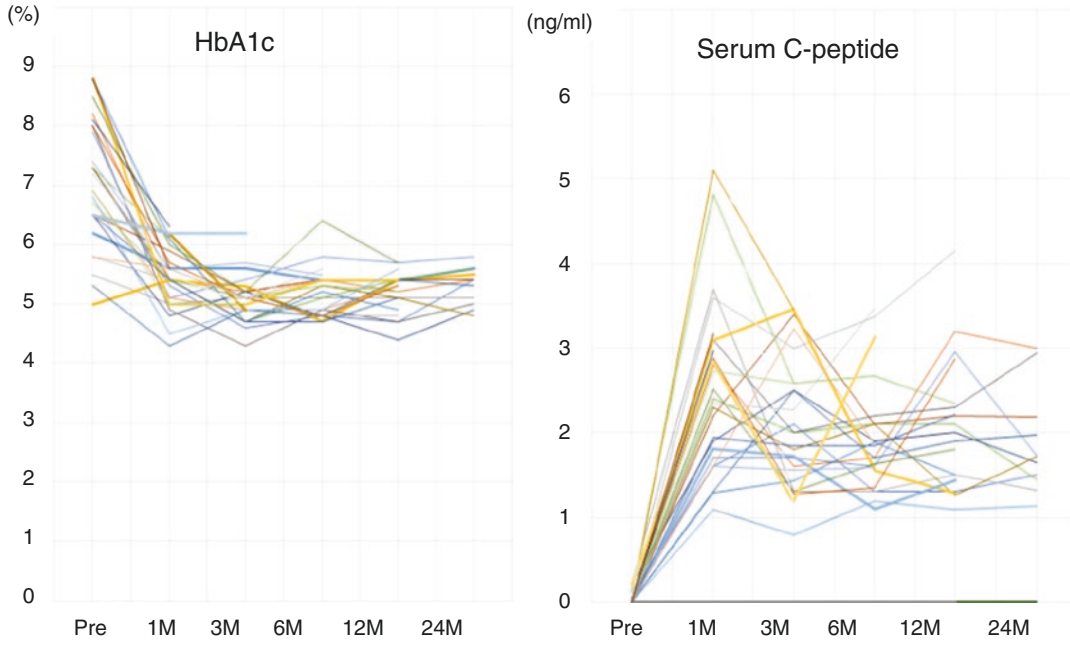


Fig. 11 Changes in HbA1c and fasting serum C-peptide levels after pancreas transplantation (Dept. of Organ Transplant Surgery, Fujita Health University Hospital, 2012.8–2019.12)

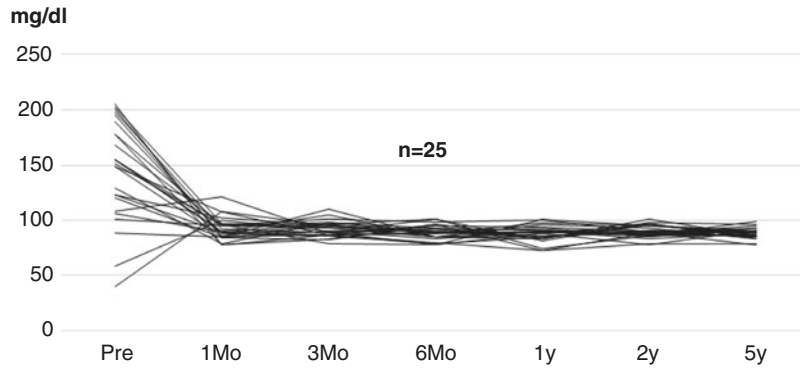


Fig. 12 Changes in fasting blood glucose levels after pancreas transplantation (Fujita Health University Hospital, 2012.8–2019.12)

up to 2 years after transplantation. The fasting serum C-peptide level was maintained at 1.0 ng/mL or higher, showing the good endocrine function of the pancreas graft (Fig. 11). The blood glucose level remained in the normal range for a long period of time (Fig. 12).

Although there is a dramatic recovery in insulin secretion after pancreas transplantation, attention should also be paid to impaired glucose tolerance associated with increased insulin resistance due to the side effects of calcineurin inhibitors and steroids as immunosuppressants. We examined changes in various indicators of insulin secretory capacity and insulin resistance in our case (Table 6). The indicators of insulin secretion of ⊿CPR, HOMA-β, and SUIT index by the glucagon stimulation test are well leaned even 2 years after transplantation. Matsuda Index, which shows insulin resistance, decreased after 1 year, suggesting that insulin resistance worsened, but it tended to improve after 2 years. However, the insulin secretion index, which tends to decrease in the early stages of type 2 diabetes, did not decrease within 1 year after transplantation.

From these results, the effect of pancreas transplantation on blood glucose normalization

Table 6 Changes in the indicators of insulin secretory capacity and resistance (Dept. of Endocrinology and Metabolism, Fujita Health University Hospital, 2012.8–2019.12)

	1 Month	1 Year	2 Years
HbA1c (%)	6.8 ± 0.7	5.2 ± 0.1*	5.3 ± 0.3*
SCr (mg/dL)	0.92 ± 0.26	0.91 ± 0.44	1.07 ± 0.29
⊿CPR (ng/mL)	2.8 ± 1.5	4.0 ± 2.6	4.4 ± 4.4
Matsuda Index	5.1 ± 1.1	3.3 ± 0.8	4.5 ± 1.9
Insulin secretion index	0.98 ± 0.77	1.80 ± 0.55	1.07 ± 1.78
HOMA-R	3.09 ± 1.89	2.90 ± 0.52	2.74 ± 1.24
HOMA-β	195.8 ± 120.2	267.6 ± 137.0	273.3 ± 183.6
SUIT Index	113.5 ± 34.6	146.8 ± 86.1	173.8 ± 122.7

Table 7 Changes in diabetic polyneuropathy by pancreas transplantation (Dept. of Endocrinology and Metabolism, Fujita Health University Hospital, 2013–2015)

	Pre-transplant ($n = 25$)	Post-transplant (1 year, $n = 25$)	P value
HbA1c (%)	7.0 ± 1.0	5.3 ± 0.4	<0.001
BMI (kg/m^2)	20.3 ± 1.7	19.2 ± 4.5	0.002
Tibial N. F wave latency (m/s)	54.5 ± 6.1	52.1 ± 5.1	0.038
Tibial N. MCV (m/s)	36.8 ± 4.7	39.2 ± 5.7	0.002
Sural N. SCV (m/s)	40.0 ± 4.5	41.5 ± 5.2	0.039
Sural N. SNAP (μV)	4.8 ± 3.5	6.5 ± 6.0	0.092
Tibial N. CMAP (mV)	13.3 ± 8.8	13.3 ± 8.5	0.441
CVR-R (%)	1.47 ± 1.02	1.37 ± 0.67	0.628

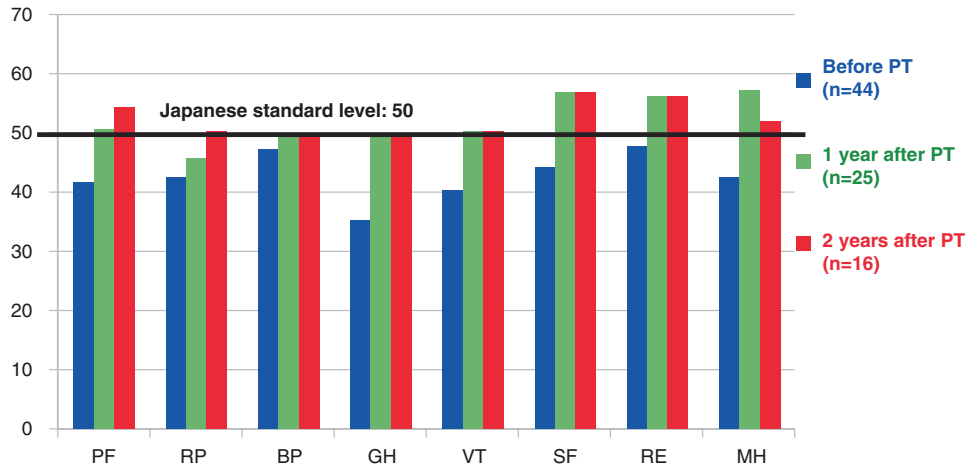
was remarkable, although glucose tolerance was impaired by immunosuppressive drugs and steroid drugs.

Nerve conduction studies were performed before transplantation (at the time of registration) and 1 year after transplantation for the purpose of evaluating diabetic polyneuropathy (DPN) before and after pancreas transplantation. The subjects were 25 patients who underwent pancreas transplantation from May 2013 to December 2015 at Fujita Health University Hospital. The age was 39.6 ± 6.5 years, and the gender was 12 males and 13 females. There were 19 SPKs and 6 PAKs. The duration of diabetes was 24.0 ± 5.0 years. The results are shown in Table 7. F wave latency of tibial nerve, tibial nerve MCV, and sural nerve SCV were significantly improved at 1 year after transplantation, and sural nerve SNAP was also improved. There was no change in tibial nerve CMAP and CVR-R. Although longer-term follow-up is required in the future, it was suggested that pancreas transplantation would improve neuropathy.

The main purpose of pancreas transplantation is to improve the QOL associated with the disappearance of hypoglycemic attacks, insulin withdrawal, and dialysis withdrawal in addition to improving the prognosis of patients in SPK. We evaluated the QOL of the patients at pre-transplant, 1 year, and 2 years after pancreas transplantation using a short-form 36 version 2 (SF36v2 ™:MOS 36-Item Short-Form Health Survey). The subjects were patients who underwent pancreas transplantation at our hospital from September 2011 to December 2017, and the background factors are shown in Table 8.

Table 8 Background of the recipient who underwent pancreas transplantation at Fujita Health University Hospital from September 2011 to December 2017

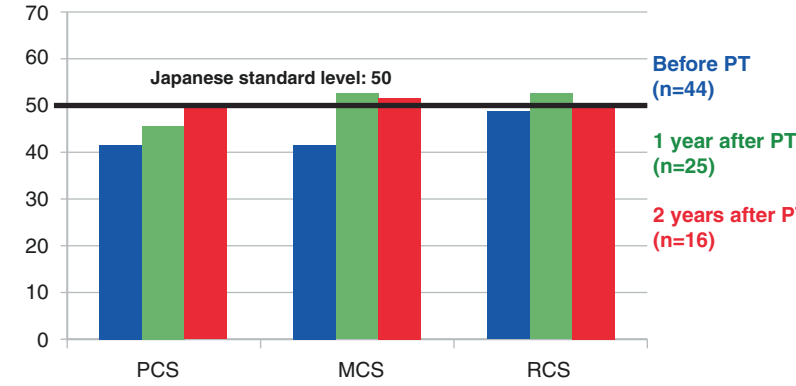
	Pre-transplant	Post-transplant (1 year)	Post-transplant (2 years)
Number	44	25	16
Gender (male:female)	19:25	7:18	4:12
Age (years old)	42.7 ± 4.9	44.9 ± 7.9	44.6 ± 7.8
SPK/PAK/PTA (number)	32/5/7	23/2/0	13/3/0
History of diabetes	26.8 ± 8.8	28.5 ± 7.3	29 ± 8.4
HbA1c (%)	7.3 ± 1.8	5.3 ± 0.3	5.3 ± 0.3



PF: physical function, RP: role limitations due to physical health problems, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: limitations due to emotional health problems, MH: mental health

Fig. 13 Changes in QOL after pancreas transplantation using SF36v2™ (Dept. of Endocrinology and Metabolism, Fujita Health University Hospital, 2011.9–2017.12)

Fig. 14 Changes in component summary score after pancreas transplantation using SF36v2TM (Dept. of Endocrinology and Metabolism, Fujita Health University Hospital, 2011.9–2017.12)



PCS: physical component summary, MCS: mental component summary, RCS: role/social component summary

Prior to pancreas transplantation, the patients had lower than the national standard for all eight items of SF-36 and had poor QOL. In particular, General health (GH) and vitality (VT) were as low as 40 or less. However, seven items except for role limitation due to physical health problems (RP) reached 1 year and all items reached 2 years after transplantation to the national standard value of 50 after transplantation (Fig. 13). In the summary score, mental component summary (MCS) and role/social component summary (RCS) reached the national standard value of 50, 1 year after transplantation, and physical component summary (PCS) also reached the national standard value 2 years after transplantation (Fig. 14). Dramatic improvement of QOL due to pancreatic transplantation was confirmed.

Taiwan

Endocrine outcomes regarding fasting blood sugar (Fig. 15) and serum HbA1c (Fig. 16) before and after pancreas transplantation were not sig-

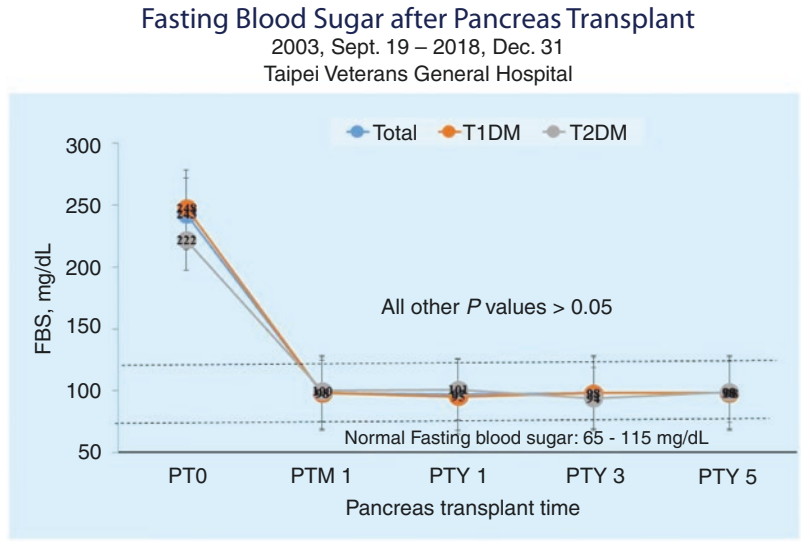


Fig. 15 Serum fasting blood sugar (FBS) before pancreas transplant day 0 (PT0), pancreas transplant month 1 (PTM 1), pancreas transplant year 1 (PTY 1), pancreas transplant year 3 (PTY 3), and pancreas transplant year 5 (PTY 5). There is no significant difference regarding FBS between these T1DM and T2DM before and after pancreas transplant

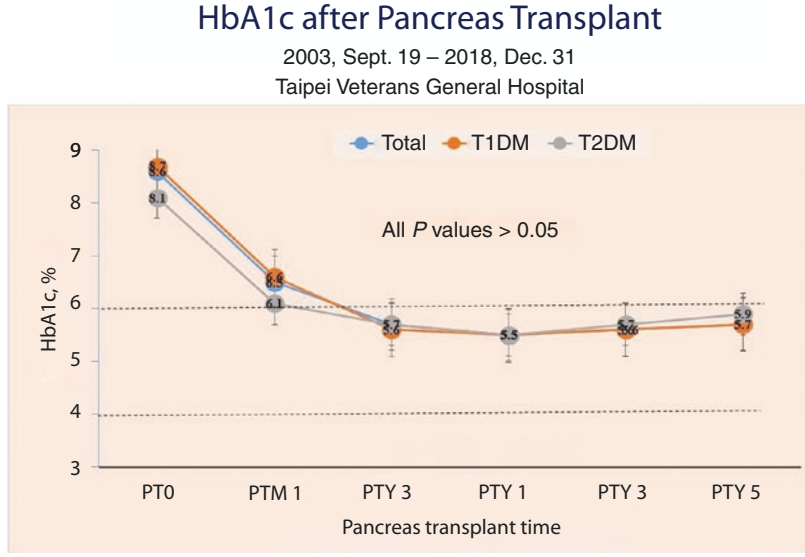


Fig. 16 Serum Hemoglobulin A1c (HbA1c) before pancreas transplant day 0 (PT0), pancreas transplant month 1 (PTM 1), pancreas transplant month 3 (PTM 3), pancreas transplant year 1 (PTY 1), pancreas transplant year 3 (PTY 3), and pancreas transplant year 5 (PTY 5). There is no significant difference regarding HbA1c between these T1DM and T2DM before and after pancreas transplant

nificantly different between the type 1 DM (T1DM) and type 2 DM (T2DM) groups. T2DM patients present significantly higher levels of serum C-peptide either before or after pancreas transplantation compared with T1DM patients (Fig. 17). There is always a high peak of serum C-peptide on a postoperative day 1 on both T1DM and T2DM patients [19].

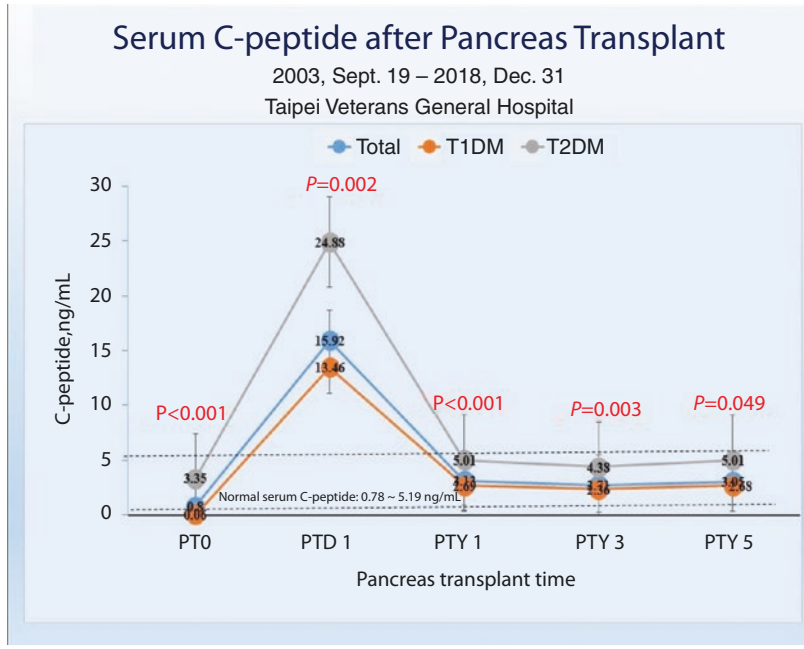


Fig. 17 Serum C-peptide before pancreas transplant day 0 (PT0), pancreas transplant day 1 (PTD 1), pancreas transplant year 1 (PTY 1), pancreas transplant year 3 (PTY 3), and pancreas transplant year 5 (PTY 5). Serum C-peptide is significantly higher in T2DM patients before and after pancreas transplant. There is usually a high peak of serum C-peptide observed on day 1 after pancreas transplant in both groups

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Complication

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General

Technical failure of the pancreas graft was a major problem in all three categories over the analyzed time (Table 1) [1]. It dropped in all three categories between the periods of 2001–2005 and 2011–2016, but this improvement was only significant in SPK and PAK (Fig. 1). In all three categories, pancreas graft thrombosis remained the major cause of technical failure, whereas the other factors such as infection, pancreatitis, anastomotic leak, and bleeding are accounted for only a small percentage of technical problems [2] (Table 1).

In SPK, the main risk factors for technical failure were donor age older than 30 years, increased preservation time over 12 h, and the recipient being obese or on dialysis pretransplant. Centers with higher transplant volume showed a significantly lower relative risk for technical failure. The model could not confirm significant changes over time. Maintenance immunosuppression remained a risk factor for technical failure, which is most likely a sign that immunologic losses were falsely reported as technical losses.

In PAK, donor age older than 30 years and low center volume were the factors that significantly affected technical graft loss.

Induction and maintenance therapy reached significance that again pointed to wrongly reported causes of graft loss. All other factors in the model did not reach significance.

In PTA, the transplant period reached significance with an increased relative risk of technical failure over time. Recipient and donor age, as well as preservation time, did not show a statistically significant impact on technical failure owing to good donor selection. As in SPK and PAK, induction and maintenance therapy reached significance.

Currently, there was a report of 14 graft duodenectomy in 312 pancreas transplants from graft duodenal bleeding or leakage [3, 4]. An aggressive and timely surgical approach was suggested for graft rescue in patients with severe duodenal graft complications occurring after pancreas transplantation. These complications are quite troublesome for control and sometimes causing graft loss [5–7].

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Table 1 The causes of early technical failures in UNOS report (2015–2019)

Reasons for Early Technical Failures

USA Primary DD Pancreas Transplants 1/1/2015–12/31/2019

	SPK			PAK			PTA		
	BD	ED	*p*	BD	ED	*p*	BD	ED	*p*
n	171	3400		4	218		9	278	
GraftThmb	3.5%	3.8%	***0.86***	0.0%	3.2%	-	22.2%	6.5%	-
Infection	0.0%	0.4%	***0.38***	0.0%	0.9%	-	0.0%	0.0%	-
Pxitis	0.0%	0.2%	***0.55***	0.0%	0.4%	-	0.0%	0.0%	-
Anas.Leak	0.0%	0.3%	***0.38***	0.0%	0.5%	-	0.0%	0.4%	-
Bleed	0.0%	0.2%	***0.56***	0.0%	0.5%	-	0.0%	0.0%	-

IPTR/UNOS

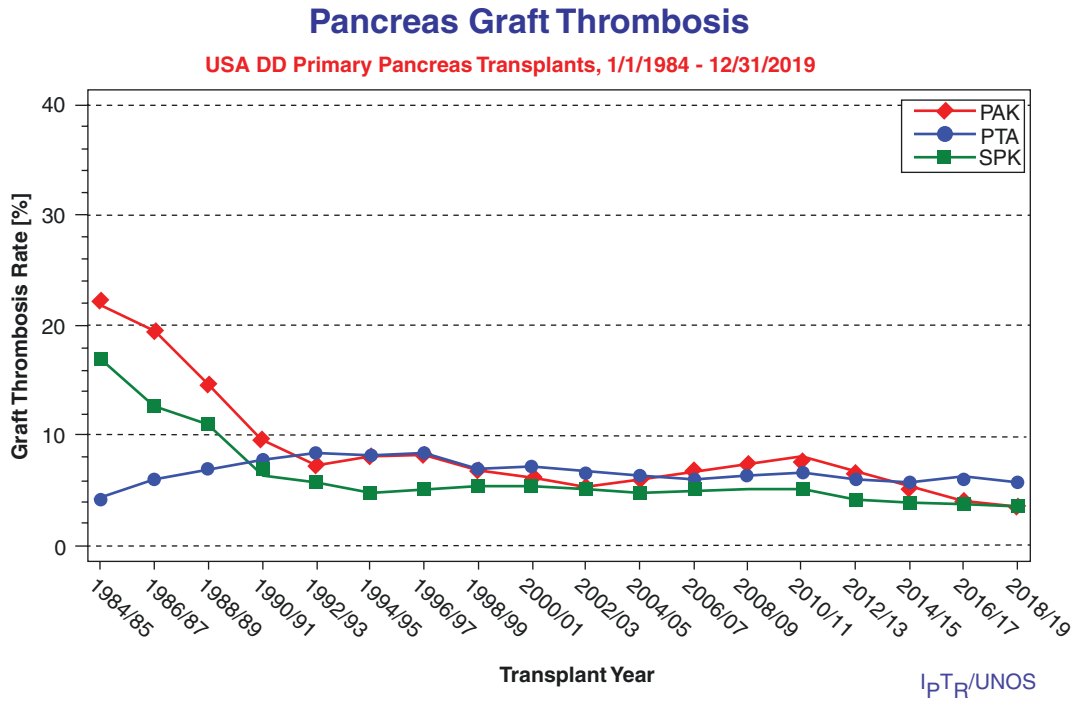

Fig. 1 Graft thrombosis in US primary DD pancreas transplantation

Korea

After the operation, 126 out of 707 (17.8%) patients had intraabdominal bleeding. In 463 cases of Asan Medical center(AMC), the incidence of bleeding was 72 (15.6%) in whom laparotomy was performed in 52 (72.2%), embolization in 3 (4.16%), and conservative management in 16 (22.2%). One patient succumbed due to the abrupt onset of intraabdominal massive bleeding. In laparotomy cases,

oozing at the operation site was detected in 37, arterial bleeding in 7, graft mesenteric site bleeding in 3, and intraluminal bleeding in 5 patients.

The most frequent serious complications were graft thrombosis which was developed in 196 out of 707 (27.7%) patients. Among them, 38 out of 196 underwent thrombectomy. In 463 cases of AMC, thrombosis was detected in 153 (33.0%) patients by early postoperative CT. Thrombectomy was performed in 25 patients in whom 9 (36%) grafts were lost.

Pancreatic juice leakage was developed in 27 out of 643 (4.2%). In AMC series, pancreatic leakage was developed in 22 (4.75%). Among the leakage, 12 (54.5%) were bladder drainage in whom enteric conversion was required in 9 patients.

Acidosis developed in 99 out of 643 (15.4%) patients. In AMC cases acidosis developed in 85 (18.4%). Among the patients with acidosis, most of them were bladder drainage (96.5%), and required enteric conversion in 59 (72.0%) patients.

Hematuria developed in 83 out of 643 (12.9%) patients. In AMC cases, hematuria developed in 66 (14.3%) patients, in whom 39 patients underwent enteric conversion.

Graft pancreatitis developed in 160 out of 643 (24.9%) patients.

Regarding the postoperative infection, UTI developed in 263 out of 643 (40.9%) patients, pneumonia in 98 out of 547 (17.9%) patients, and CMV infection in 214 out of 642 (33.3%) patients.

Postoperative ileus developed in 109 out of 643 (17.0%) patients.

During the follow-up period in the AMC series, acute cellular rejection (ACR) was developed in 106 (22.9%), in whom 49 (46.2%) were biopsy proven rejection. Rejection was developed 60/106 (63%) in PTA, 22/106 (20.8%) in SPK, 13/106 (12.3%) in PAK, and 11/106 (10.4%) in SPLK (simultaneous deceased pancreas and living donor kidney transplantation) group, in which rejection rate was highest in PTA compared other groups.

The incidence of graft failure in the AMC series was 117 (25.3%) out of 463 cases. The causes of graft failure were chronic rejection in 53 (11.4%), patient mortality in 18 (3.9%), acute rejection in 10 (2.2%), thrombosis in 10 (2.2%), noncompliance in 9 (1.9%), infection in 8 (1.7%), and others in 10 (2.2%) patients.

Japan

Among the 410 PT cases, pancreas graft loss was identified in 94 cases (22.4%) [8]. The causes were as follows; graft thrombosis in 24 cases (5.9%), recurrence of type 1 diabetes in 6 (1.5%), chronic rejection in 19 (4.6%), acute rejection in 9 (2.2%), duodenal graft perforation in 6 (1.5%), pancreatoduodenal graft-related complication other than graft thrombosis and duodenal graft perforation in 3 (0.7%), and death with functioning graft (DWFG) in 27 (6.6%) (Table 2). DWFG was due to cardiac disease in five cases, infection in five, malignancy in three, multiple organ failure in three, cerebral disease in two, pulmonary disease in two, renal insufficiency in two, gastrointestinal bleeding in one, graft-versus-host disease in one, accident in one, and unknown cause in two cases. Immunological rejection (including acute rejection and chronic rejection) was more frequently identified as the cause of pancreas graft loss in PAK/PTA cases compared to in SPK cases (Table 2).

Taiwan

The surgical complications were listed in Table 3. The technique successful rate was 97% in pancreas transplant, with five cases (3.0%) of technique failure, including three (12.5%) in PAK, one (2.6%) in SPK, one (3.6%) in PBK, and 0 in PTA, ($P = 0.021$). Surgical mortality occurred in four (2.4%) cases. The overall surgical complication rate was 46.1%, with the highest (62.5%) in PAK, followed by 60.5% in SPK, 50.0% in PBK, and lowest (32.0%) in PTA ($P = 0.008$). The most common complication was gastrointestinal bleeding (11.5%), followed by intraabdominal bleeding (6.1%), and pancreatic graft hemorrhage (5.5%). There was a rare case of malakoplakia related to *E. coli* infection in the PAK group.

Table 2 Cause of pancreas graft loss according to the PTx category

Cause	All cases (n = 410)	SPK (n = 344)	PAK/PTA (n = 66)
Graft thrombosis	24 (5.9%)	19 (5.5%)	5 (7.6%)
Chronic rejection	19 (4.6%)	6 (1.7%)	13 (19.7%)
Acute rejection	9 (2.2%)	4 (1.2%)	5 (7.6%)
Recurrence of type 1 diabetes	6 (1.5%)	3 (0.9%)	3 (4.6%)
Duodenal graft perforation	6 (1.5%)	6 (1.7%)	0 (0%)
Pancreatoduodenal graft-related complication other than graft thrombosis or duodenal graft perforation	3 (0.7%)	2 (0.6%)	1 (1.5%)
Death with a functioning graft	27 (6.6%)	22 (6.4%)	5 (7.6%)
Cardiac disease	5 (1.2%)	5 (1.5%)	0 (0%)
Infection	5 (1.2%)	5 (1.5%)	0 (0%)
Malignancy	3 (0.7%)	1 (0.3%)	2 (3.0%)
Multiple organ failure	3 (0.7%)	3 (0.9%)	0 (0%)
Cerebral disease	2 (0.5%)	2 (0.6%)	0 (0%)
Pulmonary disease	2 (0.5%)	2 (0.6%)	0 (0%)
Renal insufficiency	2 (0.5%)	2 (0.6%)	0 (0%)
Gastrointestinal bleeding	1 (0.2%)	0 (0%)	1 (1.5%)
Graft-versus-host disease	1 (0.2%)	1 (0.3%)	0 (0%)
Accident	1 (0.2%)	0 (0%)	1 (1.5%)
Unknown reasons	2 (0.5%)	1 (0.3%)	1 (1.5%)
Total	94 (22.9%)	62 (18.0%)	32 (48.5%)

Data are presented as the number of patients (percentage)
Abbreviations: *PAK* pancreas-after-kidney transplantation, *PTA* pancreas transplantation alone, *PTx* pancreas transplantation, *SPK* simultaneous pancreas-kidney transplantation

Table 3 Surgical complications after pancreas transplant for diabetic patients

	Total	SPK	PAK	PTA	PBK	*P*-value
Case number	165	38 (23%)	24 (15%)	75 (46%)	28 (17%)	
Technique failure	5 (3.0%)	1 (2.6%)	3 (12.5%)	0	1 (3.6%)	0.021
Surgical mortality	4 (2.4%)	1 (2.6%)	2 (8.3%)	0	1 (3.6%)	0.135
Complications, overall	76 (46.1%)	23 (60.5%)	15 (62.5%)	24 (32.0%)	14 (50.0%)	0.008
Gastrointestinal bleeding	19 (11.5%)	7 (18.4%)	2 (8.3%)	4 (5.3%)	6 (21.4%)	0.057
Intraabdominal bleeding	10 (6.1%)	5 (13.2%)	1 (4.2%)	1 (1.3%)	3 (10.7%)	0.057
Pancreas graft hemorrhage	9 (5.5%)	2 (5.3%)	3 (12.5%)	2 (2.7%)	2 (7.1%)	0.308
Chyle leakage	7 (4.2%)	0	1 (4.2%)	6 (8.0%)	0	0.137
Intraabdominl abscess	7 (4.2%)	1 (2.6%)	1 (4.2%)	1 (1.3%)	0	0.682
Pancreas graft leakage	5 (3.0%)	0	2 (8.3%)	1 (1.3%)	2 (7.1%)	0.120
Wound infection	4 (2.4%)	1 (2.6%)	2 (8.3%)	1 (1.3%)	0	0.202
Vascular thrombosis	3 (1.8%)	2 (5.3%)	3 (12.5%)	2 (2.7%)	0	0.120
Intestinal obstruction	3 (1.8%)	1 (2.6%)	1 (4.2%)	1 (1.3%)	0	0.682
Acute myocardial infarction	1 (0.6%)	1 (0.6%)	0	0	0	0.339
Malakoplakia	1 (0.6%)	0	1 (4.2%)	0	0	0.116
Others	10 (6.1%)	4 (10.5%)	0	5 (6.7%)	1 (3.6%)	0.357

SPK simultaneous pancreas and kidney transplant, *PAK* pancreas-after-kidney transplant, *PTA* pancreas transplant alone, *PBK* pancreas before kidney transplant

Late complications occurring after discharge during follow-up period included infection (32.7%), malignancy (3.6%), intestinal obstruction (3.6%), cerebral vascular accident (1.8%), and acute myocardial infarction (1.2%) (Table 4). The most common infection was cytomegalovirus (CMV) infection (12.7%), followed by pseudomembranous colitis (10.9%). CMV gastroenteritis (7.3%) was the most common presentation among the CMV infections, followed by CMV colitis (4%) and pneumonia (2.4%). The malignancy was post-transplant lymphoproliferative disorder(3.6%), including two cases of lymphoma, followed by Kaposi sarcoma, urinary bladder cancer, cholangiocarcinoma, and oral cancer in one (0.6%) case.

Overall rejection of pancreas graft was 24.8% including acute (18.2%) and chronic rejection (9.7%) (Table 5). Rejection was highest in the PTA group (36.0%), followed by SPK (23.7%), PAK (16.7%), and lowest in PBK (3.6%) ($P = 0.005$). There were 56 cases (33.9%) of graft loss in total, with the highest graft loss rate in PTA (38.7%), followed by PBK (38.5%), SPK (28.9%), and PAK (25.0%) ($P = 0.559$). The most common cause for the pancreas graft loss in PTA

Table 4 Late complications after pancreas transplant for diabetic patients

	Total	SPK	PAK	PTA	PBK	*P*-value
Case number	165	38 (23%)	24 (15%)	75 (46%)	28 (17%)	
Infection, overall	54 (32.7%)	19 (50.0%)	8 (33.3%)	19 (25.3%)	8 (28.6%)	0.065
CMV infection, overall	21 (12.7%)	7 (18.4%)	3 (12.5%)	9 (12.0%)	2 (7.1%)	0.587
CMV gastroenteritis	12 (7.3%)	6 (15.8%)	2 (8.3%)	4 (5.3%)	0	0.081
CMV colitis	4 (2.4%)	2 (5.3%)	0	1 (1.3%)	1 (3.6%)	0.489
CMV pneumonia	4 (2.4%)	2 (5.3%)	1 (4.2%)	1 (1.3%)	0	0.444
CMV syndrome	2 (1.2%)	0	0	2 (2.7%)	0	0.488
CMV encephalitis	1 (0.6%)	0	0	0	1 (3.6%)	0.178
CMV retinitis	1 (0.6%)	0	0	1 (1.3%)	0	0.175
Pseudomembraneous colitis	18 (10.9%)	4 (10.5%)	5 (20.8%)	5 (6.7%)	4 (14.3%)	0.245
Urinary tract infection	9 (5.5%)	5 (13.2%)	3 (12.5%)	1 (1.3%)	0	0.013
BK polyoma virus infection	8 (4.8%)	7 (18.4%)	1 (4.2%)	0	0	<0.001
Aeromonas colitis	7 (4.2%)	1 (2.6%)	3 (12.5%)	2 (2.7%)	1 (3.6%)	0.190
Pneumocystis jiroveci pneumonia	5 (3.0%)	1 (2.6%)	2 (8.3%)	1 (1.3%)	1 (3.6%)	0.379
Bacterial pneumonia	4 (2.4%)	1 (2.6%)	0	2 (2.7%)	1 (3.6%)	0.855
Fungus pneumonia	4 (2.4%)	2 (5.3%)	0	1 (1.3%)	1 (3.6%)	0.489
Varicella Zoster infection	2 (1.2%)	1 (2.6%)	0	1 (1.3%)	0	0.732
Herpes zoster infection	2 (1.2%)	0	0	2 (2.7%)	0	0.488
Mycoplasma pneumonia	2 (1.2%)	1 (2.6%)	1 (4.2%)	0	0	0.301
Tuberculosis bacilli pneumonia	1 (0.6%)	1 (2.6%)	0	0	0	0.339
Hepatitis B with hepatic failure	1 (0.6%)	0	0	0	1 (3.6%)	0.178
Others	4 (2.4%)	3 (7.9%)	0	1 (1.3%)	0	0.091
Malignancy, overall	6 (3.6%)	2 (5.3%)	1 (4.2%)	3 (4.0%)	0	0.708
PTLD	3 (1.8%)	1 (2.6%)	1 (4.2%)	1 (1.3%)	0	0.682
Kaposi sarcoma	1 (0.6%)	0	0	1 (1.3%)	0	0.751
Urinary bladder cancer	1 (0.6%)	0	0	1 (1.3%)	0	0.751
Cholangiocarcinoma	1 (0.6%)	0	0	1 (1.3%)	0	0.751
Oral cancer	1 (0.6%)	1 (2.6%)	0	0	0	0.339
Intestinal obstruction	6 (3.6%)	1 (2.6%)	0	5 (6.7%)	0	0.257
Cerebral vascular accident	3 (1.8%)	0	0	0	3 (10.7%)	0.002
Acute myocardial infarction	2 (1.2%)	0	0	0	2 (7.1%)	0.019
Others	1 (0.6%)	0	0	0	1 (3.6%)	0.178

SPK simultaneous pancreas and kidney transplant, *PAK* pancreas-after-kidney transplant, *PTA* pancreas transplant alone, *PBK* pancreas before kidney transplant, *CMV* cytomegalovirus, *PTLD* post-transplant lymphoproliferative disorder including two cases of lymphoma

Table 5 Immunological complications after pancreas transplant for diabetic patients

	Total	SPK	PAK	PTA	PBK	*P*-value
Case number	165	38 (23%)	24 (15%)	75 (46%)	28 (17%)	
Rejection, overall	41 (24.8%)	9 (23.7%)	4 (16.7%)	27 (36.0%)	1 (3.6%)	0.005
Acute rejection	30 (18.2%)	6 (15.8%)	4 (16.7%)	19 (25.3%)	1 (3.6%)	0.088
Chronic rejection	16 (9.7%)	4 (10.5%)	0	12 (16.0%)	0	0.029
Graft loss, overall	56 (33.9%)	11 (28.9%)	6 (25.0%)	29 (38.7%)	10 (35.7%)	0.559
Chronic rejection	23 (13.9%)	5 (13.2%)	0	18 (24.0%)	0	0.002
Death with functioning graft	19 (11.5%)	4 (10.5%)	3 (12.5%)	3 (4.0%)	9 (32.1%)	0.001
Acute rejection	7 (4.2%)	1 (2.6%)	0	6 (8.0%)	0	0.161
Graft necrosis	4 (2.4%)	1 (2.6%)	2 (8.3%)	0	1 (3.6%)	0.135
Primary nonfunction	1 (0.6%)	0	1 (4.2%)	0	0	0.116
Unknown	2 (1.2%)	0	0	2 (2.7%)	0	0.488
Re-transplant	8 (4.8%)	1 (2.6%)	4 (16.7%)	3 (4.0%)	0	0.027

SPK simultaneous pancreas and kidney transplant, *PAK* pancreas-after-kidney transplant, *PTA* pancreas transplant alone, *PBK* pancreas before kidney transplant

(24.0%) and SPK (13.2%) was chronic rejection ($P = 0.002$). Rejection attributed to 53.6% (30/56) of pancreas graft losses. However, the majority of pancreas graft loss in PBK (32.1%) and PAK (12.5%) were due to patient death with functioning graft ($P = 0.001$). Eight (4.8%) of the patients with loss of pancreas graft underwent another successful re-transplant following graft loss.

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Part II

Pancreas Transplantation in Living Donor

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Introduction

According to the Diabetes Atlas published by the International Diabetes Federation in 2019, 9.3% of the world population (about 463 million people) has diabetes mellitus (DM) [1]. The prevalence of DM is rapidly increasing, especially in African and Asian regions, including Korea [2] and Japan. According to recently released "Diabetes Fact Sheet in Korea," the prevalence of diabetes at the age of 30 and older is about 13.7% of the population, accounting for 4.8 million cases of DM patients. In Japan, the prevalence of diabetes at the age of 20 and older is 12.1% (male; 16.3%, female; 9.3%) of the population accounting for 10 million patients [3].

DM is associated with various complications such as retinopathy, neuropathy, and nephropathy, and its prevalence has increased steadily worldwide. These complications are the leading causes of increased mortality and morbidity in DM patients [4, 5]. Although exogenous insulin therapy can be useful for maintaining normoglycemia, it does not prevent long-term complications, Pancreas transplantation is considered to be the most efficient treatment modality for restoring normoglycemia by supplying sufficient β cells returning HbA1C levels to normal [5, 6].

Living donor pancreas transplantation has several advantages over deceased donor pancreas transplantation (DDPT), including better HLA matching, shorter ischemic and waiting times, less need for immunosuppression, and a lower risk of infection [7]. Furthermore, the shortage of deceased donors (DD) and improved graft outcomes for living donor pancreas transplantation (LDPT) can be an attractive treatment for DM patients with or without end-stage renal disease (ESRD) [8].

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LDPT shows better graft survival than DDPT due to the immunologic advantages over technical difficulty [5, 7]. However, after the introduction of tacrolimus, the graft survival rate of DDPT improved remarkably and showed results comparable with those for LDPT [7, 8], which causes LDPT less popular.

In simultaneous pancreas and kidney transplantation (SPK) from DD, the waiting time for transplantation can be extended from 4 to 5 years more, which is similar to that reported by others [9]. While DM patients waiting for a transplant, their physical condition deteriorates rapidly on dialysis and they can develop severe complications. Shortage of DD kidneys is the main factor that limits our ability to transplant potential SPK recipients in a timely manner. However, if the candidates have a living donor (LD), the operation time can be adjusted, especially for SPK recipients [9, 10]. However, in case of pancreas transplant alone (PTA) from a DD, the waiting time is shorter (about 3–6 months) than that for SPK. Thus, the shorter waiting time for DD transplant, PTA can be a better option than LDPTA [11]. Also, LDPT can be performed despite HLA antibody or major ABO incompatibilities [9]. In recipients who are highly sensitized or must avoid high-dose immunosuppression, such as ABO and/or HLA crossmatch incompatible recipients, LDPT can be performed by desensitization [9, 12].

In kidney transplantation, it has been already proven that the use of an organ from a living donor (LD) not only increases the number of transplants, but also shows excellent graft survival rates compared to a DD [13]. However, because LDPT is technically more difficult and may be associated with increased donor morbidity (including the development of DM and surgical complications), its performance has been limited [9].

At Minnesota [9], 125 cases LDPT were performed between 1978 and 2010 and all graft survival at 1, 5, and 10 years was 62%, 50%, and 34%, respectively, and pancreas graft survival rates for technically successful cases were 79%, 64%, and 44%, respectively. When analyzed according to time (Era 1, 1978–1986; Era 2, 1987–1997; and Era 3, 1988–2010), graft survival was significantly better in Era 3 (1 year, 44% vs. 58% vs. 100%; $p < 0.001$; and 10 year, 33% vs. 58% vs. 74%; $p < 0.001$). This reflects the high technical difficulty of LDPT due to the relatively small size of the splenic artery and vein. In early LDPT cases, technical failure was a problem; however, this was overcome by technical improvements and declined gradually over time. In patients with minimal risk of surgical complications, LDPT should not be avoided as a DM treatment for technical reasons.

There is no doubt that the evaluation of the outcome of LDPT should focus not only on the recipient but also on the donor [6, 10, 11]. The Minnesota group [9] experienced relatively low levels of surgical complications (<5%), which included pancreatitis, leakage, pseudocyst formation, or reoperation. However, HbA1C levels were elevated in 10/115 donors, 3 of whom required insulin treatment.

From October 1992 to December 2019, 739 cases of pancreatic transplantation were performed in Korea. Among these, 23 (3.1%) were living donor pancreas transplantation in 2 centers out of 14 pancreas transplant centers. In these, six cases (28.6%) were PTA and the rest (17/23, 74%) were

SPK. Regarding the exocrine drainage, bladder drainage was performed in eight (8/23, 34.8%) (six PTA and two SPK cases); and enteric drainage in the rest of all SPK. 14 (60.8%) were female recipients. Most of the recipients were type I DM (n = 19, 90.5%). The mean donor age was 41.95 + 9.86 (27–60) years and six (28.6%) were females. Nine donors were the parents, six were siblings, seven were spouses, and one was a cousin. ABO blood type was incompatible in two patients (father to daughter, and between spouse).

Patient survival rates were 91.3% and graft survival rates at 1, 5 years were 78.2% and 63.6%, respectively, while those were 88.2% and 75% in living SPK. There were some surgical (hematoma and minor pancreas leakages) and metabolic (DM) complications, but, they were not critical and were comparable with those reported in other centers.

From April 2000 to December 2019, 437 cases of pancreatic transplantation were performed in Japan. Among these, 27 (6.1%) were living donor pancreas transplantation (LDPT). The donors were indicated in case that they fulfilled the donor criteria for LDPT of Japanese guidelines. Also, the recipients were performed by Japanese guidelines. Categories of LDPT were SPK 21, PAK 1, and PTA 5. Bladder drainage technique was indicated in 22 patients (81.5%). Patient, pancreas and kidney grafts survival rates were 96.3, 81.5, 88.9% at 5 years and 86.6, 68.0, 61.6% at 10 years after transplantation. Among 27 donors, 2 (7.4%) developed diabetes at 7 and 11 years after operation. The patient who underwent LDPT, especially SPK obtained the improved quality of life.

However, it is clear that efforts to reduce complications and improved safety are required. Under these conditions, LDPT can be considered a secure treatment modality for DM.

In this study, we reviewed LDPT performed in Korea and Japan and analyzed the clinical characteristics that affect graft survival and donor safety.

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History of Pancreas Transplantation

Duck-Jong Han and Takashi Kenmochi

General

Since the first pancreas transplantation was performed in 1966 at the University of Minnesota, many centers have performed this operation, and the outcomes have been improved due to the use of better surgical techniques and immunosuppressants [1, 2]. Based on this improvement, various types of pancreas transplantation from deceased donors (DD) have been performed. However, living donor pancreas transplantation (LDPT) was first reported in the late 1970s, although the procedure is not performed widely [3].

Pancreas transplants using living donors have been done in all three recipient categories (SPK, PAK, and PTA). The first living donor PAK and PTA transplants were performed in the late 1970s (PAK, June 1979; PTA, May 1980) [4]. The first living donor SPK transplant was not until March 1993, in part because of concern over the magnitude of multiorgan removal [5, 6].

In 1999, in an attempt to decrease the morbidity associated with open distal pancreatectomy, the first laparoscopic donor distal pancreatectomy with the hand-assisted technique was performed at the same institution. The application of minimally invasive techniques has allowed an increased acceptance of the procedure among potential donors and may, therefore, increase the number of donors for this life-saving transplant.

In 2000, the FDA approved the robotic surgical system, Da Vinci, for general use. Since then, the case reported worldwide of robotic distal pancreatectomy and nephrectomy for living donor pancreas-kidney transplantation was successfully performed in 2006 at the University of Illinois at Chicago and proved as a promising technique [7].

According to IPTR (International Pancreas Transplant Registry), only 155 pancreas transplants using living donors have been performed worldwide through 2008 [1]. Due to the technically demanding and diminished immunologic advantage of living donor pancreas transplant in the tacrolimus era compared with the Imuran and cyclosporin, living donor PT is less popular.

Korea

From October 1992 to Dec 2019, 739 cases of pancreas transplantation were performed in Korea. Among these, 23 (3.1%) were LDPT. Here, we retrospectively review the clinical characteristics and outcomes of both recipients and donors. The first case of LDPT was performed at Asan

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Medical Center in 1992 but failed due to graft thrombosis. LDPT was restarted in 2006. Among 21 cases of LDPT who have been performed in AMC, 6 cases (28.6%) were PTA, and the rest (15/21, 71.4%) were SPK. Two procedures for exocrine drainage were performed. During the early period, bladder drainage was performed in eight (8/21, 38.1%) LDPT (six PTA and two SPK cases); however, during the later period, all LDPTs (13/21, 61.9%) were SPK with enteric drainage. One IDDM female recipient underwent ABO-incompatible SPK from her father (A to B) in 2012 [8]. Donor pancreas and kidney were harvested from mother in our last SPK patient by the laparoscopic procedure. In other center (Koryo University Hospital), two cases of living donors, including one ABO incompatible SPK, were performed with enteric drainage technique.

Japan

Although the first pancreas transplantation from a brain dead donor (DBD) was performed in 1984 in Japan, brain death had not been recognized widely in our country, 14 pancreas transplantations from using non-heart-beating donors (DCD) have been performed from 1990 to 1994. Since the Organ Transplantation Law was enforced in 1997, 437 pancreas transplantations, including 27 living donor pancreas transplantations (LDPTs), have been performed in Japan until December 2019. The number of DBD remained, however, extremely low from 1997 to 2010, which were only 3–10 per year. From the severe shortage of DBD donors in our country, the first LDPT was introduced in 2004 at Chiba-East National Hospital [9]. Until December 2019, 27 LDPTs have been performed at five centers in Japan. Among these, 18 cases (66.7%) have been performed at Chiba-East National Hospital. Since the Organ Transplantation Law was revised and enforced in 2010, the number of DBD donors increased several times and, thereafter, very few cases of LDPTs have been performed.

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Indication of Pancreas Transplantation (Donor and Recipient)

Duck-Jong Han and Takashi Kenmochi

Donor

General

The social and psychological evaluations assess the donor's voluntarism and altruism as well as the dynamics of the donor recipient relationship.

Apart from the general medical workup, potential pancreas donors must also fulfill certain criteria and undergo testing specific to their pancreatic endocrine function. Related donors must be at least 10 years older than the age at which the intended recipient was diagnosed with diabetes mellitus. No other sibling or family members other than the recipient can be diabetic. Potential donors with a history of gestational diabetes are also excluded [1, 2].

At the University of Minnesota, initial pancreas specific laboratory screening tests include serum amylase and lipase, fasting plasma glucose, and fasting hemoglobin (Hb) AIC determination. As part of their extensive metabolic evaluation, potential donors undergo specific metabolic testing oral glucose tolerance test (OGTT), intravenous glucose tolerance test, acute insulin response to arginine/acute insulin response to glucose have been done. Currently they modified: basal insulin of 9U/mL or greater and OGTT 2 h > 120 mg/dL. In addition they recommend expanding autoantibody screening to include GAD65, IA-2, and ZnT8 (Table 1) [3].

Table 1 Exclusion criteria in living donor pancreas transplantation

(1)	DMII in any first-degree relative or gestational diabetes in donor
(2)	First-degree relative with DM I (other than recipient)
(3)	BMI > 30 kg/m^2
(4)	>56 years old
(5)	Age of donor <10 years greater than age of diagnosis of DM I in recipient
(6)	Impaired glucose tolerance or diabetes (e.g., poly cystic ovarian syndrome)
(7)	Clinical evidence of insulin resistance (e.g., Polycystic ovarian syndrome)
(8)	Evidenxe for >1 autoimmune endocrine disorder (thyroid, adrenal, pituiary, gonads)
(9)	HgbA1C > 6%
(10)	Glucose disposal rate <1% during NGTT
(11)	Elevated titer of autoantibodies (ICA, GAD65, IA-2, and ZnT8)
(12)	Glucose value >120 mg/dl during 75g. OGTT
(13)	Basal, fasting insulin >9 U/ml (marker of insulin resistance)
(14)	Acute insulin response to glucose or arginine <300% basal insulin
Additional requirements	
(1)	Counseling to comply with postdonation diet and exercise program to prevent weight gain
(2)	Detailed informed consent

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Korea

Apart from the general medical workup, potential pancreas donors must also fulfill certain criteria and undergo testing specific to their pancreatic endocrine function. Body mass index (BMI) is below 27 kg/m^2. No other sibling or family members other than the recipient can be diabetic. Potential donors with a history of gestational diabetes are also excluded. Initial pancreas specific laboratory screening tests include serum amylase and lipase, fasting plasma glucose, fasting hemoglobin (Hb) A1C, and C-peptide. As part of their extensive metabolic evaluation, potential donors undergo oral and IV glucose tolerance tests and studies to determine their insulin secretion and functional insulin secretory reserve by C-peptide stimulation test using glucagon (0 and 6′). There is no autoantibody (glutamic acid and decarboxylase 65: GADA). Related donors must be at least 10 years older than the age at which the intended recipient was diagnosed with diabetes mellitus.

Japan

Donor safety including mortality and morbidity, especially the decreased pancreatic function and the onset of diabetes is essential for performing LDPT. We have consisted the working group both in the Japanese Pancreas and Islet Association (JPITA) and the Japan Society for Transplantation (JST) and determined the donor indication and the criteria (Table 2).

According to the ethical guideline of JST [4] concerning living donor organ transplantations including kidney and liver transplantation, the donor was restricted within the relatives (≤6th degree) and relative-in-law (≤3rd degree). The donor and the recipient must take separately more than two interviews by psychiatrist and clinical psychologist. Voluntary motivation without mental pressure and money transfer has to be confirmed.

Donor criteria for LDPT are shown in Table 2. In addition to this criteria, we performed CT volumetry to determine the volume both of pancreas head and body & tail [5] and C^{11}-methionine positron emission tomography (PET) to evaluate the pancreatic function of the head, and body with tail separately [6, 7].

Table 2 Donor criteria for live donor pancreas transplantation (The Japan Society for Transplantation, 2010.6)

Indications
1. Age: <65 years
2. No family history of diabetes except for the recipient
3. Normal endocrine function
   (a) 75g-OGTT: normal pattern (Any blood glucose levels: <180 mg/dl)
   (b) Insulinogenic Index: >0.4
   (c) HOMA-beta: >40%
   (d) HOMA-R: <2.5
   (e) HbA1c: <5.5%
4. Negative anti-GAD antibody, anti-IA2 antibody, anti-insulin antibody
5. BMI: <25 kg/m^2

Contraindications
1. Active infectious disease
2. HIV(+), HTLV-1(+), HBs antigen(+), HCV antibody(+)
3. Creutzfeldt–Jakob disease
4. Malignancy

OGTT oral glucose tolerance test, *HOMA-beta* homeostasis model assessment beta cell function, *HOMA-R* homeostasis model assessment ratio, *HbA1c* hemoglobin A1c, *GAD* glutamic acid decarboxylase, *IA2* insulinoma associated antibody 2, *BMI* body mass index

Recipient

General

Most pancreas transplants have been done in patients with type 1 diabetes who are absolutely β-cell deficient. However, pancreas transplants have also been done for type 2 diabetes. The patient became insulin dependent even though C-peptide type was present pretransplant, indicating persistence of at least some endogenous β-cell function [8]. Patients with progressive secondary complications of diabetes are also destined for blindness, amputations, and kidney failure that exceed the usual side effects of immunosuppression. Diabetes per se is sufficient for a

patient to opt for a β-cell transplant, accepting the risks of immunosuppression over those of diabetes. Living donors for solitary pancreas transplants are now used if the recipient is highly sensitized (panel reactive antibody >80%) and has a low probability of receiving a cadaver graft; must avoid high dose immunosuppression; or has a nondiabetic identical twin or a 6-antigen-matched sibling [9].

Pancreas transplant recipients can be divided into two broad classifications: those with nephropathy to such a degree that they also undergo a kidney transplant, either simultaneously or sequentially, and those, usually without end-stage renal disease, who undergo only a pancreas transplant. The traditional categories are as follows: SPK transplant, PAK transplant, PTA, and kidney after pancreas (KAP) transplant. In the SPK category, the most common scenario is for both organs to come from same cadaveric donor, with a small percentage being from a living donor. However, simultaneous cadaveric donor pancreas and living donor kidney transplants have also been done. As a pre-emptive transplant, it avoids dialysis and induces insulin independence with one operation and with the lowest rejection rate.

Korea

Most of the living donor pancreas transplant have been done in IDDM patients requiring insulin. However pancreas transplants have been done in non-obese type 2 diabetic patients who use insulin for glucose control. In early diabetic stage without diabetic complication, pancreas transplant alone can be done in the case in whom blood glucose is hardly controllable by exogenous insulin use and early development of diabetic complication. In these conditions, post-transplant immunosuppressant should be understandable compared with insulin therapy. Diabetes with end-stage renal disease will be the ideal candidate for SPK under the physical condition available for major operation. Pancreas transplant following kidney transplantation can be performed if the patient wants insulin off or to avoid the diabetic complication afterwards.

Table 3 Criteria of the recipient for pancreas transplantation (Central Committee for pancreas transplantation in Japan, 2010.7.5 revised)

Indications
#1. Diabetic patient with end-stage renal disease is indicated for simultaneous pancreas and kidney transplantation or pancreas after kidney transplantation.
*Decreased serum C-peptide levels.
#2. Diabetic patient with normal renal function is indicated for solitary pancreas transplantation.
*Decreased serum C-peptide levels.
*Unstable blood glucose levels under control by diabetologist.
Age <60 years is preferable.
Contraindications
#1. Progressive retinopathy
#2. Active infection, active liver dysfunction, active peptic ulcer
#3. Malignancy
#4. Unapproved case by regional committee for indication

Japan

Indication for the recipient of LDPT is the same as pancreas transplantation from DBD donors. As shown in Table 3 [10]. The best indications of pancreas transplantation are simultaneous pancreas and kidney transplantation (SPK) or pancreas after kidney transplantation (PAK) for the diabetes patient with end-stage renal disease and decreased serum C-peptide levels. Decreased serum C-peptide levels (CPR) were defined that fasting CPR is ≤0.3 ng/ml and stimulated CPR with glucagon stimulation test are ≤0.5 ng/ml. Solitary pancreas transplantation (PTA) may be indicated to the diabetes patients with normal renal function but with unstable blood glucose levels and a frequent hypoglycemic unawareness even under control by diabetologist in addition to decreased serum C-peptide levels. This is because that the purpose of PTA is rather an improvement of quality of life (insulin independency) than life saving.

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Preoperative Evaluation and Management

Duck-Jong Han, Joo Hee Jung, and Takashi Kenmochi

Donor Evaluation

General

Informed consent should be given to the donor with all donation relevant information. And also the donor has to have time to understand and process all the information, and has the freedom to choose for donation.

All potential donors undergo thorough medical, social, and, frequently, and psychological evaluation. Initial screening usually rules out volunteers with major health problems, e.g., current or previous disorders of the pancreas, active infections or malignancies, major personality disorders, and drug or alcohol dependence, Single parents of minor children are also turned down. The social and psychological evaluations assess the donor's voluntarism and altruism as well as the dynamics of the donor–recipient relationship.

The medical evaluation of potential pancreas donors includes both pancreas-nonspecific and -specific tests. The former are the same as for kidney donation. Pancreas-nonspecific donor tests include the following: electrocardiogram and chest radiograph; ABO blood typing and tissue typing; leukocyte crossmatch and PRA tests; biochemistry profile (e.g., electrolytes, serum creatinine and clearance, blood urea nitrogen, uric acid, serum protein and albumin); liver function tests; lipid profile (fasting cholesterol, triglyceride, and high-density lipoprotein [HDL] levels); complete blood count; coagulation profile international normalized ratio (INR), partial thromboplastin time [PTT]); hepatitis A, B, and C tests; cytomegalovirus (CMV), human immunodeficiency virus (HIV), and rapid plasma regain (RPR) testing; urine analysis and urine culture; in women; 55 years old, serum pregnancy test; in women, 40 years old, mammogram and Pap smear in all women, pelvic and breast examination, and in men >50 years old, prostate-specific antigen (PSA) test. In addition, all potential donors must undergo a history and physical examination. SPK donors must also undergo serial blood pressure measurements.

In addition potential pancreas donor must also fulfill criteria for donation as illustrated in previous donor indication section. Once the potential donor has cleared all of the above tests, he or she still needs to undergo a radiographic study to determine the anatomic suitability of the pancreas. Living kidney donors often have multiple arteries on one (or both) sides, but in living pancreas donors the splenic artery's supply to the distal pancreas shows little variation. But, even in the presence of an anatomic variant (e.g., splenic

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artery off the suprarenal aorta), a distal pancreatectomy (including the splenic artery) is usually feasible. Until the mid-1990s, aortography was the gold standard for assessing the vascular anatomy of the donor's pancreas (and kidney, if both organs were to be donated at the same time).

But, magnetic resonance imaging (MRI) and angiography (MRA) have become increasingly popular because of their less invasive nature [1]. In addition, MRI/MRA provides details of parenchymal structure and allows 3D reconstruction of not only arterial but also venous anatomy. Another alternative to MRI/MRA is computed tomography (CT) angiography, which—like MRI/MRA—also allows 3D vascular reconstruction. In contrast to MRI/MRA and CT angiography, conventional aortography has the advantage of better detecting subtle luminal changes (such as fibromuscular dysplasia of the renal artery in SPK donors). A drawback is that aortography causes most complications that occur during the preoperative donor evaluation, including allergic reactions to radiographic dye, hematoma, false aneurysm at the arterial puncture site, and, rarely, femoral artery thrombosis. Currently, MRI/MRA or CT angiography is the diagnostic study of choice for evaluating the anatomy of the donor pancreas (and kidney). If several medically suitable pancreas donors are available, the final selection is based on the histocompatibility result: An HLA-identical sibling is the ideal choice (provided all other criteria for pancreas donation are met).

Korea

Before donation, all donors were assessed with respect to social and psychological status (to ensure that consent was voluntary and their reasons were altruistic). Donors underwent a general medical work-up for cardiopulmonary function and renal function test especially in SPK donor, and immunologic test which included ABO blood typing, HLA typing, cross-matching of donor T-lymphocytes and recipient serum. Evaluation of pancreatic exocrine and endocrine function for insulin secretory and resistance (serum amylase and lipase, fasting plasma glucose, fasting hemoglobin [Hb] A1C levels, C-peptide, oral glucose tolerance test, and intravenous glucose test), and measurement of islet cell autoantibodies (anti-GAD antibodies) were done. Donor BMI is limited below 27 kg/m^2. The donor safety from post donation hyperglycemia was finally confirmed by the endocrinologist. In addition, three-dimensional angiography was performed by dynamic computed tomography (CT) of the abdominal cavity to evaluate the anatomy of the pancreas and kidney.

Japan

In case that the patient fulfills the indication criteria including the process of ethical studies, we performed physical examinations to evaluate the safety of the donor operation, including cardiac function, screening of malignancy, and evaluation of arteriosclerosis to evaluate vascular anatomy in regard to surgical aspect. Excellent endocrine function was necessary for the donor candidate. Insulin secretory capacity was studied with Insulinogenic Index, HOMA-β, insulin/C-peptide secretion during 75g-OGTT. Furthermore, urine C-peptide (24 h) was also a good indicator. Insulin resistance was evaluated by fasting serum insulin level, pattern of insulin secretion of 75g-OGTT and HOMA-R or HOMA-IR. Abnormal glucose metabolism was studied with HbA1c and 1,5-AG. All data of the examinations have to be within normal range. Also, as the risk factors of postoperative onset of diabetes, anti-GAD autoantibody, anti-IA2 antibody and anti-insulin antibody have to be negative. Since an obesity is also a risk factor of diabetes, BMI should be less than 25 kg/m^2. In addition to these criteria, our group performed three-dimensional angiography to evaluate the anatomy of the pancreas and kidney, especially celiac artery, splenic artery, superior mesenteric artery, renal artery, portal vein, superior mesenteric vein, and renal vein constructed by dynamic CT.

Furthermore, CT volumetry was calculated to determine the cutline of the pancreas [2]. We determined the cut line to make the segmental pancreatic graft to 50% volume. Also, we confirm the functional volume both of the head (residual) and body-tail using C^{11}-methionine positron emission tomography (PET) to evaluate the pancreatic function of the head and the distal segmental pancreatic graft [3, 4]. We have reported C^{11}-methionine PET which reflects the endocrine function as well as the exocrine function.

Recipient Evaluation

General

A meticulous preoperative evaluation, including a complete history and physical examination, is crucial to ensure optimal patient and graft outcomes. Preoperative evaluation also allows for assessment of acute medical issues (e.g., infectious diseases) that would contraindicate surgery. In pancreas transplant recipients, significant emphasis must be placed on three areas; (1) cardiovascular status, (2) kidney function, and (3) glucose control in addition to a general medical work-up. Immediate preoperative cardiac evaluation is pivotal. Previous hospital records pertaining to cardiac evaluations and procedures (e.g., angioplasty, bypass) are considered carefully. For this reason, patients should undergo appropriate cardiovascular evaluation every 6 months to 1 year while on waiting list. It may be necessary to proceed with additional noninvasive stress testing or directly with coronary arteriography. Because of diabetic micro-and macroangiopathy, attention must also be given to peripheral vascular disease and especially with respect to aortoiliac atherosclerosis. In uremic candidates, the need for hemodialysis must be determined prior to transplantation. Knowledge of dialysis status and preoperative fluid management (including electrolyte, acid base, and volume status) is vital to the proper choice of a uremic recipient for organs from a particular donor.

Korea

Preoperative evaluation includes complete history and physical examination. Preoperative evaluation also allows for assessment of acute medical conditions (e.g., infectious diseases) and cardiovascular status, kidney function, and glucose control in addition to a general medical work-up. Previous hospital records pertaining to cardiac evaluations and procedures (e.g., angioplasty, bypass) are examined carefully. It may be necessary to proceed with additional noninvasive stress testing or directly with coronary arteriography. Because of diabetic micro-and macroangiopathy as a diabetic complication, evaluation of opthalmic retinopathy, renal function status, and peripheral nervous system for sensory and motor nervous conduction velocity in addition to peripheral vascular disease and aortoiliac atherosclerotic occlusive disease status has to be done. Regarding the diabetic status, glucose control by fasting glucose and HbA1C, insulin requirement, status of endogenous β-cell function assay by C-peptide and glucose challenge test should be done. In uremic patients, the need for hemodialysis must be determined prior to transplantation. As described in donor evaluation, ABO typing and immunologic test which included HLA DNA typing, cross-matching of donor T and B lymphocytes and recipient serum, flow-cytometry antibody test (living donor only), and Luminex assay for donor specific antibody screening should be done.

Japan

Since the recipient has a long history of diabetes, condition of various complications should be evaluated in addition to the usual preoperative medical assessment. The progressive retinopathy has to be treated before transplantation. Evaluation of cardiac function and a check of the existence of ischemic heart disease are most important. Not only ECG and echocardiography but also myocardial scintigraphy or coronary angiography should be performed even in young

patients. If there is a coronary artery stenosis, coronary artery bypass grafting or coronary stenting should be done before transplantation. For evaluation of arteriosclerosis, especially in common, and external and internal iliac arteries with severe stenosis of iliac artery, angiography should be done for a successful transplant surgery. Concerning diabetic neuropathy, both sensory and motor nerve conduction velocity should be examined. Autonomic nervous system examination, such as head up tilt test, CVR-R of ECG, urination function test, and gastric excretion function test should be recommended. Status of diabetes is evaluated with HbA1c, insulin amount, and C-peptide levels of glucagon stimulation test. Immunological evaluation includes ABO blood type (A subtype; A1 or A2), DNA typing of HLA both of donor and recipient, and direct crossmatch/flow cytometry crossmatch must be studied. Also, Luminex assay for the screening of donor specific antibody should be done. In ABO incompatible cases, the titer of anti-A or anti-B antibodies has to be measured. In Japan, T-cell positive in direct crossmatch is usually a contraindication for living donor kidney transplantation. In the case of ABO incompatible and positive anti-donor HLA antibodies, desensitization using rituximab and plasma exchange are needed (See Chapter 19 on ABO-incompatible Living Donor Transplantation).

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Surgical Aspect of Pancreas Transplantation

Takashi Kenmochi and Duck-Jong Han

Donor Surgery

General

Distal pancreatectomy for a variety of pancreatic diseases is a common general surgical procedure, but removing the distal pancreas for transplantation is somewhat different: gentle dissection is critical to diminish the risk of pancreatitis both in the (healthy) donor and in the recipient after revascularization. Vascular supply via the splenic artery and vein must be preserved.

As with the open procedure, laparoscopic procurement can involve the distal pancreas only or the distal pancreas in combination with a kidney. Although laparoscopic donor nephrectomy was not performed until 1995 [1], it is increasingly replacing open nephrectomy. Short- and long-term outcomes are equivalent for the laparoscopic and open techniques, in regard to donor safety and kidney graft quality. And, laparoscopic (vs open) nephrectomy shortens the donor's hospital stay and convalescence as well as reduces the need for postoperative analgesic medications [2–4].

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As with laparoscopic nephrectomy, laparoscopic pancreatectomy was first done for a variety of diseases: It was cost effective, shortened the patient's hospital stay, allowed earlier resumption of a normal diet, reduced the need for medications, caused less pain, and facilitated a faster recovery.

Thus, laparoscopic removal of the distal pancreas (with or without concurrent nephrectomy) offers a number of advantages over the open procedure. The following is a description of distal pancreatectomy using the hand-assisted technique. After induction of general endotracheal anesthesia, the donor is placed on the operating table, first in the supine position and then in the right lateral decubitus position. The table is then flexed at a point midway between the patient's iliac crest and rib cage and rotated 45° to allow easy access to the left kidney. Nasogastric suction, Foley catheter bladder drainage, prophylactic antibiotics, and sequential compression devices are all used. The operating surgeon and scrub nurse stand on the patient's right and the assistant and camera operator on the left. Standard laparoscopic instrumentation and two TV monitors are used. Depending on the size of the surgeon's wrist, a midline incision of 6–8 cm is made 2 cm above (alternatively, just below) the patient's umbilicus, and the peritoneal cavity is entered. A HandPort System (Smith and Nephew Inc, Andover, MA) or Gelport System (Applied Medieal Resources Corp, Rancho Santa

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Margarita, CA) is applied to the midline incision. The system's external and internal rings are insufflated, and the surgeon's hand is placed inside the abdomen. After a pneumoperitoneum (12 mmHg) is created, three trocars are placed: The first 12 mm trocar is placed 2 cm below the umbilicus and slightly left to the midline for the 30° laparoscope and camera; the second 12 mm trocar is placed in the left midabdomen (anterior axillary line); and the third 12 mm trocar is placed in the left upper abdomen 2 cm below the rib cage (posterior axillary line). Using electrocautery or the harmonic scalpel (Ethicon Endosurgery Inc, Cincinnati, OH), dissection begins by mobilizing all adhesions between the descending colon and lateral abdominal wall. After retracting the colon medially, the abdominal aorta is exposed down to its bifurcation. With the exception of the splenocolic ligament, all attachments of the spleen, in particular the gastrosplenic ligament, are preserved. Using the harmonic scalpel, the inferior margin of the pancreas is dissected free; the inferior mesenteric vein is clipped and divided close to its entrance in the splenic vein. A small hole is made in the avascular plane between the superior margin of the pancreas and the retroperitoneal attachments. A tunnel is created along the undersurface of the pancreas. A blue vessel loop is passed through to allow for retraction of the tail of the pancreas and for separation of the distal pancreas from the splenic hilum. The splenic vein and splenic artery (and their tributaries) are selectively dissected free in the splenic hilum, then dipped twice on both sides and divided. The rest of the intervening tissue between the pancreas and spleen may be taken down with a 35-mm vascular stapler (ETS Flex Endoscopic Articulating Linear Cutter, Ethicon Endosurgery Inc, Cincinnati, OH). The splenic vein is dissected all the way up to its confluence with the superior mesenteric vein by taking down all attachments between the undersurface of the pancreas and retroperitoneum. The splenic vein is circumferentially dissected free at the level of the confluence. The splenic artery is traced back to its takeoff from the celiac axis and also circumferentially dissected free. Thus, the neck of the pancreas is completely mobilized above the anterior surface of the superior mesenteric and portal veins. The patient is given 70 U/kg of heparin. The splenic artery is clipped twice, dose to its origin in the celiac artery, and divided. The vein is also dipped twice, dose to the portal vein, and divided. Protamine is used to reverse the heparin effect. The pancreas is then stapled across with a 45-mm stapler (ETS Flex Articulating Linear Cutter, Ethicon Endosurgery Inc, Cincinnati, OH) that is reloaded once. The pancreas is removed through the HandPort or Gelport System. The abdomen is inspected for signs of bleeding. Then, a single 4-0 nonabsorbable suture is used to laparoscopically oversew the staple line on the cut surface of the proximal pancreas, to minimize the risk of a pancreatic fistula or leakage. Hemostasis is ensured and the viability of the spleen is cheeked. Only in ease of oozing from a capsular tear of the spleen can a drain be left in the abdomen, right next to the spleen. The abdomen is irrigated and the trocars are removed under visualization. The fascia of the trocar sites are dosed with Vicryl sutures placed by a Carter-Thompson Fascial Closure Device (Inlet Medical Inc, Eden Prairie, MN). The 7-cm midline incision is dosed in standard fashion. Postoperative care is the same as for the open procedure. However, the hospital stay is usually under 7 days. The donor resumes a normal diet earlier and requires less pain medication than after the open procedure. Advantages of the hand-assisted laparoscopic technique (vs the standard laparoscopic technique without hand assistance) include improved tactile dissection, reduced graft extraction time, and reduced warm ischemia time. A disadvantage is the creation of a midline incision in the upper abdomen is more noticeable than the Pfannenstiel incision in the lower abdomen.

Korea

Living donor PT was performed electively when both the recipient and the donor were in optimal condition. The donor and recipient operation was performed at the same time by the same surgical team.

In an open laparotomy procedure by an upper midline incision, either right or left nephrectomy was performed, followed by a distal pancreatectomy with splenectomy for simultaneous pancreas and kidney transplantation (SPK). However, pancreas transplant alone (PTA) patients underwent only distal pancreatectomy with splenectomy. After nephrectomy, the lesser sac was opened to visualize the body and tail of the pancreas. Mobilization and detachment of the inferior border of the distal pancreas were always performed meticulously with mobilization of the spleen. The upper border of the distal pancreas was mobilized to the level of the splenic artery. After visualizing the celiac trunk, the splenic, hepatic, and left gastric arteries, the pancreas neck was dissected from behind the portal vein. Transaction of the pancreatic neck over the left side of the portal vein was then performed. Following identification of the pancreatic duct, bleeding from both sides of the transected pancreas neck was controlled by ligation with a fine suture. The proximal pancreatic duct was ligated and the distal pancreatic duct was marked with a fine suture. The end of the proximal pancreas was then oversewn. After systemic heparinization, the proximal splenic vein and artery at the junction of the superior mesenteric vein and common hepatic artery, respectively, were clamped and divided. Removal of the pancreas from a living donor must be done gently because it is critical to reduce the risk of graft pancreatitis and to preserve the splenic artery and vein. The last three SPK were harvested by laparoscopic approach.

After procurement, the splenic artery was cannulated and the pancreas was flushed with low pressure (20–30 cm H_2O) ice cold UW (University of Wisconsin) or HTK (histidine–tryptophan–ketoglutarate) solution (200–300 mL) via the splenic artery cannula to clear the blood. Splenectomy was performed ex vivo.

Japan

Technique of the distal pancreatectomy and nephrectomy as a donor operation differed depending on the transplant teams. We firstly performed both distal pancreatectomy and nephrectomy under open laparotomy. Since 2005, we have introduced hand-assisted laparoscopic surgery (HALS) in Chiba-East National Hospital (Fig. 1). Under general anesthesia, we fixed the patient was at a supine position. After a 7-cm of

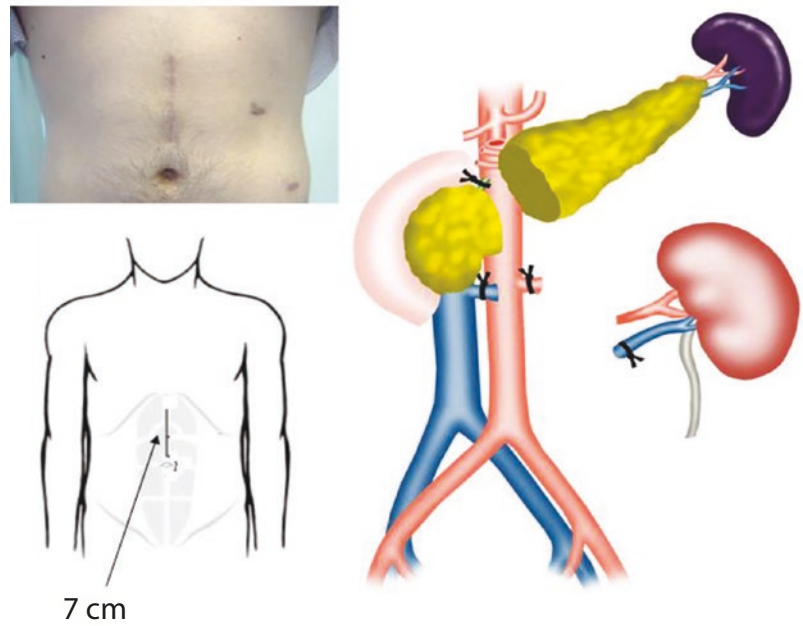

Fig. 1 Hand-assisted laparoscopic surgery (HALS) in Chiba-East National Hospital

upper midline incision, a hand-assist disk (Gel Port®, Applied Medical, CA, USA) was installed followed by the insertion of 12 mm trocar at perinavel position on the left clavicle median. After performing pneumoperitoneum, another 12 mm trocar was inserted at two finger's upper position from the navel on the left anterior axillary line. Firstly, left nephrectomy was performed. Division of the renal artery and vein was done using surgical stapling devices. Thereafter, the distal pancreatectomy with the spleen was performed. The body and tail of the pancreas with spleen were mobilized from surrounding tissue. Superior mesenteric vein, splenic vein, celiac artery, and splenic artery must be identified. Thereafter, a hand-assist disk was removed from the abdominal wall and transfer to open surgery. Dissected vessels are taped. Dissection of the pancreas was done using a laparoscopic coagulating shears (LCS). The main pancreatic duct of the residual pancreas was double ligated and stump was closed with nodule sutures. Finally, the splenic artery and splenic vein were divided with double ligation followed by the procurement of the segmental pancreas graft with a spleen was completed.

The graft was transferred to the back table and a drip from a height of 1 m with a cold (4 °C) University of Wisconsin solution via the splenic artery was started. Usually, 500 mL of UW solution was enough to wash out the blood and cool the graft. Spleen was removed from the graft on the back table.

Recipient Surgery

General

In the University of Minnesota series, of 120 pancreas transplants using living donors, 98% were primary and 2% were retransplants. Exocrine pancreatic secretions were managed with enteric drainage in 47% of all pancreas transplants (SPK, PAK, PTA), bladder drainage in 41%, duet injection in 8%, and open duet drainage in 4%. In HLA-identical transplants, enteric drainage was the preferred technique for management of pancreatic exocrine secretions; in non-HLA-identical transplants, the ability to monitor for rejection and the proximity of the graft to the recipient's bladder were the main reasons that bladder drainage was frequently used. In contrast to whole-organ grafts, venous drainage was, in the vast majority of cases, into the systemic circulation, using the recipient's external (or common) iliac vein.

If the distal pancreas is procured laparoscopically along with the left kidney, the kidney is dissected and removed first. Using electrocautery or the harmonic scalpel, dissection begins by mobilizing the left colon from the splenic flexure down to the iliac vessels. Not only the aorta but also the left common and external iliac arteries, left ureter, and left gonadal vein are exposed (in contrast to laparoscopic procurement of the distal pancreas alone, in which only the aorta is exposed). The left ureter and left gonadal vein are both dissected at the level of the common iliac artery and mobilized free, up to the lower pole of the kidney. The left gonadal vein is dissected all the way up to the left renal vein. The left gonadal vein is then ligated with staples and divided dose to its entrance in the left renal vein. The left adrenal vein is identified, clipped, and divided at its entrance in the left renal vein. The left renal vein is circumferentially dissected free, down to and partly across the aorta. Any lumbar veins draining posteriorly into the renal vein are clipped on both sides and divided.

Complete mobilization of the left renal vein usually exposes the renal artery. Most commonly, the renal artery is slightly cranial and posterior to the renal vein. The proximal renal artery is dissected down to its origin in the aorta; adjacent lymphatic and nerve tissues are taken down. After the vascular supply of the left kidney is completely dissected free, the kidney is exposed laterally by incising Gerota's fascia. The perinephric adhesions are dissected from the superior pole downward. The adrenal gland is dissected off the upper pole of the kidney using the harmonic scalpel. During mobilization of the kidney, high urine output must be maintained through vigorous intravenous hydration. Mannitol and furosemide are given to promote

diuresis. After the kidney is completely mobilized, the ureter is clipped distally twice, then divided proximally at the level of the common iliac artery. The patient is given heparin (70 U/kg) intravenously. The renal artery is clipped three times at its origin in the aorta, then divided distally. The renal vein is divided below the stump of the left adrenal vein with a 35-mm vascular stapler (ETS Flex Endoscopic Articulating Linear Cutter, Ethicon Endosurgery). Heparin is reversed with protamine sulfate. The kidney is removed through the HandPort or Gelport System and passed to the recipient team. After a pneumoperitoneum is reestablished, the abdomen is inspected to assure hemostasis in the kidney bed. Attention then turns to the pancreas. During dissection of the left kidney, the inferior margin of the distal pancreas is already partly mobilized. Other than that, dissection of the distal pancreas is no different than without concurrent left nephrectomy.

Procurement of the Right Kidney and Distal Pancreas

If the left kidney cannot be procured (e.g., because of multiple arteries vs a single artery on the right), a right laparoscopic nephrectomy should be performed. One earlier report noted a higher incidence of renal vein thrombosis and graft loss with right-sided laparoscopic donor nephrectomy [5]. But, according to a retrospective review of 97 right-sided laparoscopic nephrectomies (performed at seven transplant centers), results were no different than with left-sided donor nephrectomy [6]. Surgical technique does vary when the right (vs left) kidney is procured laparoscopically: (1) the donor is initially placed in the left lateral decubitus position; after the right kidney is removed, the donor must be repositioned from the left to the right lateral decubitus position to facilitate mobilization of the distal pancreas; (2) a fourth (5 or 10 mm) trocar is placed in the right epigastrium 2 cm below the rib cage and about 4 cm to the right of the midline for a liver retractor; (3) attachments between the lower right lobe of the liver and the lateral abdominal wall are taken down, as is the hepatorenal ligament, to facilitate dissection of the upper pole of the kidney; (4) the right colon and duodenum are retracted medially to expose the intrahepatic vena cava; dissection of the right (vs the left) renal vein is easy because of the absence of tributaries (the right adrenal and gonadal veins drain separately in the vena cava). Except as just noted, dissection, mobilization, and procurement are no different with the right kidney than with the left kidney. In the past, concerns over the magnitude of the open procedure, with its large incision and long recovery time, have been obstacles to widespread pancreas donation. The laparoscopic technique, with its rapid recovery time, makes pancreas donation from living donors more attractive [7].

Segmental Transplants from Living Donors

In principle, the surgical technique for solitary segmental pancreas, or combined segmental pancreas and kidney, transplants from living donors is not different from segmental pancreas transplants from cadaver donors. The pancreas is preferentially implanted on the right side and the kidney on the left side of the pelvis. In combined transplants, the kidney is usually transplanted first and anastomosed to the recipient external iliac artery and vein; for ureteral implantation, usually an extravesical or anterolateral approach (standard Lich or modified one-stitch Lich technique) is used, sparing the recipient a long anterior cystostomy required for the transvesical or posterolateral approach. The splenic artery and splenic vein of the segmental graft are usually anastomosed to the external iliac artery and vein as described above; on occasion, the hypogastric artery is used for arterial inflow. For diversion of exocrine pancreatic secretions, bladder or enteric drainage may be used, applying the same techniques as described above. For both bladder and enteric drainage, a two-layer anastomosis is created either by directly anastomosing the pancreatic duct to the bladder urothelium (ductocystostomy) or to the jejunal mucosa (duc-

tojejunostomy) or by telescoping the whole cut surface of the pancreatic neck into the bladder (pancreaticocystostomy) or into the jejunum (pancreaticojejunostomy). Only on rare occasions have duct injection or ureteral drainage (e.g., size-matched pancreatic duct and ipsilateral ureter, short pancreatic neck) been used. The pancreatic duct is always stented with a small catheter and tagged with a single 6-0 or 7-0 absorbable suture to the anastomosis. The stent is either spontaneously excreted through the urethra or cystoscopically removed 3–4 weeks post-transplant.

Korea

After a midline incision, the external iliac artery and vein were mobilized. The segmental pancreas was placed in the right iliac fossa. The donor splenic vein and artery were anastomosed to the recipient external iliac vein and artery, respectively, in an end-to-side fashion. In bladder drainage, the splenic arterial anastomosis was lateral and proximal to the splenic vein anastomosis due to the anatomical arrangement of the distal pancreas. For enteric drainage, the splenic arterial anastomosis was medial and distal to the splenic vein anastomosis due to cephalad position of the pancreas neck. After administration of intravenous heparin (70 U/kg), the pancreas graft was reperfused. In SPK, kidney transplantation was performed before pancreas transplantation in the left iliac fossa using standard techniques.

For enteric drainage of the pancreas graft, a Roux-en-Y limb of the upper jejunum was anastomosed to the whole cut surface of the body of the pancreas using the double-layer invagination technique, and the pancreatic duct was cannulated with a stent. An end-to-side jejunojejunostomy was performed about 40–50 cm distal to the pancreaticojejunostomy. For bladder drainage, the cut surface of the pancreas was anastomosed to the bladder by two-layer closure with pancreatic duct stent insertion (Fig. 2).

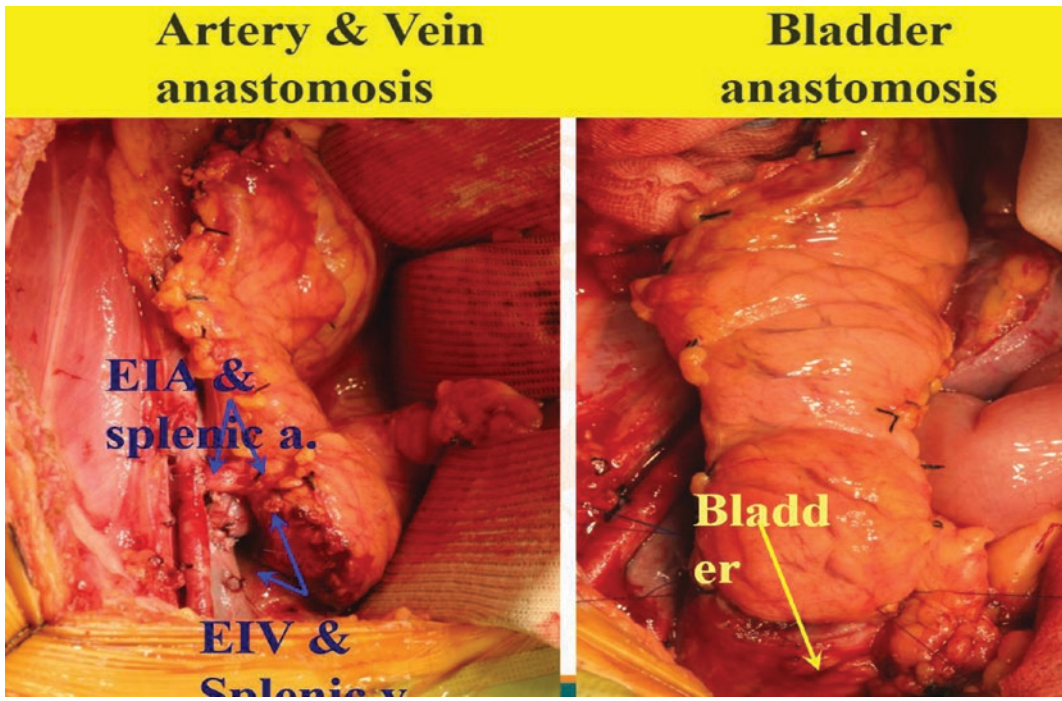

Fig. 2 Living donor segmental pancreas transplantation with bladder drainage (AMC)

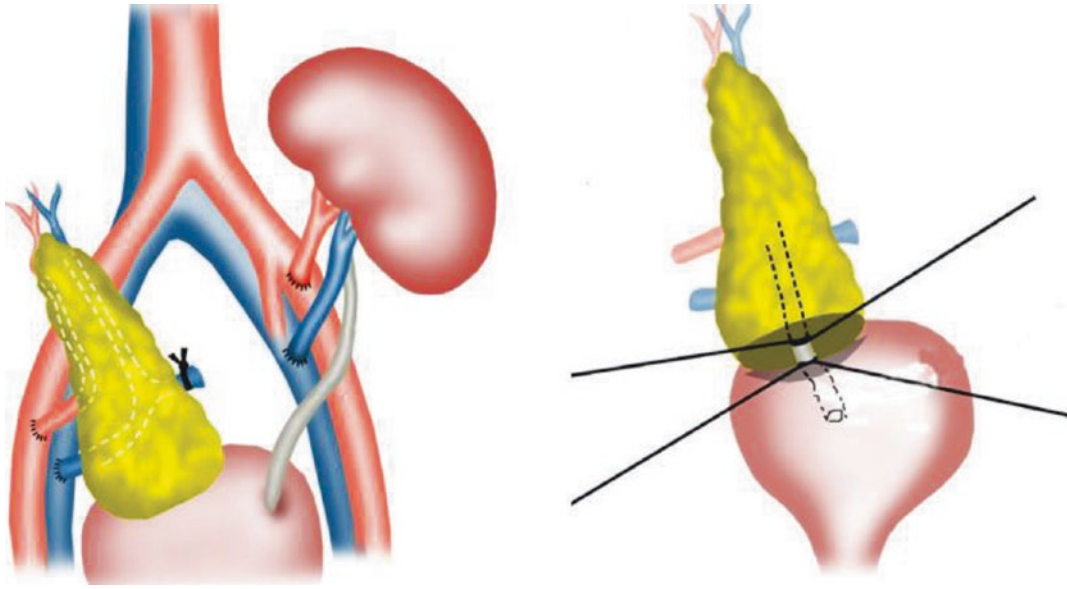

Fig. 3 Schematic view of living donor SPK with bladder drainage

Japan

Firstly, under an arc incision in the left lower abdomen, the kidney graft was transplanted into the left retroperitoneal space as the same technique as a living donor kidney transplantation in our institution. After, closing the wound of kidney transplantation, the pancreas transplantation was started by a separate skin incision in right lower abdomen. 200–400 units/h of heparin administration was started before pancreas transplantation. Since, we selected the bladder drainage technique in almost all cases, the pancreas transplantation was placed in the right iliac fossa retroperitoneally. Graft's splenic artery and vein were anastomosed to the external iliac artery and vein, respectively. Pancreatico-cystostomy was achieved using a two-layer technique including an anastomosis between pancreatic duct and mucosa of the urinary bladder. The stent tube was inserted into the pancreatic duct and the opposite side was opened into the bladder (Fig. 3). Two Penrose drains were inserted into the retroperitoneal space and connected to J-VAC® closed drainage system. Before the recovery from an anesthesia, we check the blood flow of both pancreas and kidney grafts with a Doppler ultrasonography in the operating room.

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Peri- and Postoperative Management

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Perioperative Management

Donor

General

Postoperative care of living pancreas donors is similar to that of any patient undergoing a major abdominal procedure.

The donor is usually extubated in the recovery room and then returned to the general surgery ward. Vital signs are monitored closely over the first 12 h. Serial hemoglobin levels are determined to monitor for possible postoperative bleeding, serum amylase levels to assess exocrine function, and plasma glucose levels to assess endocrine function of the remaining pancreas. Oral intake usually resumes within the first 3 days. Because the spleen is preserved in most cases, donors with postoperative shoulder or left flank pain undergo splenic radionuclide or CT scans to ensure viability of the spleen and rule out the formation of an abscess. Sequential 99mTc-sulfur colloid scans of the spleen in the early postoperative period have shown markedly decreased or absent uptake. But, in most cases, over a period of 2 weeks, splenic blood flow and function return to normal or near normal.

All pancreas donors received pneumococcus, Haemophilus influenza type B, and meningococcal vaccines before surgery to decrease the risk of Gram-positive sepsis in cases when splenectomy was performed [1].

Korea

After confirmation of preoperative evaluation as a proper candidate for living donor which was described in preoperative evaluation section, routine pre-op evaluation for major operation is performed. Postoperative care of living donors is not different from that of routine distal pancreatectomy or nephrectomy patients. Preoperative vaccination against pneumococcus, Hemophilus influenza type B, and meningococcus are used due to splenectomy at the time of donor pancreatectomy as a routine donor operation procedure in our center. As vital signs are monitored, serial hemoglobulin level, serum amylase and lipase, serum glucose, and serum creatinine level are evaluated in SPK donors. In addition, amylase and lipase from the drainage catheter fluid are checked. As a routine, postoperative third-generation cephalosporin (cefotaxime) is administered at operation date. After confirmation of free from perioperative site hematoma, fluid collection, pancreatic leakage, or abscess formation confirmed by abdominal CT, drainage catheter

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is removed and discharged around postoperative 7–10 days.

Japan

The donor of LDPT should receive pneumococcal, meningococcal, and Haemophilus vaccines before operation because of a need for splenectomy at the donor operation. The donor was usually extubated in the operating room and stayed in intensive care unit overnight. Then, the donor was returned to the organ transplant center or general surgery ward. Perioperative management for the donor was similar to the patient who undergoes pancreatic surgery including pancreaticoduodenectomy and distal pancreatectomy. In addition to vital signs, a blood chemistry especially serum amylase, lipase, trypsin, creatinine, blood urea nitrogen (BUN), cystatin-C, C-reactive protein (CRP), aspartate aminotransferase (AST), alanine transaminase (ALT), and lactate dehydrogenase(LD) was monitored. In addition, urinalysis was important to detect urine protein, hematuria, and albuminuria. Amylase and lipase levels of drainage tube fluid were important to detect a development of pancreatic fistula. Antibiotics were administrated intravenously for 5 days after transplantation. Gabexate mesilate (600 mg/day) was given for 7 days for the purpose of inhibition of residual pancreatitis. After 3 days' fasting, the patient starts oral intake. Drainage tube was removed when no bleeding and a low level of amylase and lipase were confirmed. The donors underwent CT scan to rule out a hematoma, fluid collection, a formation of pancreatic cyst, and an abscess before discharge from the hospital. The patient is usually discharged from 7 to 14 days after operation.

Recipient

General

To minimize morbidity following pancreas transplantation, patient care actually begins pre- and intraoperatively. In addition, early post-op management is important for the successful outcome with emphasis on avoiding preventable complications. Postoperative care for living donor and cadaver donor pancreas recipients is similar. However, for living donor pancreas recipients, routine systemic anticoagulatory prophylaxis is recommended, given their relatively high rate of vascular thrombosis. Living donor recipients should be started intraoperatively (at a dose of 200 U/h of heparin, increased to therapeutic levels within the first 8 h posttransplant). Subsequently, they should switch to coumadin (DuPont Pharma, Wilmington, DE) after a 2-day overlap with heparin. Systemic anticoagulation is continued for 6 months (target INR, 2.0–2.5), followed by indefinite administration of acetylsalicylic acid (162.5–325 mg/day) [2].

In uremic candidates, the need for hemodialysis must be determined prior to transplantation. Knowledge of dialysis status and preoperative fluid management(including electrolyte, acid–base, and volume status) is vital to the proper choice of a uremic recipient for organs from a particular donor. Adequate pretransplant hemodialysis not only simplifies perioperative management but also reduces the risk of hyperkalemia during surgery.

The duration of pretransplant hemodialysis should be discussed by the transplant surgeon and nephrologist to minimize the surgical risk as well as minimize graft cold ischemic time so as to not compromise graft function.

If the patient is on peritoneal dialysis, peritonitis should be ruled out by Gram stain examination [3].

As described in donor evaluation immunologic test which included cross-matching of donor T-lymphocytes and recipient serum flow cytometry antibody test, and Luminex assay for donor-specific antibody screening should be done. Another important area of evaluation is glucose control and close monitoring of blood sugar is mandatory. One-third to one-half usual dose of insulin is recommended while the patient is NPO. This period usually ranges from a minimum of 3–5 h due to the time required by the histocompatibility laboratory to complete the crossmatch. The preoperative orders should be complete and the results of all admission tests reviewed. Preoperative shower and rectal enema should be given early to ensure evacuation of

fecal content. Dialogue with the patient regarding the expected risks and benefits of the surgical procedure must take place and conclude with the signing of consent. To maximize information transfer and patient accrual, personnel most familiar with a particular experimental protocol should conduct the discussion and consent process [1].

Successful intraoperative management depends on cooperation and teamwork between the surgeons, anesthesiologists, and nursing staff involved.

A nasogastric tube and bladder catheter should be placed immediately. Pulmonary artery catheters and arterial lines are most commonly used in recipients with compromised cardiovascular status.

Prior to the incision, appropriate antibiotics and immunosuppressants are administered per protocol. Intraoperative antibiotic is needed. Fluids are administered to maintain a CVP in the 12–15 mmHg range. Most centers prefer colloid to minimize the fluid overload.

Blood glucose is monitored hourly and usually controlled with an insulin drip; blood glucose levels should be maintained at 110–150 mg/dL. At the time of organ reperfusion, bleeding from the allograft(s) may be problematic, especially from the pancreas. Adequate volume status is imperative at this time point. Aggressive use of blood products may be required, so adequate communication and preparation by the anesthesiology and nursing staffs must ensure that immediate infusion can begin if necessary. Before revascularization, diuretics are frequently given to promote early kidney graft function in SPK recipients and reduce pancreas graft swelling. Upon completion of the procedure, the abdomen is copiously irrigated with antimicrobial solutions (e.g., containing bacitracin and amphotericin). Closed-suction drains are rarely placed.

Recipients are brought to the postanesthesia care unit or intensive care unit. Hemodynamic and ventilatory assessment is paramount during recovery [1].

The first 24–48 h posttransplant are the most crucial. The goal is to support the patient's body systems in maintaining a steady state during a period when fluid shifts and medical management are most difficult.

In the phase of recovery, three major processes are evolving: (1) The recipient is undergoing the physiological response to surgical trauma, (2) the transplanted organs are in a varying degree of reperfusion injury/recovery, and (3) the recipient is now immunosuppressed [1].

Obviously, blood pressure control is closely related to fluid and electrolyte management. Both hypo- and hypertension must be avoided. Hypotension increases the risk of arterial graft thrombosis, especially in the immediate postoperative period. Further, a low-flow state may enhance thrombus formation (either arterial or venous) at the site of a fresh anastomosis and thus increase the risk of graft loss. Prolonged hypertension, if severe enough, can also induce cerebral vascular events or increase cardiac demand, resulting in ischemia and infarction.

Maintaining a systolic pressure between 120 and 160 mmHg for the first 24 h safely maintains graft perfusion while minimizing the risk of a serious adverse event. In longstanding DM patients, coronary and peripheral vascular compliance is compromised. In most cases, a CVP between 8 and 14 mmHg is adequate.

The maintenance solution commonly used following pancreas transplantation is ½ NS with 10 mEq/HCO_3. By tradition, bicarbonate replacement has been especially important for recipients with bladder drainage of pancreatic exocrine secretions. However, in our experience, even enteric-drained SPK recipients have an acidosis that requires bicarbonate replacement in the immediate postoperative period [4–6].

A dextrose infusion may unnecessarily prolong the use of an insulin drip. When in use, an insulin drip should be infused at a rate to keep the blood sugar less than 150 mg/dL.

Maintenance fluids are usually infused at an In = Out rate once hemodynamic stability is obtained. I=O infusion is usually maintained for the first 24 h, incorporating the above guidelines with CVP monitoring. Because of this approach, dextrose is not added in the maintenance or replacement fluids unless the blood glucose level drops below 100 mg/dL. In kidney and pan-

creas transplant patients where the creatinine plateaus early or in situations of a concerning cardiac history, replacement is adjusted to 0.5 cc/cc output [1].

After the first 24 h, most patients are converted to a straight rate of IV fluid ranging from 75 to 150 cc/h depending on the recipient's size and volume status. Living donor pancreas after kidney and PTA recipients usually do not have large fluid requirements and in general are more stable with respect to volume status in the uncomplicated postoperative course.

When delayed graft function occurs following SPK transplantation potassium, calcium, and phosphorus balance may become problematic. Early dialysis may be necessary for hyperkalemia. For patients who are hypokalemic, potassium is administered on a supplemental basis.

Ionized calcium levels should be followed to maintain an appropriate calcium state.

Further, magnesium levels should be maintained above 2 mg/dL according to current cardiac recommendations. Early stabilization of potassium, calcium, and magnesium will minimize cardiac irritability and help reduce risks for a cardiac event. Although many SPK recipients may have had problems with hyperphosphatemia while on dialysis, hypophosphatemia usually ensues with good renal function.

In inherently immunocompromised diabetic patients, prophylactic coverage against microorganisms is paramount during the perioperative period. Broad-spectrum agents covering Gram-negative, Gram-positive, and anaerobic bacteria are recommended. Various single agents or combinations are available and should be given over the first 24–48 h posttransplant.

Recipients with positive urine cultures (from preoperative specimens) or positive intraoperative duodenal stump cultures should have antibiotic coverage for 3–7 days. Retrospective studies have demonstrated that pancreas recipients are at high risk for losing a second pancreatic allograft to the same infectious agent when their first graft was lost to infection.

Due to the duodenal anastomosis in pancreas transplantation and the potential contamination of the operative field with small-bowel contents, many centers also recommend antifungal prophylaxis with fluconazole.

Cytomegalovirus (CMV) prophylaxis is recommended for any positive combination of a donor–recipient pair. However, when antilymphocyte therapy is utilized CMV prophylaxis is almost always administered. Gancyclovir and, more recently, valgancyclovir are at present the antiviral agents of choice in pancreas transplantation and can first be initiated intravenously or per nasogastric tube in the immediate postoperative period, and then orally. When the patients are intolerant to gancyclovir they may tolerate valacyclovir, which provides adequate prophylaxis against CMV infection in renal only transplantation [7].

Most centers begin sulfamethoxazole/trimethoprim immediately postoperatively and continue long-term prophylaxis against *Pneumocystis carinii* and norcardial infections.

The most critical period to obtain adequate immunosuppressive levels occurs within the first 24–48 h. Most centers give the first doses of immunosuppression within the few hours just prior to the transplant, and then continue intraoperatively [8]. Quadruple immunosuppression is typically utilized for induction therapy, consisting of an anti T-cell agent (first administered intraoperatively), a calcineurin inhibitor, an antimetabolite, and steroids.

While most centers use antilymphocyte preparations (antithymocyte globulin [ATG], OKT3, or thymoglobulin), others have adopted the use of synthetically structured, chimeric-antibody preparations designed to block interleukin-2 (IL-2) receptor (daclizumab, basiliximab); still others use a combination of antilymphocyte therapy and IL-2R blockers. Tacrolimus has become the calcineurin inhibitor of choice. Most centers agree that early levels of tacrolimus should be around 10 ng/mL. Calcineurin inhibitors should be reduced dramatically or held when ATN or delayed graft function (DGF) has occurred. Mycophenolate mofetil (MMF) has virtually replaced azathioprine as the antimetabolite agent of choice. It can be administered either IV or orally and titrated to 1.5–3 g/day (in two divided doses) depending on gastrointestinal tolerance.

High doses of steroids are administered intravenously during the first few days perioperatively and are usually tapered to 20–30 mg/day by the end of the first 7–10 days. By 6 months, most recipients should have their prednisone tapered to 5 mg or less [9].

Judicious use of blood products is a necessary component for protective care of vascular patency maintaining a Hgb > 10 mg/dL. For pancreas recipients with an underlying coagulopathy or liver dysfunction, fresh frozen plasma may be needed. In extreme cases, cryoprecipitate may be needed for consumptive coagulopathies resulting from hemorrhage or disseminated intravascular coagulation.

The incidences of graft thrombosis reported in the literature range from 5.5% to 27% [10–14].

Graft loss from thrombosis is 25% (6/24) in thrombosis compared with 12/79 (15.2%) in non-thrombosis [15].

Thrombosis is determined by US or CT which are ordered at the provider's discretion based on serum glucose, amylase. A severe thrombosed graft is only salvageable within a short time of initial thrombosis formation, highlighting the importance of close postoperative monitoring [14, 16, 17].

There is currently no consensus on the optimal strategy for the prevention and management of vascular thrombosis [17]. Preventative approach is more desirable. The rationale for the use of anticoagulation is to avoid early graft thrombosis, which causes graft pancreatectomy. Thus, it is better to re-explore the recipient for bleeding which has little impact on graft function than for thrombosis which causes graft loss [1].

After segmental pancreas transplantation from a living-related donor, initial systemic heparinization followed by coumadin therapy for up to 6 months is recommended.

Interventions at salvaging the graft may be pharmacological, surgical, or by use of percutaneous interventional radiology. Noncomplex thrombosis (i.e., partial or those isolated to the SV) can be managed with systemic anticoagulation [15, 17, 18]. Arterial signal abnormalities, such as absence or reversal of diastolic flow in US require urgent operative intervention. Graft survival at 1 m was poor in relaparotomy group (77%) than no relaparotomy (91.2%).

Early graft function of pancreas or kidney can be monitored by various means.

Declines in serum blood urea nitrogen, creatinine, amylase, and lipase levels along with normal blood sugar levels are all required to assess good graft function in SPK.

Some centers routinely obtain sonograms or nuclear scintigraphy on all recipients. Ultrasonography is usually the first mode of imaging utilized to evaluate organ dysfunction, as indicated by an unexpected laboratory value or physical finding. Ultrasonography can determine vascular abnormalities, ductal or ureteral obstruction, and the presence of perigraft fluid collections.

Computerized axial tomographic scan of a portal drained pancreas can be helpful in determining peripancreatic fluid collections, pancreatic necrosis, and possibly duodenal obstruction or leak. The role of magnetic resonance imaging/angiography as well as positron emission tomography scanning remains to be determined.

Creatinine clearance and urine protein, C-peptide levels, and HbA1c can be periodically obtained to assess long-term graft function.

For pancreas recipients with bladder-drained exocrine secretions, urinary amylase levels can be monitored.

Serum amylase and lipase levels provide additional means for following pancreas function, especially for enterically drained grafts. However, these markers lack the sensitivity and specificity of urinary amylase.

Regarding the general care in stable graft function (day 3–7), patient hemodynamics usually stabilizes by the close of the first 48 h while graft function steadily improves. Following this phase of recovery, the recipient can be transferred to the transplant ward for less intense nursing care and monitoring.

The nasogastric tube placed intraoperatively can usually be removed when signs of bowel function have returned.

Given the high incidence of autonomic neuropathy in this patient population, many recipients alternate between constipation and diarrhea during the early postoperative period.

With enteric drainage, upper gastrointestinal bleeding may occur as bowel function returns. Such hemorrhage usually results from the duodenojejunal anastomosis and should be self-limited. However, transfusion may be required; only rarely is surgical intervention required.

Timing of Foley catheter removal varies according to surgeon preference, usually within 1–3 weeks posttransplant.

The recipients with thin bladder walls or tenuous anastomosis will probably benefit from longer decompression of the bladder. Similarly, recipients with known neurogenic bladders may need to wait until they are capable of self-catheterization prior to Foley removal. Patients with extremely small bladders may require a short period of "bladder training" prior to catheter removal. Typical protocols call for clamping for half-hour periods, steadily increasing to no more than 4 h. The clamp is released as soon as the patient experiences a sensation of fullness or suprapubic pain. The training process may take 3–5 days and possibly more.

The patient should be encouraged to be out of bed and ambulate no later than postoperative day three.

Poor wound healing secondary to long-standing diabetes and immunosuppression is always a concern in this patient population. For a noninfected wound, skin staples remain for 2–3 weeks prior to removal. In most cases, oral intake can begin by postoperative day 4 or 5 and advance as tolerated.

The patient should initially obtain laboratory studies three times a week [1].

Korea

Intraoperative cooperation and teamwork between the surgeons, anesthesiologists, and nursing staffs are important steps for successful operation, especially in pancreas transplantation.

A nasogastric tube and urinary catheter should be placed immediately at OR. Intraoperative cardiac monitoring via transesophageal Doppler and arterial lines are most commonly used in recipients with compromised cardiovascular status.

Prior to the incision, appropriate antibiotics and immunosuppressants are administered. Fluids and colloids are administered to maintain a CVP around 10 mmHg range.

Blood glucose is monitored hourly and usually controlled with an insulin drip; blood glucose levels should be maintained at 110–150 mg/dL. At the time of organ reperfusion, bleeding from the allograft(s) should be prepared for copious bleeding, especially from the pancreas. Adequate volume status is imperative at this time point. Aggressive use of blood products may be required, so adequate communication and preparation by the anesthesiology and nursing staffs must ensure that immediate infusion can begin if necessary.

During the postanesthesia care or intensive care unit, hemodynamic and ventilatory assessments are crucial during recovery, especially the first 24–48 h posttransplant. Judicious use of blood products is a necessary component, maintaining a Hgb > 10 mg/dL. For pancreas recipients with an underlying coagulopathy or liver dysfunction, fresh frozen plasma may be needed.

Obviously, blood pressure control is closely related to fluid and electrolyte management. Both hypo- and hypertension must be avoided. Maintaining a systolic pressure between 120 and 160 mmHg for the first 24 h safely maintains graft perfusion while minimizing the risk of a serious adverse event. If necessary, IV labetalol or nicardipine is used. However, the choice of agent and dose must be carefully selected and monitored due to side effects. The maintenance solution commonly used following pancreas transplantation is 5% D/W (1.5 L/day) and ½ NS for urinary replacement with CVP around 10 mmHg. Bicarbonate replacement has been especially important for recipients with bladder drainage of pancreatic exocrine secretions. Early dialysis may be necessary for hyperkalemia. For patients who are hypokalemic, potassium is administered on a supplemental basis. Ionized calcium levels should be followed to maintain an appropriate calcium state. Further, magnesium levels should be maintained above 2 mg/dL.

During the first postoperative week, intravenous insulin was administered continuously unless blood glucose levels were maintained less than 200 mg/dL. Blood glucose levels were mea-

sured every 3 h to determine the rate of insulin infusion. Therefore, the cumulative insulin dose was determined by summing up the amount of insulin infused. Subsequently, blood glucose levels greater than 200 mg/dL were treated with subcutaneous exogenous insulin.

Anticoagulation is usually administered both during and after operation.

In living donor pancreas transplants, anticoagulation therapy is mandatory both during and after surgery. Continuous intravenous heparin (400–1000 U/h) was administered and the activated partial thromboplastin time (aPTT) was monitored every 6 h, after which oral warfarin was administered for 3–6 months. The target level of aPTT and prothrombin time (international normalized ratio) was 1.5–2× the upper reference range. If a thrombus was found on CT angiography, the aPTT level was targeted to 2× the upper reference range, with weekly or biweekly monitoring of graft patency by CT angiography [18].

Before 1999, OKT3 was used for induction and tacrolimus/cyclosporine, mycophenolate mofetil, and steroids for maintenance. From 1999 to 2004, basiliximab was used for induction, and maintenance with tacrolimus, mycophenolate mofetil, and low-dose prednisolone. From 2004, rabbit antithymocyte globulin (thymoglobulin) was used for induction, and tacrolimus and mycophenolate mofetil, coupled with steroids for maintenance immunosuppressants.

Total ATG dose was 4.5–5.0 mg/kg regardless of the type of transplant. The first dose (1.5 mg/kg) was intraoperatively administered and followed by 1 mg/kg ATG on postoperative days 1, 2, 4, and 6. Patients received acetaminophen or diphenhydramine prior to infusion, thus reducing the chance of an adverse reaction to ATG. All patients received 500 mg methylprednisolone intraoperatively, which was subsequently tapered and most of the SPK patients were weaned from steroid within 1 week after transplantation. A target tacrolimus level of 9-11ng/mL was achieved within 7 days in 90% of patients.

Bacterial and fungal prophylaxis consisted of ampicillin/sulbactam for 5 days after transplantation, and oral sulfamethoxazole-trimethoprim was administered for 6 months to prevent *Pneumocystis jirovecii* pneumonia infection. CMV monitoring was performed on a weekly basis using CMV DNA assay during early postoperative period. CMV prophylaxis (valganciclovir) was administered for 6 months only if CMV-negative recipients received CMV-positive transplants.

Japan

The patient stayed in ICU for 5–7 days after operation. General care for the patient was almost the same as those in other centers.

Continuous intravenous administration of heparin was started before pancreas transplantation during operation at a rate of 200–400 units/h. After administration, 5,000–10,000 units/day of heparin were continuously given intravenously for 10 days. The amount of heparin was adjusted to be 180–200 s of activated clotting time (ACT). Subsequently, biaspyrin or warfarin was administrated orally for 6 months after transplantation. In the early period after transplantation, the patient tended to show hyperglycemia because of surgical stress, high amount of steroid administration, and hyperalimentation. We used exogenous insulin intravenously or subcutaneously to maintain 100–150 mg/dL of blood glucose level for 1 week in order to protect the β cells from hyperglycemic injury. Blood glucose levels were measured every hour for 3 days and four times a day thereafter. After starting a meal, almost all patients became insulin-free status. Recently, we utilize an artificial pancreas to maintain the blood glucose levels for an early period (3 days) after transplantation.

For the purpose of inhibiting a graft pancreatitis due to reperfusion injury, 100,000 units of ulinastatin was given intravenously for the first 3 days. Also, 600 mg of gabexate mesilate was continuously administrated for 7 days. From 8 days after transplantation, camostat mesylate was orally administrated at a dose of 600 mg/day. The dose of camostat mesylate decreased to 300 mg at 6 months and off at 1 year. To decrease the secretion of pancreatic juice from the graft and protect pancreatico-cystostomy, 100 units of octreotide were given at every 12 h for 5 days after transplantation.

Immunosuppressive protocol was according to that for living donor kidney transplantation. Tacrolimus, mycophenolate mofetile (MMF), and predonisolone were used as a maintenance immunosuppression. Induction therapy was achieved by ATG (rabbit antithymocyte globulin:thymoglobulin) or basiliximab according to center policy.

The antibacterial prophylaxis was the administration of piperacillin for a week, and antifungal prophylaxis was fluconazole for a week, antifungal prophylaxis was consisted by the administration of fluconazole for a week. Concerning a treatment for cytomegalovirus, gancyclovir was prophylactically administrated for 3 months to the recipient whose anti-CMV antibody was negative and the donor's anti-CMV antibody was positive.

Postoperative nutrition was achieved by central venous nutrition for a week after transplantation. Oral water intake is started at four and meal was given at seven postoperative days.

Postoperative Management and Follow-Up

Recipient

General

Serum amylase and lipase levels provide means for evaluation of pancreas function, especially for enterically drained grafts. However, these markers lack the sensitivity and specificity of urinary amylase in bladder drainage. Serum human anodal trypsinogen (HAT) has been shown to complement serum amylase and lipase levels in the determination of graft dysfunction. But, few laboratories are equipped to monitor this factor [1, 19].

The sentinel sign of rejection in SPK recipients still remains a rise in serum creatinine. In some SPK recipients, serum amylase or lipase levels may rise while creatinine levels remain stable. In such situations, a transplant pancreas biopsy is still warranted, especially if an enteric-portal drained pancreas is present.

Creatinine clearance and urine protein, C-peptide levels, and HbAlc can be periodically obtained to assess long-term graft function. For some pancreas transplant recipients, blood sugar levels never fully normalize despite what is believed to be adequate insulin and C-peptide levels. A few hypotheses attempt to explain the cause of persistent hyperglycemia or glucose intolerance following pancreas transplantation. First, the diabetogenic effects of steroids and calcineurin inhibitors(especially tacrolimus) are thought to play a significant role. Second, some recipients have developed insulin resistance and are confronted with a situation no different from type 2 (adult-onset) diabetes mellitus. Third, for portal-enteric drained pancreas recipients the hepatic "first pass" of insulin may offset the hyperinsulinemic effects of systemically venous-drained pancreases. In other words, systemic venous drainage possibly counteracts the diabetogenic effects of immunosuppression or overrides the receptor defect occurring with insulin resistance. Thus, the recipients with portal drained pancreas may have a tendency toward slightly higher blood glucose levels.

Only a few cases of recurrent insulitis resulting in pancreatic graft failure have been described [1, 20].

For pancreas recipients with bladder-drained exocrine secretions, urinary amylase levels can be monitored.

It has been shown, however, that in an SPK recipient, one organ may have independent rejection while the other organ remains rejection free. For PTA and PAK recipients, the ability to follow rejection is somewhat more difficult. Finally, biopsies are warranted either percutaneously via US or computed tomography (CT) guidance or transcystoscopically, assisted by US guidance. Further, if serum or urinary amylase levels are suggestive of rejection the option of a transcystoscopic, transduodenal biopsy is still available should the pancreas not be approachable via US- or CT-guided percutaneous biopsy.

Currently, triple-drug immunosuppression (now with Tacrolimus and MMF) has remained the gold standard for maintenance therapy in pancreas transplantation. In the late 1990s, in selected pancreas recipient categories, triple immunosuppression for maintenance therapy

was sometimes abandoned by steroid withdrawal or avoidance. The principles of maintenance therapy for pancreas recipients are the same as for other solid organ recipients. But, because of the high immunogenicity of pancreas transplants, the amount of immunosuppression required is more than for kidney, liver, or heart transplants.

Type 1 diabetes recurrence (T1DR) is traditionally considered very rare in immunosuppressed recipients of pancreas grafts from organ donors, representing the majority of recipients, and immunological graft failures are ascribed to chronic rejection. Burke et al. [21, 22] have been performing simultaneous pancreas-kidney (SPK) transplants for over 25 years and find that 6–8% of the recipients develop T1DR, with symptoms usually becoming manifest on extended follow-up. T1DR is typically characterized by (1) variable degree of insulitis and loss of insulin staining, on pancreas transplant biopsy (with most often absent), minimal to moderate and rarely severe pancreas, and/or kidney transplant rejection; (2) the conversion of T1D-associated autoantibodies (to the autoantigens GAD65, IA-2, and ZnT8), preceding hyperglycemia by a variable length of time; and (3) the presence of autoreactive T cells in the peripheral blood, pancreas transplant, and/or peripancreatic transplant lymph nodes. There is no therapeutic regimen that so far has controlled the progression of islet autoimmunity, even when additional immunosuppression was added to the ongoing chronic regimens [23].

Korea

During hospitalization and after discharge, the serum glucose, C-peptide level, amylase, lipase, blood cell count, electrolyte, and creatinine, were monitored 2–3 weeks intervals until 3 months, then monthly until 1 year, and then 2–3 months interval. In cases of bladder-drained patients, exocrine secretion such as urine amylase or lipase levels were monitored to evaluate graft function. In some cases, intravenous insulin or oral hypoglycemic agents were used to maintain the glucose level at <200 mg/dL during the early postoperative period. Graft failure was defined at the time at which the reuse of exogenous insulin was required.

In enteric drained patients, serum amylase and lipase can be a biomarker for graft rejection ahead of glucose elevation, low C-peptide, or elevated HbA1C. In SPK serum creatinine can be a surrogate marker of rejection for pancreas as well as kidney.

Standard maintenance immunosuppressants are tacrolimus and mycophenolate mofetil, coupled with the early withdrawal (within 1 week) of steroids especially in SPK. In PAK or PTA, maintenance immunosuppressants are tacrolimus and mycophenolate mofetil, coupled with steroids.

Anticoagulation therapy with heparin which is administered during and just after living donor transplant, was followed by oral anticoagulants administered with warfarin which is recommended for 3–6 months.

Bacterial and fungal prophylaxis consisted of ampicillin/sulbactam for 5 days after transplantation, and oral sulfamethoxazole-trimethoprim was administered for 6 months to prevent *Pneumocystis jirovecii* pneumonia infection. CMV monitoring was performed on a weekly basis using CMV DNA assay during early postoperative period. CMV prophylaxis (valganciclovir) was administered for 6 months only if CMV-negative recipients received graft from CMV-positive donors.

Bk virus by DNA assay is checked at post-op period periodically.

In the case of hyperglycemia under normal urine amylase and lipase in bladder drainage cases as well as enteric drainage, we evaluate GADA autoantibody for the autoimmune islet destruction in addition to biopsy of pancreas.

In the case of elevated serum creatinine/BUN or proteinuria, initial screening of graft kidney by sonogram or renal scan to evaluate the extrarenal cause of abnormality. If renal rejection is suspected, serum antibody screening by luminex assay and renal biopsy are recommended. In the case of elevated serum amylase/lipase or decreased urine amylase/lipase more than two consecutive times in bladder drained patients, pancreatic biopsy is recommended as well as serologic antibody test by luminex assay.

Elevation of serum glucose, HbA1c, or decrease of serum C-peptide are also an indication of pancreatic biopsy and antibody screening.

At the time of rejection confirmed by pathologic examination, steroid pulse therapy for acute cellular rejection is performed initially. If the response is refractory to pulse treatment or a severe form of rejection(>grade2), thymoglobulin is used for both kidney and pancreas. In the case of humoral rejection, plasmapheresis, low dose IV Ig, rituximab, and/or bortezomib are used.

Japan

After discharge, the recipient should come to the hospital every 2 weeks for 3 months and then every month after transplantation. The recipient should report the daily blood pressure (two times a day), body temperature, body weight, and urine volume. The doctors and the coordinators check their reports before medical examination in outpatient clinic.

Pancreatic graft function is evaluated by blood and urine examinations.

(1) Blood glucose, HbA1c, and serum C-peptide levels are measured when the recipient came to the hospital every month to confirm the normal pancreatic endocrine function. (2) serum amylase, lipase, trypsin, and pancreatic secretory trypsin inhibitor (PSTI) levels are measured every month to confirm a normal pancreatic exocrine function. (3) 75g-OGTT, glucagon tolerance test are studied at discharge, 3 months, 6 months, and 1 year after transplantation. Thereafter, these were performed every year. Glucagon tolerance test was performed at discharge, 6 months, and 1 year after transplantation. (4) Serum BUN, creatinine, cystatin-C, and eGFR are measured each month to evaluate kidney graft's function. (5) Urine sugar, urine protein, urine albumin, and urine occult blood are measured each month to evaluate both pancreas and kidney grafts function.

Doppler ultrasonography is indicated according to our protocol at 6 months and every year after transplantation. In case when both grafts's dysfunction is observed, it is indicated in an outpatient basis or at admission. Recently, we have introduced contrast-enhanced ultrasonography (CEUS) [24] to evaluate the graft blood flow to detect vessels thrombus and diagnose a rejection. Urine amylase and lipase levels were measured to determine the amount of pancreatic juice from the pancreas graft to monitor the graft function in case of bladder drainage.

Acute rejection for the kidney graft was diagnosed according to our protocol for kidney transplantation. When the increased levels of serum creatinine, BUN, cystatin-C, urine protein, and albumin, as well as decreased urine volume, eGFR, and abnormality in contrast-enhanced ultrasonography (CEUS), the kidney graft's biopsy were performed. Also, blood glucose, serum C-peptide, amylase, lipase, c-reactive protein (CRP), and pancreatic secretory trypsin inhibitor (PSTI) levels were studied to diagnose the rejection of the pancreas graft. Since rejection usually occurred both in kidney and in pancreas graft in SPK patients, we did not perform the biopsy of the pancreas graft considering a bleeding and a leakage of pancreatic juice from the pancreas graft. In PAK and PTA patients, however, the biopsy of the pancreas graft was recommended to diagnose the rejection.

Treatment for acute cellular rejection was the same as that for kidney transplantation. Firstly, steroid pulse therapy using bolus intravenous infusion of 500–1000 mg methylprednisolone for 3–5 days was introduced. When the rejection was resistant to steroid, thymoglobulin was used for 5–10 days. In case of antibody-mediated rejection, PEX, IV-IG, rituximab in addition to a steroid pulse therapy were used as the rejection therapy. Hemodialysis was indicated to the patient who showed oligouria and anuria.

Donor

General

Postoperative management is similar to that of patients undergoing a major abdominal operation, it varied based on open versus laparoscopic technique. Routine monitoring included vital signs, urine output, serial hemoglobulin, amylase and lipase, and plasma glucose level. Additional annual postdonation follow-up studies included

fasting serum glucose, glycosylated hemoglobulin A1C (HbA1C), and sometimes OGTT [25] if needed.

Korea

During hospitalization and after discharge, the endocrine function of the residual pancreas in each donor was monitored by measuring serum glucose, HbA1C, serum C-peptide levels, and amylase/lipase as well as blood cell count, electrolyte, and creatinine, especially in SPK donor at regular yearly basis.

Japan

The donor was managed after operation in the same manner as those in other centers. 75-OGTT was performed at discharge, 3 month, 6 month, and every year after operation, and C^{11}-methionine positron CT was done to evaluate the residual pancreatic function at 1 year after operation.

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Outcome

Takashi Kenmochi, Duck-Jong Han, Joo Hee Jung, and Young Min Ko

Recipient

General

Considering the technical issues in living donor pancreas transplant, and donor morbidity under the improved graft survival in deceased donor pancreas transplant, living donor PT program has been decreased even in US (Table 1, Figs. 1 and 2) [1]. However, living donor graft survival in SPK is compatible with deceased donor SPK (Table 2, Figs. 3 and 4).

In an earlier report of the 2056 pancreas transplants at Minnesota 1978–2010, 125 (6%) were from living donors and 1931 from deceased donors. Approximately, two-thirds of both living donor and deceased donor transplants were solitary, PTA (42% of deceased donor, 26% of living donor) or PAK [27% of living donor (four-fifths same donor) and 39% of deceased donor]; whereas, approximately, one-third were SPK (30% of living donor, 35% of deceased donor). Three living donor (2%) and 228 deceased donor (12%) cases were retransplants. Regarding the technical failure, in Era 1 (1978–1986) more than one-third of living donor cases were technical failures, nearly double that of deceased donor cases. The technical failure rates then declined in Era 2 (1987–1997), but more so for living donor cases. By Era 3 (1998–2010), technical failures had been eliminated in the living donor cases, whereas it was 10% in the deceased donor cases. For living donor cases the lowest technical failure rate was in the SPK category (5%), but living donor-SPK transplants were not done until midway through Era 2, by which time the technical failure rates were declining in all categories. Surgical technique evolved from open to laparoscopic hemipancreatectomy in the donor [2], and from duct injection to enteric or bladder drainage, with orientation of the splenic vessels to avoid twisting in the recipient. Even though historically the

Table 1 Living donor SPK

Adult LD SPK Tx characteristics			
47 USA LD primary pancreas transplants 10/1/1987–12/31/2017			
	1987–1997	1998–2007	2008–2017
N	23	23	1
Age Median[Range]	35 [20–50]	37 [23–57]	27
% Male recipient	35.0	48.0	0
% ReTx	0.0	0.0	0.0
Donor age Median[Range]	43 [29–58]	41 [19–57]	47
% Male donor	39.0	43.0	0
% Biological	100.0	65.0	0

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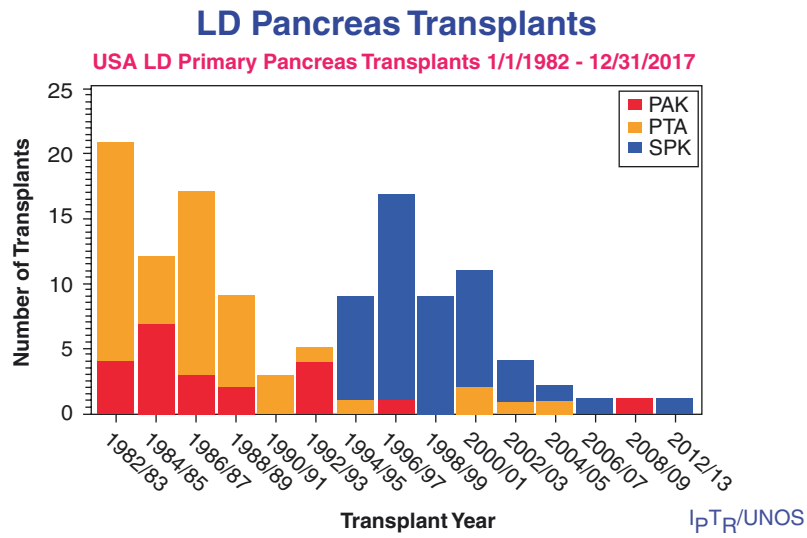

Fig. 1 Living donor pancreas transplantation in US

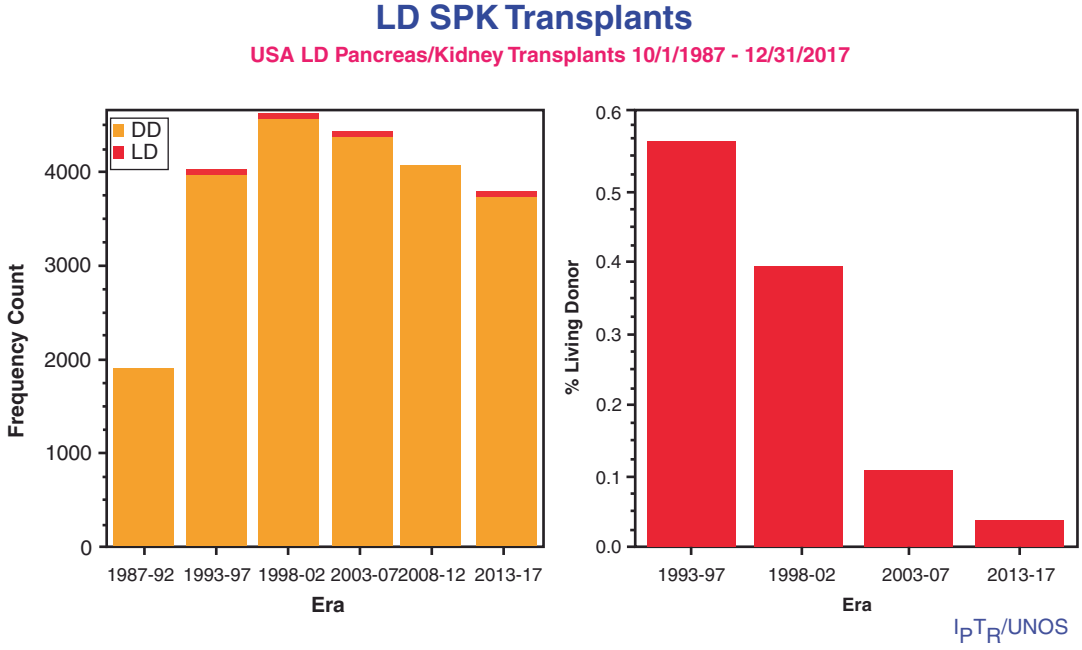

Fig. 2 Living donor SPK in US

Table 2 Pancreas graft survival in SPK; DD vs LD

SPK primary pancreas graft survival						
USA primary pancreas/kidney transplants 10/1/1987–12/31/2017						
				Survival [years]		
Age group	Era	Donor type	*n*	75%	50%	*p*
Adult	1987–1997	DD	5850	2.3	9.9	0.31
		LD	23	2.5	9.9	
	1998–2007	DD	8853	3.8	12.2	0.9
		LD	23	3.8	9.2	
	2008–2017	DD	17841	5.9	–	–
		LD	1	–	–	

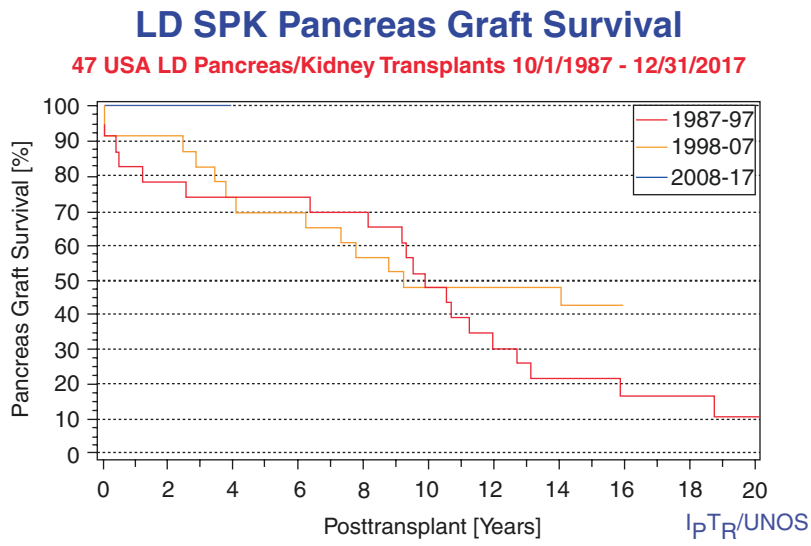

Fig. 3 Living donor pancreas graft survival in SPK

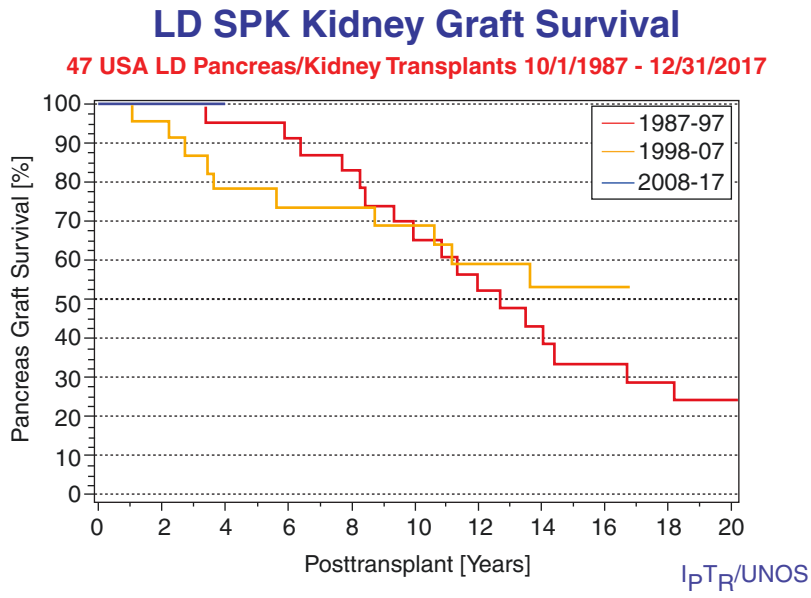

Fig. 4 Living donor kidney graft survival in SPK

results with living donors are not better than deceased donors, they are at least equal now, especially in SPK (Tables 3 and 4). Because of the higher technical failure rate of the early living donor cases, the 1-year graft survival rates are significantly lower. Thereafter, there are no differences in graft survival rates for living donor vs. deceased donor cases in any category. There are no significant differences at any time point.

Finally, patient survival rates over the entire period (1978–2010) for primary living donor vs. deceased donor cases in the various recipient categories are shown with no significant differences (Table 4). More than 90% of pancreas recipients are alive at 1 year. More than three-quarters of living donor and nearly two-thirds of deceased donor recipients are alive at 10 years and more than half of living donor and a third of deceased donor recipients at 20 years [3].

Table 3 Pancreas graft survival by donor source and all cases of the University of Minnesota: 1978–2010

	Erg1. 1978–1986	Erg2. 1987–1997	Erg3. 1998–2010	*p*
LD (N)	55	50	20	
1 year	44%	58%	100%	<0.001
10 year	33%	58%	74%	<0.001
DD (N)	122	652	1157	
1 year	30%	68%	77%	<0.001
10 year	9%	37%	53%	<0.001

Table 4 Patient survival rates by donor source and recipient category for primary pancreas transplants at the University of Minnesota: 1978–2010

	PTA		PAK		SPK		ALL	
	LD (51)	DD (397)	LD (33)	DD (746)	LD (38)	DD (670)	LD (122)	DD (1663)
1 year	92%	94%	100%	96%	100%	88%	97%	92%
5 year	92%	85%	88%	81%	95%	77%	92%	81%
10 year	80%	72%	80%	72%	81%	65%	78%	66%
20 year	53%	42%	45%	40%	66%	33%	51%	37%

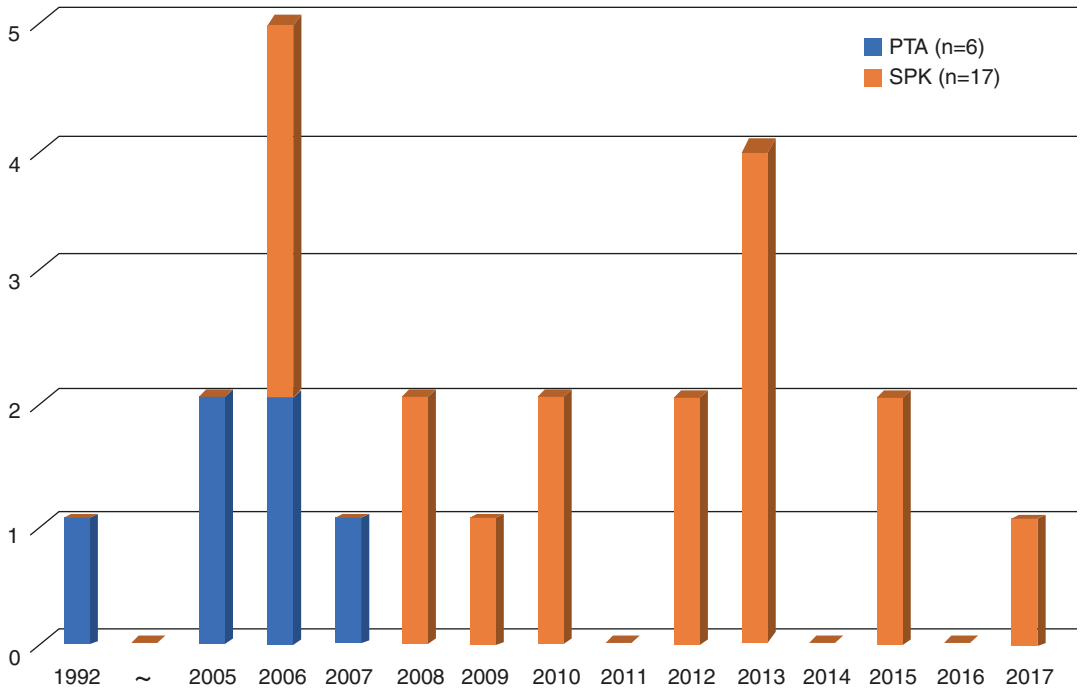

Fig. 5 LDPT in Korea by recipient category

Korea

From 1992 to Dec 2019, 23 (3.1%) of 739 pancreas transplants were LDPTs. The latter were performed at only two Korean transplant centers. In general, LDPT outcome is comparable with DDPT outcome in Korea.

The first case of LDPT was performed at Asan Medical Center in 1992, but failed due to graft thrombosis. Of the 23 LDPTs, 6 (26.1%) were PTA and 17 (73.9%) SPK transplants (Fig. 5). Two exocrine drainage techniques were utilized. In the early period, bladder drainage was performed in 8 LDPTs (6 PTA and 2 SPK); in the

current period, 15 (mostly SPK) transplants were enteric drained (Fig. 6).

The characteristics of the recipients and donors are as follows: mean recipient age was 30.80 ±8.02 (range, 17–49) years and 14 recipients were female. Most recipients had type 1 DM (n = 21); the mean age at diabetes onset was 16.50 ±6.98 (range, 10–39) years. The mean donor age was 41.95 ±9.86 (range, 27–60) years and seven donors were female. Nine donors were parents, six were siblings, seven were spouses, and one was a cousin. ABO blood type was incompatible in two patients (transplants from father to daughter and between spouses).

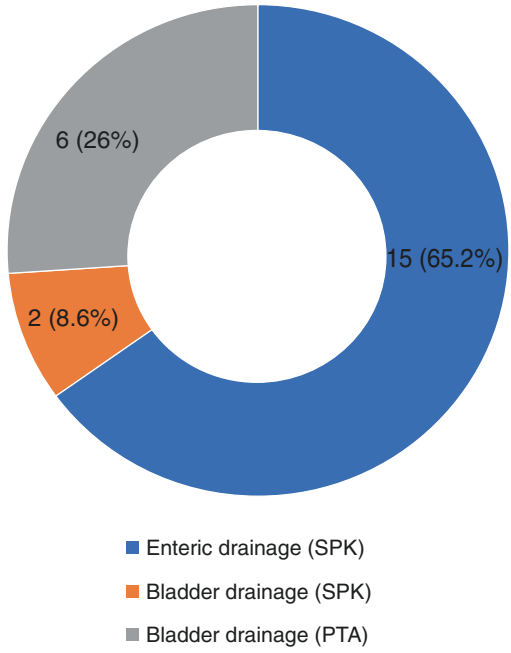

Fig. 6 LDPT in Korea by duct management

The recipients received thymoglobulin for induction therapy and tacrolimus, MMF, and steroids for maintenance therapy.

Patient survival at 1, 5, and 10 years was 95%, 95%, and 75%, respectively (Fig. 7).

In our series, the 1- and 5-year graft survival rates for DDPT and LDPT were different (91.2% vs 78.2% and 76.4% vs 63.6%, respectively; p = 0.010) (Fig. 8).

According to recipient category, graft survival in LD PTA recipients at 1, 3, 5, and 10 years was 50%, 33.4%, 16.7%, and 16.7%, respectively; graft survival in LD SPK at 1, 5, and 10 years was 88.2%, 71.4%, and 62.5% (p = 0.022) (Fig. 9). In fact, most of our PTA transplants in the early period failed (5/6, 83.3%); since 2008, we have performed LDPTs in the SPK category only because of significantly improved outcomes.

In contrast, 1- and 5-year graft survival rates for DD SPK and LD SPK were comparable

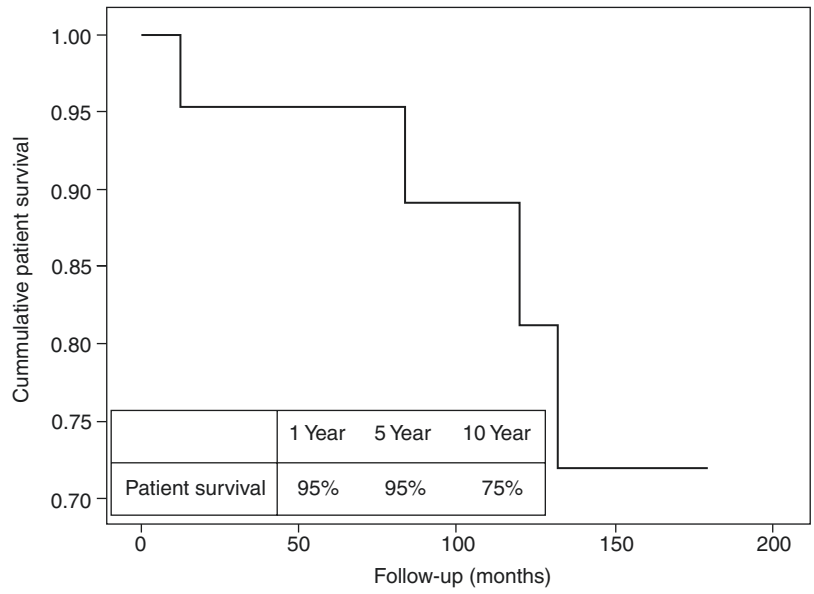

Fig. 7 Patient survival of LDPT in Korea

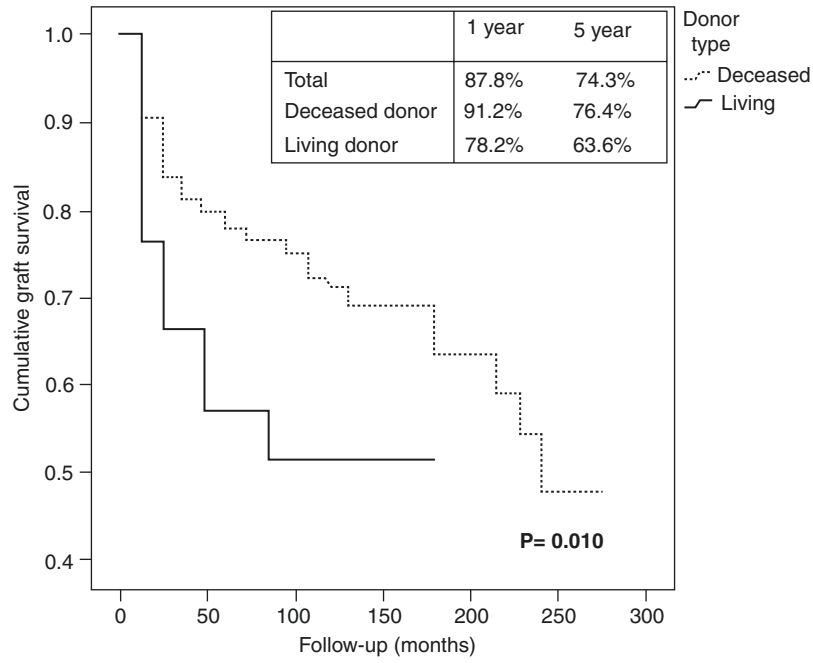

Fig. 8 Graft survival of LDPT vs. DDPT in Korea

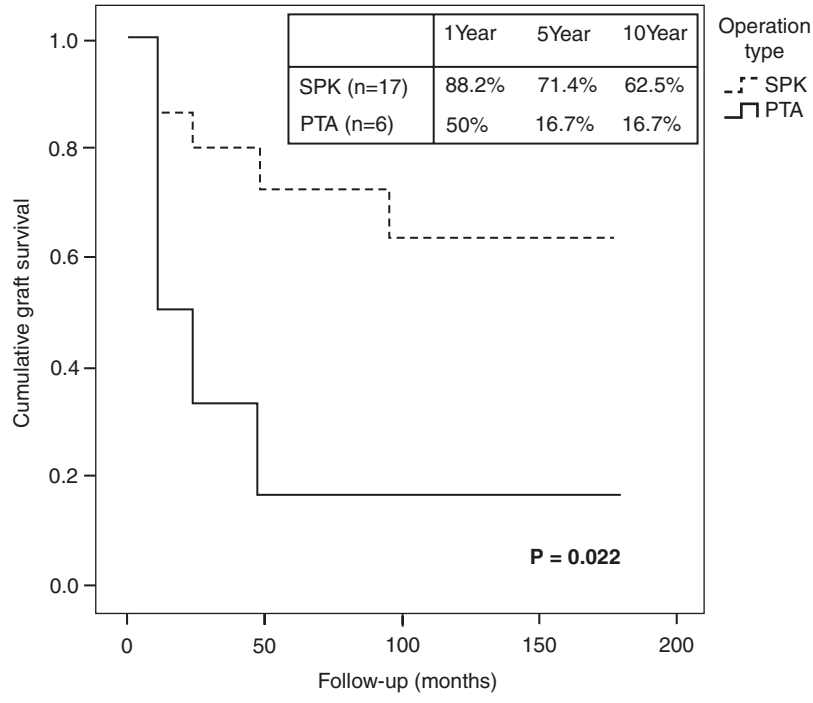

Fig. 9 Graft survival after living donor pancreas transplantation according to operation type

(97.8% vs 88.2% and 91.3% vs 71.4%, respectively; $p = 0.149$) (Fig. 10).

With regard to the exocrine pancreas drainage technique, LDPTs with enteric drainage had better graft outcome than LDPTs with bladder drainage. Only one graft with bladder drainage (1/8, 12.5%) maintained function, whereas most LDPTs with enteric drainage (12/13, 92.3%)

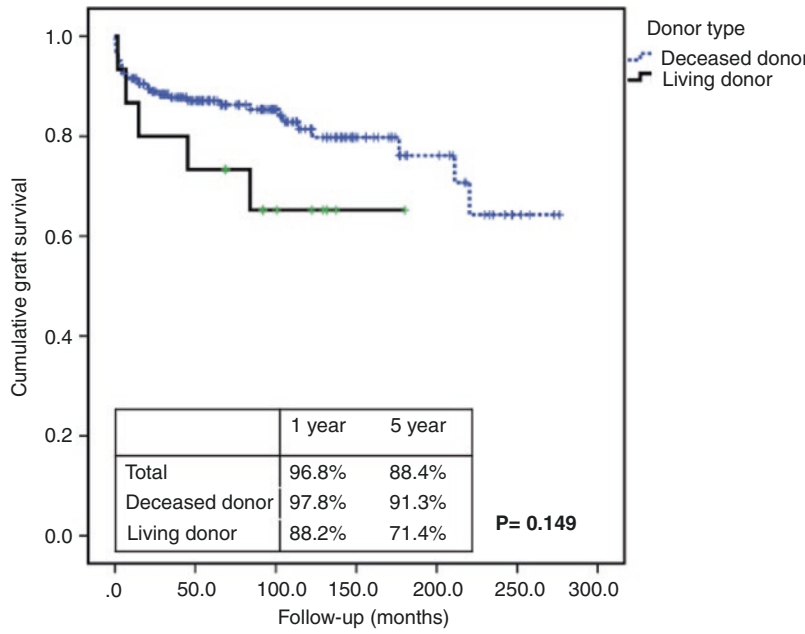

Fig. 10 SPK graft survival in Korea, LDPT vs. DDPT

maintained stable function over time ($p < 0.05$). Based on these results, it is our opinion that LD SPK with enteric drainage is a viable treatment option for patients with DM and ESRD in Korea.

We experienced ten cases of graft failure, five of which developed during the early period (1992–2006). After 2007, there were also five cases of graft failures. In total, there were three failures to thrombosis, four failures due to rejection, two failures due to poor compliance, and one case due to rejection after delivery.

Kidney graft survival in SPK was 87.5% as of December 2020. Acute kidney graft rejection occurred in three recipients, but was reversed with steroid pulse therapy in all cases.

Japan

Out of 437 patients who underwent pancreas transplantation for 20 years from 2000 to 2019, 27 patients underwent LDPTs including six ABO incompatible cases.

Characteristics both of the donor and recipients, operation, and immunosuppression are shown in Table 5. All of the donors were family members including the parents (77.8%) and siblings (22.2%). The donors fulfilled the donor criteria for LDPT of Japanese guidelines. Their HbA1c levels were 4.7–5.6% (median: 5.2%). All of the recipients were type 1 diabetic patients who had a long history of diabetes from 14 to 38 years. Median duration of hemodialysis in SPK and PAK patients was 736 days. Twenty-one

Table 5 Risk factors for prediction of postdonation diabetes

Risk factor	Diabetics	Nondiabetics
FPG > 100 mg/dL ($n = 4$)	100%	0%
FPG < 100 mg/dL ($n = 36$)	22%	78%
Basal insulin >9 U/mL ($n = 5$)	80%	20%
Basal insulin <9 U/mL ($n = 19$)	16%	84%
OGTT2h > 120 mg/dL ($n = 5$)	100%	0%
OGTT2h < 120 mg/dL ($n = 30$)	17%	83%
BMI > 15% ($n = 7$)	86%	14%
BMI < 15% ($n = 32$)	19%	81%

Risk factor	RR 95% CI	p
FPG > 100 mg/dL	5.6 (2.4–8.3)	<0.001
Basal insulin >9 U/mL	5.1 (1.6–15.6)	0.005
OGTT2h > 120 mg/dL	6 (2.6–13.4)	<0.001
BMI > 15%	4.6 (2.1–10.0)	<0.001

No. of risk factor	Diabetics	Nondiabetics
0 ($n = 21$)	0	100%
1 ($n = 8$)	75%	25%
>2 ($n = 6$)	100%	0

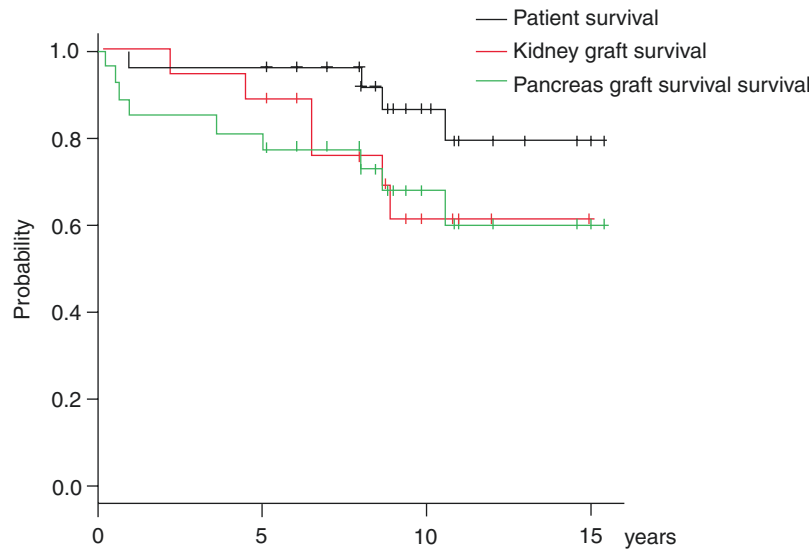

Fig. 11 Patient, and graft survival of kidney and pancreas transplant in Japan

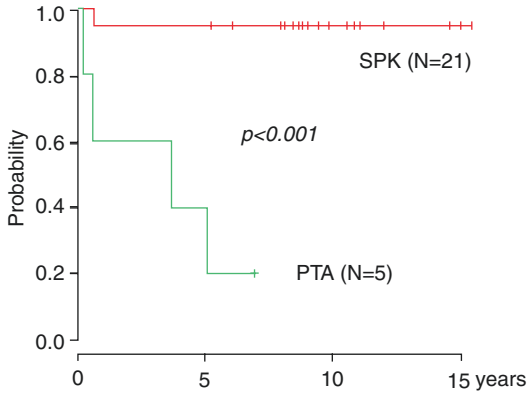

Fig. 12 LDPT pancreas graft survival by recipient category in Japan LDPT vs. DDPT

patients (77.8%) underwent SPK, one patient (3.7%) underwent PAK and five patients (18.5%) underwent PTA. Bladder drainage technique was adopted in 22 patients (81.5%). As an induction therapy, ATG was used in 22 patients (84.6%) and basiliximab was used in other five patients. Tacrolimus was used as a maintenance immunosuppression in 23 patients (85.2%).

The patient survival rates of all 27 LDPT patients were 96.3% at 5 years and 86.6% at 10 years. Pancreas graft survival rate was 81.5% at 5 years and 68.0% at 10 years. Kidney graft survival rate was 88.9% at 5 years and 61.6% at 10 years, respectively (Fig. 11). These data were similar to the outcome of deceased donor pancreas transplantation except for lower kidney graft survival rate in LDPT in Japan. Since one PAK patient died of cerebral infarction at 1 year after transplantation, SPK and PTA were compared by death-censored pancreas graft survival. The 5-year pancreas graft survival in SPK patients was 95.2%, which was significantly higher than 20.0% in PTA patients ($p < 0.001$) (Fig. 12).

Donors

Korea

No donor suffered mortality from distal pancreatectomy and/or unilateral nephrectomy. One donor underwent reoperation the day after the initial operation due to hematoma at the nephrectomy site. Seven donors (33.3%) experienced minor pancreatic juice leakage at the distal pancreatectomy site, which was controlled with conservative management. Hyperglycemia developed in five donors (at 1 and 90 months after donation) and was treated with oral hypoglycemic agents alone. The rest maintained normoglycemia and had normal renal function (HbA1C, 5.87 2.80; C peptide 1.76±0.81ng/mL; serum glucose level, 110.95±12.57mg/dL; and sCr, 0.94±0.20mg/dL after donation).

Japan

No death was experienced in 27 donors. Although three donors (11.1%) developed minor leakage of pancreatic juice from the cut surface of residual pancreas, the leakage healed by conservative therapy. One patient developed pancreatic pseudocyst at 6 months after operation due to a delayed leakage of pancreatic juice from the cut surface of residual pancreas. The pseudocyst disappeared by a puncture through endoscopic ultrasonography. No donors developed diabetes or renal failure at 1 year after operation. At 1 year after surgery, HbA1c was 5.7 ± 0.25%, fasting serum C-peptide level was 1.31 ± 0.37 ng/mL and serum creatinine level was 0.95 ± 0.18 mg/dL. In 75g-OGTT performed at 1 year, 23 patients showed a normal glucose curve and, however, four patients showed borderline pattern. Nondiabetic paten was observed. During the period from 7 to 11 years, two patients, however, developed diabetes and needed the oral diabetes drugs. No patients developed renal failure.

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Complication

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Recipient

General

In contrast to kidney transplantation, the technical failure rate and in particular the arterial or venous thrombosis rate were initially higher for pancreas transplantation using living (vs cadaver) donors. The reason is that only a segment of the pancreas is transplanted and the vessels used for engraftment (splenic artery and vein) are small in diameter, short, and less flexible (as compared with a standard Y-graft, which is used for whole-organ grafts); segmental grafts are also more prone to bending or twisting at the anastomotic sites. In addition, the blood supply of the segmental pancreas depends completely on a single vessel (splenic artery), whereas collateral flow can maintain whole-organ graft viability even if one of the two arteries that provide flow to the whole-organ graft is thrombosed. Thus, partial or complete thrombosis is more detrimental for a segmental pancreas than for a whole organ-graft, which has the advantage of relying on a dual blood supply (superior mesenteric artery and splenic artery). The anastomosis of the pancreatic duct is the Achilles heel of the procedure because it is tedious to do and prone to (partial or complete) breakdown. The anastomotic leak rate is 6% in bladder-drained transplants. Most leaks can be managed conservatively by the placement of a percutaneous drain and Foley catheter. The cut edge of the pancreas is usually small in diameter; simple invagination of the pancreatic cut edge into the bladder may decrease the risk of anastomotic leakage. Invagination obviates the need for a tedious duct-to urothelium anastomosis, but it can create problems from exposure of exocrine pancreatic tissue to the urine. Factors responsible for the low incidence of rejection in living donor pancreas recipients are (1) good matching, (2) immunosuppressive maintenance therapy with TAC and MMF, and (3) precise diagnosis of rejection by routine percutaneous CT- or ultrasound-guided biopsy (1).

Korea

After operation, seven recipients (33.3%) had intra-abdominal bleeding and hematoma, and four of them required laparotomy for hematoma evacuation. Posttransplant bleeding from graft duodenum was developed in three patients. Active bleeding from duodenojejunostomy was detected in one patient. However, bleeding focus

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cannot be detected with only hematoma evacuation from the graft duodenum in two patients.

The most frequent serious surgical complication was pancreas graft thrombosis. Six recipients (28.6%) experienced partial vascular thrombosis of the graft. In two out of six patients, there were small sizes of isolated splenic vein thrombus, which were incidentally detected on routine postoperative follow-up CT. After maintenance of systemic anticoagulation, thromboses were spontaneously resolved. In other three cases, splenic arterial thromboses lead to pancreatic necrosis. Pancreas graft salvage could not be done in those cases. In all cases, thrombosis occurred within 5 weeks posttransplant (posttransplant 1 day to 5 weeks).

Pancreatic juice leakage developed in three patients (14.2%) of duodenocystostomy during pancreas transplantation. Early (<4 weeks) posttransplant leak occurred in two patients. Maintenance intra-abdominal drainage catheter and indwelling foley catheter drainage were helpful for these patients. Interestingly one patient developed pancreas juice leakage with a complaint of sudden-occurred abdominal discomfort, which was detected on CT at posttransplant 1 year. The patient was treated by enteric conversion.

During the follow-up period, acute cellular rejection (ACR) was observed in four recipients (4/21, 19%). All recipients with ACR received steroid pulse therapy. Among these, one recipient completely recovered from pancreas graft rejection. Eight recipients (five PTA and three SPK cases) lost their graft function. The causes of graft failure were graft thrombosis (three), rejection (two), reflux pancreatitis (one), and poor compliance (two). In PTA, two recipients lost graft function due to poor compliance. One recipient who received a graft from her mother experienced severe DM gastropathy and had difficulty taking oral immunosuppressants. She became hyperglycemic and insulin-dependent 17 months after PTA. The other received a graft from her husband. At 35 months after the operation, she was under personal stress and did not take immunosuppressants properly. Her urine amylase level fell and graft rejection could not be recovered. In SPK, two recipients lose their graft function. One recipient with bladder drainage experienced recurrent reflux pancreatitis and pancreatic juice leakage, resulting in pseudocyst formation at 14 months after SPK. Pancreas graft tail was removed and retrograde pancreaticoenterostomy was performed. After surgery, the peripancreatic fluid collection and pancreatic duct dilatation issues were resolved. However, the graft lost function a few months later. The other recipient received kidney, and pancreas from her mother. From 1 year posttransplantation, T cell-mediated rejection occurred repeatedly, and at posttransplant 3 years she started hemodialysis and using insulin after all.

Japan

One PTA patient developed a primary nonfunction of the pancreas graft. Blood flow was maintained in the pancreas graft and no thrombus was detected both in the artery and in the vein. The cause of this primary nonfunction remained unknown. Postoperative bleeding from the pancreas graft was seen in four patients (14.8%) and three patients needed reoperation. Bleeding from arterial anastomosis in one patient and bleeding from the small arterial branch of the pancreas graft in two patients. Venous thrombosis was detected in the splenic vein in five patients (18.5%). The thrombus disappeared by increased amount of heparin, administration of urokinase, and/or interventional radiology (IVR) treatment in the four patients. One patient, however, developed a large thrombus at the venous anastomosis and a graftectomy was performed at 3 days after transplantation. Acute rejection occurred in four patients (14.8%) from 1 year to 12 years after transplantation. All patients recovered from acute rejection by steroid pulse therapy (methylprednisolone 500–1000 mg × 3–5 days) and maintain the pancreas graft function. Fourteen patients (51.9%) developed posttransplant complications except for rejection. Cytomegaloviral infection that was needed antiviral agent was observed in four patients (14.8%). Three patients (11.1%) developed posttransplant lymphoproliferative disorder (PTLD) and needed chemotherapy using rituximab. Pneumocystis pneumonia (PCP)

occurred in two patients (7.4%) and one patient needed a respirator in addition to the administration of trimethoprim-sulfamethoxazole agent and steroid pulse therapy. Other complications included urinary infection, retinal hemorrhage, cerebral infarction, ileus, acute enteritis, and femoral head necrosis.

Donor

General

Donor nephrectomy in the case of living SPK can result in post-nephrectomy-related minor complications such as wound infection or hemata, and also severe sometimes even life-threatening complications such as pneumonia, urine leak, or deep vein thrombosis. The feasibility of kidney transplant using living donor is based on the presence of two kidneys.

In the case of pancreatectomy for donation, the surgical and medical aspects of donating single organ have been more complicated than with kidney donation. The first extrarenal organ to be successfully transplanted using a living donor was the pancreas. Nonetheless, the concern over potentially serious surgical and metabolic complications in the donor has hampered more widespread use of living pancreas donors. However in contrast to living kidney or living liver donors, the mortality rate of living pancreas donors, according to the IPTR, has been 0% [1]. Pancreas donor morbidity includes both surgical and medical complications as well as adverse metabolic changes.

In general, surgical complications are rare; relaparotomies are required in <5% of donors. The most common surgical complication in the donor is splenectomy, either at the time of the distal pancreatectomy (most commonly due to bleeding from the spleen) or postoperatively (most commonly due to splenic ischemia). Intraoperatively, five (11%) donors required blood transfusion. Cumulative incidence of splenectomy was 20%; five (11%) donors underwent splenectomy at the time of donation and four (9%) required splenectomy during the reexploration for splenic infarct [2]. For prophylaxis against overwhelming postsplenectomy infection (OPSI), donors should receive pneumococcus vaccine preoperatively. Postoperatively, six (13%) donors developed symptomatic pseudocyst/peripancreatic fluid collections, all of which were managed by the interventional radiology; two (4%) donors were diagnosed with pancreatitis. Other complications included three (7%) incisional hernia, five (11%) nausea/vomiting, and one (2%) wound infection. There was no statistical significance in perioperative complications based on open versus laparoscopic approach [2].

Serum amylase levels postdonation usually return to normal range within 3 days.

Simultaneous removal of a kidney increases the spectrum of complications, but only slightly increases the overall risk of surgical complications. The median operative time for donors undergoing both distal pancreatectomy and nephrectomy is reported at 6 h and 50 min. Although only a few donors (<10%) require blood transfusions, autologous blood transfusions are recommended; one or two units of donor blood should be stored up to 6 weeks before the scheduled procedure [1].

As with any major abdominal procedure, pancreas donors can develop minor medical complications postoperatively (e.g., atelectasis, urinary tract infection, and prolonged bowel dysfunction). These conditions are usually. Serious medical complications include pneumonia and deep vein thrombosis. The latter can cause pulmonary embolism, the most frequent cause of death in living kidney donors.

Postdonation DM requiring oral hypoglycemic management was diagnosed in 7 (15%) donors with a mean time of onset postdonation of 9.2 (±3.3) years (range, 5–14.8 years). Insulin-dependent DM was diagnosed in 5 (11%) donors with mean time of onset postdonation 7 (±5.4) years (range, 0.5–12.8 years). All donors in this group had at least HgbA1C of 6.5 or greater at diagnosis (Table 1).

Predonation profile was compared between three postdonation groups: nondiabetic donors, donors requiring oral hypoglycemics, and insulin-dependent donors [2]. The following

Table 1 Incidence of diabetes

	% of affected donors (*n*)	Mean time of onset from donation (years)
Oral inpoglyimics dependent	15% (7)	92 ± 33 (range, 5–15.8)
Insulin dependent	11% (5)	7 ± 54 (range, 0.5–12.8)

Table 2 Predonation risk factors for diabetes in donors

	OGTT 2h,mg/mL	Basal insulin,U/mL	Fasting glucose,mg/dL
Nondiabetic	94 ± 15	5.6 ± 2.6	87 ± 7
Oral hypoglycemics	96 ± 4	12 ± 7.6	92 ± 10
Insulin dependent	125 ± 6	12 ± 7.1	100 ± 16

parameters were reviewed: relation to the recipient, BMI, systolic blood pressure, cholesterol, renal function (creatinine and glomerular filtration rate), Hgb A1C, FPG, OGTT 2h, basal insulin, AIRa. Predonation, OGTT 2h, and FPG were found to be higher in insulin-dependent donors as compared to nondiabetic: 125 ± 6 mg/dL OGTT and 100 ± 16 mg/dL FPG vs 94 ± 15 OGTT mg/dL and 87 ± 7 FPG, respectively ($P \leq 0.05$). Basal insulin was higher in both groups requiring oral hypoglycemics and insulin as compared with nondiabetic group: 12 ± 7.6 μU/mL and 12 ± 7.1 μU/mL vs 5.6 ± 2.6 μU/mL ($P \leq 0.05$) (Table 2). Predonation, there was a trend toward higher BMI in diabetic groups versus nondiabetic, but that did not achieve statistical significance; in contrast, during postdonation follow-up, both oral hypoglycemics and insulin-dependent groups had significantly higher BMI as compared with the nondiabetic group: 30 ± 7 kg/m^2 and 29.1 ± 5.5 kg/m^2 vs 24.8 ± 3.1 kg/m^2, respectively ($P \leq 0.05$). There was a trend toward lower AIRa in diabetic groups as compared with nondiabetic but it was not significant. Remainder of the abovementioned predonation parameters was not found to be different between the groups. Although baseline BMI did not significantly impact postdonation DM development, ΔBMI greater than 15% (= [postdonation BMI − predonation BMI]/predonation BMI × 100) over the observation period was a significant RF for development of postdonation DM [2] (Table 3).

Table 3 Predonation and postdonation donor BMI

	BMI, kg/m	
	Pre	Post
Nondiabetic	24.9 ± 3.2	24.8 ± 3.1
Oral hypoglycemics	26.4 ± 4.8	30 ± 7
Insulin dependent	27.3 ± 5.3	29.1 ± 5.5

Table 4 Risk factors for prediction of postdonation diabetes

Risk factor	Diabetics	Nondiabetics
FPG > 100 mg/dL (*n* = 4)	100%	0%
FPG < 100 mg/dL (*n* = 36)	22%	78%
Basal insulin >9 U/mL (*n* = 5)	80%	20%
Basal insulin <9 U/mL (*n* = 19)	16%	84%
OGTT2h > 120 mg/dL (*n* = 5)	100%	0%
OGTT2h < 120 mg/dL (*n* = 30)	17%	83%
BMI > 15% (*n* = 7)	86%	14%
BMI < 15% (*n* = 32)	19%	81%

Risk factor	RR 95% CI	*p*
FPG > 100 mg/dL	5.6 (2.4–8.3)	<0.001
Basal insulin >9 U/mL	5.1 (1.6–15.6)	0.005
OGTT2h > 120 mg/dL	6 (2.6–13.4)	<0.001
BMI > 15%	4.6 (2.1–10.0)	<0.001

No. risk factor	Diabetics	Nondiabetics
0 (*n* = 21)	0	100%
1 (*n* = 8)	75%	25%
>2 (*n* = 6)	100%	0

Relative risk for postdonation DM associated with predonation FPG of 100 mg/dL or greater, basal insulin of 9 μU/mL or greater, OGTT 2h of 120 mg/dL or greater, and postdonation ΔBMI greater than 15%, ranged between 4.6 and 6 with high specificity (0.82–1), but low sensitivity. Using these RFs, RSM was created to assist in predicting the risk for development of postdonation DM among potential donors as well as for predonation counseling on postdonation risk modification (Table 4). Risk stratification model showed that presence of 2 or greater RFs associated with 100% rate of becoming diabetic postdonation; at the same time, none of the donors with "0" RFs became diabetic.

Korea

There was no postoperative surgical complication like leakage and bleeding in donors. Five donors (23.8%) developed postoperative diabetes. All of them control blood glucose levels by taking oral hypoglycemic agent, without insulin. Average value of HbA1c checked prior to surgery was 5.4%. An average value of HbA1c measured 5 years after surgery was 6.6%.

Japan

As shown in the outcome, three donors (11.1%) developed minor leakage of pancreatic juice from the cut surface of residual pancreas. One patient developed pancreatic pseudocyst at 6 months after surgery. Although all donors maintained both pancreatic and renal function at 1 year after operation, two patients (7.4%) developed diabetes at 7 and 11 years after operation. Both patients showed over 15% weight gain after operation and the serum C-peptide levels were positive (0.8 and 0.6 ng/mL). It was considered that obesity induced type 2 diabetes. Both patients obtained normal levels of blood glucose using antidiabetic agents. They did not need to use insulin. No patients developed renal failure.

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The Effect of Pancreas Transplant on the Diabetic Complication

Takashi Kenmochi and Duck-Jong Han

General

As with kidney donors, most pancreas donors stand by their decision to donate. In a retrospective study, pancreas donors were asked if they believed they had made the correct decision by donating: 43 of 46 said yes. A subgroup of 16 SPK donors were asked if they had experienced social, marital, financial, or employment problems associated with donating: 2 of 16 donors reported social problems (1 irritability, 1 depression); 2, marital problems (decreased libido); and 1, financial problems (difficulty paying for medication). Of the 16 SPK donors, 2 had health problems associated with donating: 1 reported weight loss and low energy level, and 1 had a gastric ulcer. None of the donors reported employment problems [1].

In a small quality of life study involving 14 SPK recipients at the University of Minnesota, all 14 felt their general health posttransplant (vs pretransplant) was improved. When asked if they would elect another transplant if they lost graft function, 13 of the 14 recipients said yes [1].

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All the patients who received living donor pancreas transplanted and followed in clinic in 16 out of 21 patients, felt that their quality of life improved after surgery. But diabetic-related complications namely diabetic neuropathy, and diabetic nephropathy in PTA tend to progress after transplantation. At the time of transplantation, diabetic retinopathy was already occurred 15 out of 21 recipients (71.4%). Even though there was not a newly development of neuropathy after pancreas transplantation, in recipient who already had peripheral sensory or motor nerve damage from diabetes at the time of transplantation, transplant could not help to prevent or reverse the progression of nerve damage.

Japan

Among 26 LDPT recipients except for one patient who died of cerebral infarction 1 year after transplantation, 22 patients (84.6%) returned to society within 1 year after discharge. Other four patients were also rehabilitated within 3 years after discharge. According to our previous report which evaluates a quality of life of living donor SPK using short-form 36 version 2 (SF36v2:MOS 36-Item Short-Form Health Survey), quality of life was poor before transplantation [2]. In SF-36, physical component

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summary score (PCS) was 12.9 and mental component summary score (MCS) was 34.3, which was extremely lower than the standard level of Japanese people; 50. At 2 years after transplantation, PCS and MCS significantly increased to 52.9 and 57.3, which exceeded the Japanese standard level. While, the donors maintained both PCS and MCS during 2 years after operation.

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Part III

Immunology: ABO Incompatibility

Duck-Jong Han,
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Introduction

In organ transplantation, ABO incompatibility has been a barrier for successful living donor transplantation [1–3].

Currently, preoperative desensitization with plasmapheresis and rituximab pave the way for acceptable graft survival similar to ABO compatible transplantation, especially in kidney and liver transplantation.

In pancreas transplantation, ABO incompatible living donor transplantation is rarely performed due to the scarce source of live donor in this program and resulting in poor activity.

Kidney transplantation (KT) is the best renal replacement therapy in patients with end-stage renal diseases [4]. Advances in immunosuppressants and desensitization have enabled kidney transplantation across immunologic barriers such as blood group A/B or human leukocyte antigen (HLA) incompatibilities. Transplantation from an HLA-incompatible (HLAi) donor has been reported to have survival benefits compared with receiving a KT from a deceased donor or waiting on the transplant list [5, 6]. ABO-incompatible (ABOi) or HLAi KT recipients carry distinct immunologic risks that have significant impacts on the postoperative course and graft outcomes. Currently, ABOi KT was shown to have comparable outcomes to ABO-compatible (ABOc) KTs, but some larger studies suggested that ABOi KT is associated with early incidences of graft failure or higher posttransplant mortality [7, 8]. Studies comparing HLAi KT and HLA-compatible (HLAc) KT continue to show conflicting results, especially in cases with high mean fluorescence intensity (MFI) levels of donor-specific antibodies (DSA) in terms of long-

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term outcomes [9–11]. In addition, recipients receiving ABOi or HLAi KT need potent immunosuppression, including desensitization treatments and are thus at a higher risk of infection following KT [12, 13].

Previously, we reported the outcomes of ABOi and HLAi KT including positive flow-cytometric (FC) crossmatch (XM) and complement-dependent cytotoxicity (CDC) XM KT, and suggested that DSA is a predominant predictor of acute rejection [7, 14]. Importantly, whether the combination of ABO and HLA incompatibilities has an additional effect on clinical outcomes compared with either ABO or HLA incompatibility has not been thoroughly investigated. In a nationwide cohort study reported the results of ABOi and HLAi KT, we evaluated the clinical outcomes of KT stratified by ABO and HLA incompatibilities and identified the factors affecting clinical outcomes of ABOi and HLAi KT for the support of ABOi pancreas transplantation in a clinical setting [15].

Following the experience of ABO incompatible kidney transplantation, this program can be applicable in diabetic patients in whom living donor is available especially in HLA identical situation or sensitized condition.

Here we report the ABO incompatible pancreas transplantation experienced in Asian countries especially in Japan and Korea.

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History of ABO Incompatible Pancreas Transplantation

Duck-Jong Han and Takashi Kenmochi

General

ABO-incompatible transplants are rare but have been successfully performed in liver [1–3], heart [4], kidney [5, 6], and pancreas [7] transplants. ABO-incompatible transplants are usually performed only in life-threatening emergencies or in the presence of special immunologic conditions. One such condition is a transplant from blood group A2 donors to blood group 0 recipients. Its feasibility is based on the low expression of A2 (vs Al) determinants. Favorable outcome of A2 organs transplanted into 0 recipients had already been reported in the early 1980s [8, 9]. The recipient's IgM anti-A2 titer appeared to be a key factor: Transplants with titers <1:64 usually succeeded, whereas titers ≥1:64 tended to fail. To avoid hyperacute rejection, prospective ABO-incompatible recipients require additional treatment: elimination of ABO isoagglutinins by plasmapheresis or immunoadsorption with or without concurrent recipient splenectomy [10, 11]. Removal of antiblood group IgM isoagglutinins prevents the development of hyperacute rejection early posttransplant; the return of those isoagglutinins after several weeks posttransplant appears to have no effect on graft function.

The largest single-center experience with ABO-incompatible kidney transplants has been done in Japan, where, despite great efforts to promote cadaver transplants, about 98% of all transplants were transplanted from living related donors. Japan's extreme shortage of cadaveric organs, coupled with the frustration of having to turn away even HLA-identical living donors because of ABO incompatibility, has almost forced transplant surgeons and physicians there to develop safe, successful strategies for ABO-incompatible transplants.

Treatment modalities to avoid hyperacute rejection after ABO-incompatible transplants have evolved over time. In 1981, it was shown for the first time that plasmapheresis effectively controls hyperacute rejection [12], in 1987, it was shown that immunoadsorption has a similar effect [13]. Plasmapheresis and IV Ig can also be used, in combination, until isoagglutinin titers are <1:16. One controversial issue is whether ABO-incompatible recipients should undergo splenectomy at the time of the transplant, as initially recommended by Alexandre et al. [14]. Other investigators have suggested that when the anti-AB IgG titer is <1:16 in particular with the A2 (lower expression of antigen than A1) or B subgroups, ABO-incompatible kidney transplants can safely and successfully be performed without splenectomy or plasmapheresis. The

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potential spectrum of complications with minor incompatibility between blood groups in a pancreas recipient was first reported by Sindhi et al. [15]. They presented a case of severe hemolysis and graft ischemia after a 37-year-old blood group A2 female received a 3-HLA-antigen-matched pancreas graft from a blood group Al male donor. The donor was rhesus negative and the recipient rhesus positive. On posttransplant day 9, the recipient developed severe fatigue, dizziness, anemia, and hypotension. Extravascular hemolysis was the cause of acute anemia. No IV Ig or antithymocyte globulin was administered. This report demonstrated that hemolysis, as a manifestation of graft-vs-host disease (GVHD), can occur with pancreas transplants with minor blood group incompatibility.

Sindhi et al. recommended that if the donor had a history of pregnancy or blood transfusion, at least his or her rhesus-negative plasma should be screened for preformed irregular antibodies. If antibodies were to be detected, the donor organs could then be triaged to an antigen-negative recipient. This strategy will not prevent hemolysis due to antibodies in rhesus-positive donors, yet it could have prevented 80% of reported hemolytic episodes due to irregular donor antibodies. In the University of Minnesota series, three patients received ABO-incompatible pancreas grafts. In two living donor recipients, preemptive protocols were used and the third recipient (accidentally) received an ABO-incompatible cadaver graft.

Korea

Since the first ABO incompatible kidney transplantation in Korea in 2007 [16] under the desensitization protocol with rituximab (initial 500 mg then 200 mg), plasmapheresis and IVIg, and without splenectomy. Immunosuppressants were induced with IL-2 receptor blocker (basiliximab) and early use of tacrolimus, MMF, and steroid. Preoperative anti-ABO antibody monitoring was performed with IgM and IgG (indirect Coomb' test). By the accumulated experience with favorable graft survival in ABO incompatible KT which is comparable with ABO compatible cases, 20–25% of living KT are ABO incompatibility these days (Fig. 1). To evaluate the clinical outcomes of ABOi KT, a total of 263 patients with ABO incompatible and HLA-positive crossmatch were analyzed in Asan Medical Center(AMC).

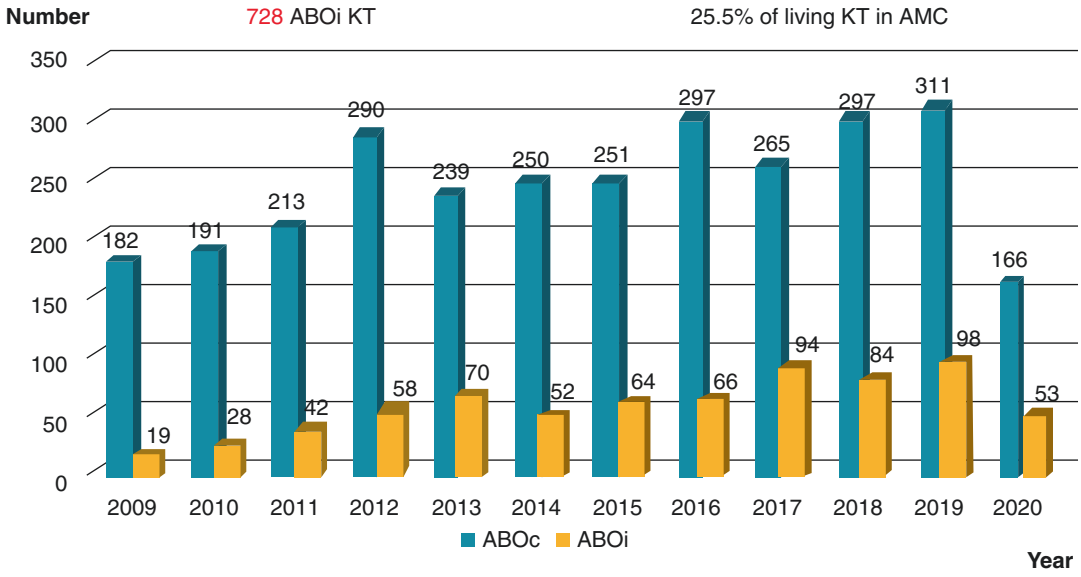

Fig. 1 ABO incompatible KT in AMC, Korea

These results were comparable with ABO compatible donors, especially under modified desensitization and immunosuppressant [17].

> From these experiences, we performed ABO incompatible (A to B) SPK in 40-year-old Russian female patient who underwent simultaneous kidney and pancreas transplant from her father in April 2012 in AMC. Another case of 38-year-old male ABO incompatible (A to O) pancreas transplant patient was performed in other hospitals with a total number of two cases in Korea.

Japan

Since ABO blood groups were discovered by Karl Landsteiner in 1901 [18], ABO-incompatible (ABOi) kidney transplantation (KT) had been considered to be contraindication for many years. Alexandre et al. were the first to design a transplant procedure using plasma exchange for pretransplant removal of anti-A/anti-B antibodies. They also strongly emphasized the importance of splenectomy in achieving long-term graft survival [19, 20].

In Japan, since the number of deceased donors is extremely low because of social circumstances, a frequency of living donor kidney transplantation (LDKT) exceeds 90% of kidney transplantation. Since the first successful ABOi KT with use of double filtration plasmapheresis (DFPP) combined with immunoadsorption for pretransplant removal of antibodies and splenectomy at the time of transplantation was introduced in 1989 [21–24], ABOi KT has increased year after year and ABOi KT occupied over 30% recently (Fig. 2). 6246 ABOi KTs were performed from 1989 to 2019, which was 20.0% of 31,231 LDKTs in Japan. In the first decade from 1989 to 2001, 441 ABOi KTs were performed in Japan. Immunosuppressive therapy was achieved by (1) extracorporeal immunomodulation to remove serum anti-A, anti-B antibodies before transplantation, (2) pharmacotherapy (pharmacological immunosuppression), (3) splenectomy, and (4) anticoagulation therapy. Initially, immunoadsorption with Biosynsorb® (Unicom Corporation, Tokyo, Japan) was carried out in 51 of 441 patients [25, 26]. However production of

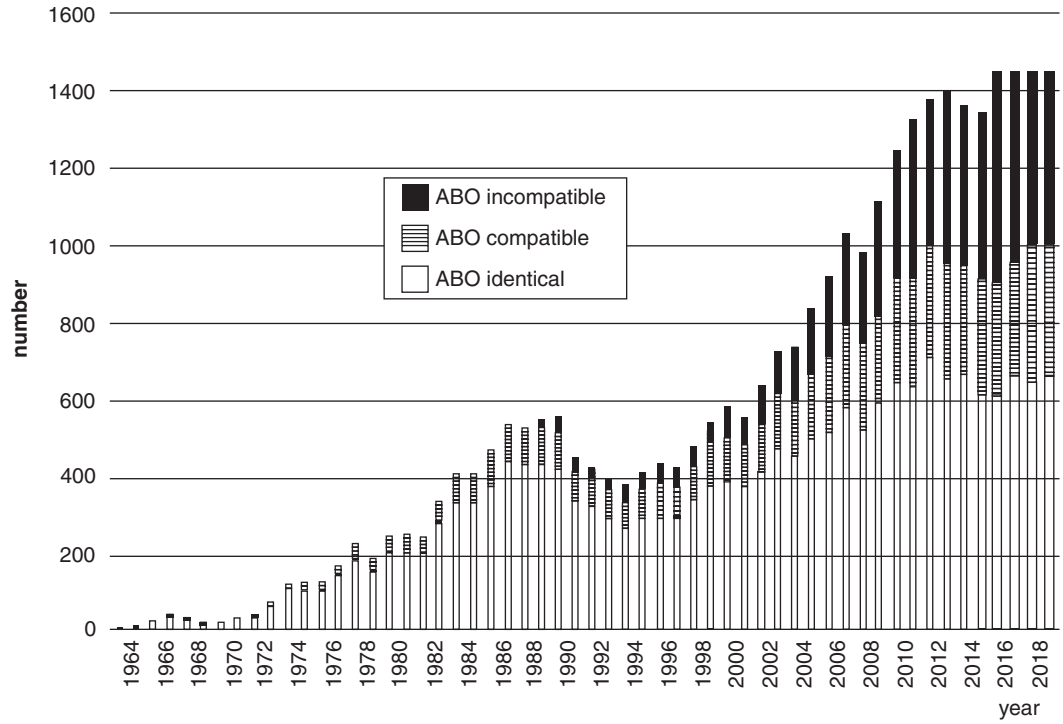

Fig. 2 ABO incompatible KT in Japan

Biosynsorb® was discontinued, only plasmapheresis was used to remove antibodies before transplantation. Splenectomy, one of the major organs producing anti-A, anti-B antibodies was performed in 433 (98%) of 441 patients. The eight patients who did not undergo splenectomy were children in whom the operation was considered unfeasible or patients who were B-incompatible with a low antibody titer. Because AMR after transplantation is considered local (intrarenal) disseminated intravascular coagulation (DIC), anticoagulation therapy was prophylactically administered at 60% of the transplant centers [26, 27]. After transplantation, 223 patients (51%) received anticoagulation therapy. The patients given anticoagulation therapy received a target dose of 250–300 mg/day of nafamostat mesilate (FUT), a short-acting anticoagulant, by 24-h continuous infusion for 3–7 days after transplantation. After the patients' general condition had stabilized, an oral platelet aggregation inhibitor (ticlopidine or aspirin) was given continuously as long as the graft remained viable. Overall patient survival rates at 1, 3, 5, 7, and 9 years after ABOi KT were 93%, 89%, 87%, 85%, and 84%, respectively. Corresponding overall graft survival rates were 84%, 80%, 71%, 65%, and 59%. After ABOi KT, graft survival rates were significantly higher at young age (<30) and in patients who received anticoagulation therapy. There were no significant differences between A-incompatible and B-incompatible recipients with respect to clinical outcomes. Long-term outcome in recipients of ABOi KT was excellent. Thereafter the use of rituximab and MMF became available in Japan, and multicenter prospective clinical study was performed [28]. Patient and graft survivals were both 100% after 1 year and no severe adverse effect by this protocol was observed.

Based on the successful results of ABOi KT, we have introduced the first ABOi living donor pancreas transplantation (ABO-i LDPT) in January 2006. Six ABO-i LDPTs have been, so far, performed in our country, and all of them were performed in Chiba-East National Hospital from 2006 to 2010 by our transplant team.

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Indication of Pancreas Transplantation (Donor and Recipient)

Takashi Kenmochi and Duck-Jong Han

Donor

See the Living Donor chapter.

Recipient

General

See the Living Donor chapter.

Korea

The indication of ABO incompatible living donor pancreas transplantation is the same as the ABO compatible living donor pancreas transplantation (See the Living Donor chapter). However, when IgG titer below 1:64 or IgM titer below 1:8 cannot be achieved especially in blood O-type recipient following desensitization, operation was held regardless of initial anti-ABO titer.

Japan

Indication for the recipient of ABOi LDPT is the same as ABO compatible LDPT as shown in Chapter 10. However, we indicated ABOi LDPT only for SPK category because the biopsy of the transplanted kidney was essential for monitoring antibody-mediated rejection (AMR) due to ABO incompatibility. In addition, the recipient whose anti-A or -B antibodies was extremely high, which showed over 512-folds, was considered to be a relative contraindication because of the possibility of high risk of AMR. Also, the crossmatch both of T cell and B cell with flow cytometry, in addition, to direct crossmatch should be negative in the recipient.

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Preoperative Evaluation

Takashi Kenmochi and Duck-Jong Han

Donor

See the Living Donor chapter.

Recipient

General

See the Living Donor chapter.

Korea

Most of the preoperative recipient evaluation is illustrated in Chapter 11.

For the measurement of anti-AB blood type antibody isoagglutinin titer, the standard tube method was used to determine ABO isoagglutinin titers [1]. The isoagglutinin titer was measured before the initial plasmapheresis and identified before each plasmapheresis and after the last plasmapheresis.

Isoagglutinin titration was performed with the use of standardized techniques as outlined in the literature [2]. The immediate spin (IS) tube method at the room temperature (RT) phase was used for the titration of IgM isoagglutinins. Serial twofold dilutions of patient serum were prepared using 0.1 mL of saline, and 0.1 mL of commercialized 3% A1 or B cell suspension (Affirmagen, Ortho-Clinical Diagnostics) was added and mixed thoroughly. After centrifugation (1000 × *g*, 15 s), the titer was determined as the reciprocal of the highest dilution level showing trace reactivity. IgG isoagglutinin titer was measured using the anti-human globulin (AHG) phase. After completing the IS tube test, samples were incubated at 37 °C for 30 min, washed three times with saline, and 0.1 mL of polyspecific AHG (Bioscot anti-C3d/IgG, Millipore) was added to each tube. After centrifugation, test results were interpreted as with the IS method. The IgM isoagglutinin titers were measured every day from the initiation of pre-kidney transplant (KT) total plasma exchange (TPE) until discharge. The IgG isoagglutinin titers were tested (1) before the initiation of pre-KT TPE to measure the initial baseline level, (2) after the last session of pre-KT TPE on the day of KT, and (3) after KT at 2 weeks, 1 month, and subsequent follow-up visits. For group O patients whose donors were group AB, isoagglutinin titers for both anti-A and anti-B were measured, and the higher value was used for data analysis.

The rationale for checking the IgM in ABOi kidney transplantation was from our previous study [1] in which 120 patients who underwent

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ABO-i KT between 2012 and 2014 were analyzed retrospectively. Preoperative plasma exchange was performed until the IgM isoagglutinin titer was 4 or less, regardless of the IgG titer. Clinical data were compared between patients with pre-KT IgG isoagglutinin titer 16 or greater (high IgG; titer range, 16–256; $n = 39$) and 8 or less (low IgG; titer range, −8; $n = 81$) (Fig. 1, Table 1). The median follow-up periods were 59 (high IgG) and 55 (low IgG) months. Patient survival at 5 years ($p = 0.314$) was 100% (high IgG) and 97.4% (low IgG). Graft survival at 5 years ($p = 0.480$) was 100% (high IgG) and 98.7% (low IgG). AMR by anti-ABO antibody occurred in only one patient in the low-IgG group. Patients with high pre-KT IgG isoagglutinin titers had equally successful outcomes as those with low IgG titers. Therefore ABO-i KT can be successfully performed by reducing the pre-KT IgM isoagglutinin titer to 4 or less, as determined by the immediate spin tube method.

However, we experienced hyperacute type of rejection at immediate posttransplant period in blood type O recipient who underwent transplant from his son as a donor of A type, in whom the initial titer was 1:16 (IgM), and pre KT titer was 1:4 (IgM) and 1:128 (IgG). After then we added the IgG isoagglutinin titration in recipient of blood type O.

Two cases of ABO incompatible LD SPK were undertaken in two centers each. In addition to preoperative evaluation, blood group antibody was screened. One ABO incompatible LD SPK recipient was the daughter of blood type B and the donor was father of blood type was A. The isoagglutinin titer of anti-A antibody fell from 1:256 of preconditioning to 1:2 just prior to transplantation. The other ABO incompatible LD SPK recipient was blood type O and that donor was A. Initial isoagglutinin titer of anti A antibody was 1:16 and after preconditioning, it fell to 1:4.

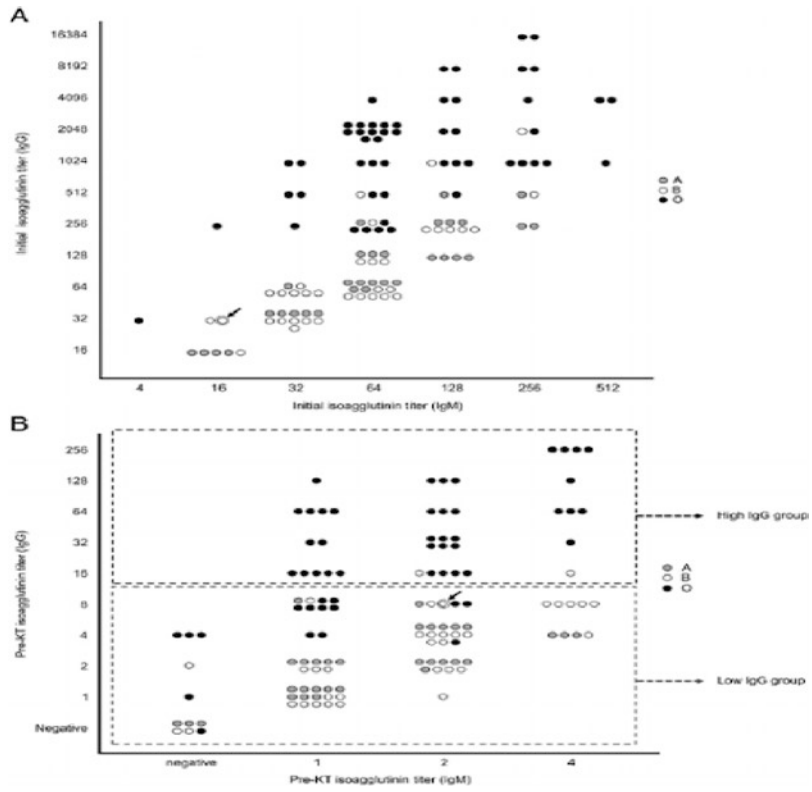

Fig. 1 Distribution of initial (**a**) and final pre-KT (**b**) isoagglutinin titer of the ABOi patients

Table 1 Univariate logistic regression analysis results for the relationship of isoagglutinin titers and AMR (by de novo anti-HLA antibody), TCMR, and BK virus infection

	AMR (by de novo anti-HLA)			TCMR			BK virus infection		
Variable	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Pre-KT IgG group (titer ≥16 or ≤8)	0.493	0.100–2.441	0.386	0.547	0.167–1.787	0.318	0.552	0.213–1.426	0.220
Initial baseline IgM titer (log_2)	0.823	0.485–1.397	0.471	0.700	0.459–1.069	0.099	1.062	0.756–1.491	0.730
Initial baseline IgG titer (log_2)	0.845	0.640–1.116	0.235	0.830	0.668–1.030	0.091	0.927	0.785–1.095	0.373
Final pre-KT IgM titer (log_2)	1.159	0.545–2.466	0.701	1.762	0.955–3.254	0.070	0.570	0.342–0.949	0.031
Final pre-KT IgG titer (log_2)	0.956	0.720–1.271	0.759	1.001	0.807–1.242	0.991	0.858	0.709–1.039	0.117

AMR antibody-mediated rejection, *CI* confidence interval, *HLA* human leukocyte antigen, *KT* kidney transplantation, *TCMR* T-cell–mediated rejection

Japan

In addition to the standard evaluation for LDPT recipients (See Chapter 11), ABO blood type (A subtype; A1 or A2), DNA typing of HLA both of the donor and of the recipient were studied. Direct crossmatch and flowcytometry crossmatch were performed. Also, Luminex assay for the screening of donor-specific antibody was performed. The titers of anti-A or anti-B antibodies (IgM, IgG) were measured and the recipient whose titers of both IgM and IgG exceeded 512 folds were not eligible for ABOi LDPT. To measure antibody titer, the indirect Coombs' test was used for IgG and the saline method for IgM [2]. In ABOi LDPT, the negative studies of T-cell and B-cell crossmatch as well as flow cytometry were required.

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Surgical Aspect of Pancreas Transplantation

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The Donor

See the Living Donor chapter.

Recipient

See the Living Donor chapter.

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Peri- and Postoperative Management

Takashi Kenmochi, Duck-Jong Han, and Joo Hee Jung

Perioperative Management: Desensitization Protocol and Immunosuppression

Recipient

General

Most of the perioperative management is the same as that in living donor pancreas transplantation in the Living Donor chapter.

In the University of Minnesota series [1], as a desensitization protocol, they have done pretransplant plasmapheresis reducing anti-ABO antibody titer of IgM and IgG, and immunosuppressant of induction with thymoglobulin for 5 days and five doses of zenapax (Roch pharmaceutical Com), and maintenance with Prograf, CellCept, and steroid. Anticoagulation with heparin was initiated immediately posttransplant.

Korea

In our initial desensitization protocol in ABOi KT (era 1), patients received a single dose of anti-CD20 monoclonal antibody (rituximab; Genentech, Inc., South San Francisco, CA, USA) (500 mg) 1 week before plasmapheresis.

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For ABOi recipients, we administered a single dose of rituximab (100–200 mg) 7 days before the start of plasmapheresis. Total plasma exchange (PP) was performed until the preoperative Ig M isoagglutinin titer against blood group A or B was reduced to ≤1:4, and postoperative PP was performed when the rebound isoagglutinin titer was ≥1:16 (COBE® Spectra; Gambro BCT, Lakewood, CO, USA) [2]. In blood type O, titer of IgG is checked as well as IgM. The IgG titer is recommended below 1:32 as the pre-op value for operability.

HLA incompatible patients were treated with 200 mg of rituximab 1–2 weeks before PP. PP was maintained until the CDC crossmatch (XM) and T-cell FCXM became negative. Splenectomy or intravenous immunoglobulin injection was not performed.

Numbers of plasmapheresis and additional treatment, such as intravenous immune globulin or bortezomib, were dependent on the follow-up results of ABO Ab titers and FCXM results during desensitization treatment. Postoperative plasmapheresis was performed when the rebound isoagglutinin titer was ≥1:32. The titer reduction rate is the average titer reduction per one plasmapheresis session and was calculated using the following equation: titer reduction rate = (isoagglutinin titer before the initiation of plasmapheresis − last isoagglutinin titer before transplantation)/number of preoperative plasmapheresis [3].

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Two cases of ABO-incompatible LDSPK were undertaken in two centers each. One ABO-incompatible LDSPK was performed in 40-year-old female IDDM patient in AMC. The recipient, daughter, blood type was B and the donor, father, blood type was A. As a preconditioning regimen, the recipient received a single dose of rituximab (200 mg) 1 week before plasmapheresis; plasmapheresis was performed four times. After preconditioning, the isoagglutinin titer of anti-A antibodies fell from 1:256 to 1:2. The other ABO-incompatible LD SPK was performed in a 38-year-old male IDDM patient in Koryo University Hospital. The blood type of the recipient was O and that of the donor (spouse) was A. For preconditioning, the recipient received a single dose of rituximab (500 mg) 1 week before plasmapheresis. Plasmapheresis was performed totally two times before the transplant. The initial isoagglutinin titer of anti-A antibody was 1:16, and after preconditioning, it fell to 1:4.

After segmental pancreas transplantation, from a living-related donor, initial systemic heparinization followed by coumadin therapy (for up to 6 months) is recommended.

For induction in kidney transplantation, 20 mg anti-IL-2 receptor antibody (basiliximab) was administered on day 0 and again on day 4. The maintenance immunosuppression regimen consisted of a calcineurin inhibitor (tacrolimus, cyclosporin), a corticosteroid, and mycophenolic acid. We maintained the tacrolimus trough level at 8–10 ng/mL and administered 1.5 g/day of mycophenolate mofetil (MMF) during the first 3 months. After we experienced lethal infectious complications, a modified immunosuppression protocol was applied from January 2012 (era 2). We reduced the dose of rituximab from 500 to 200 mg in ABOi patients unless patients showed positive FCXM. Tacrolimus was given at an initial level of 8 ng/mL and reduced to 3–8 ng/mL 1 week after transplantation. Then gradually decreased to 3–6 ng/mL after 1 year. The dose of MMF was reduced from 1.5 to 1 g/day after the seventh postoperative day.

We selectively used cyclosporine as a first-line CNI for patients 55 years old or older. The target trough concentrations of cyclosporine ranged from 100 to 150 μg/L, which was reduced to 70–100 μg/L.

Those patients were also given acyclovir for CMV prophylaxis. To prevent cytomegalovirus (CMV) and human polyomavirus BK (BKV) infection, we performed preemptive therapy with monitoring the presence of viremia using polymerase chain reaction (PCR) from the patients' blood sample. PCR was performed at 1, 2 weeks, 1, 3, 6 months, and 1 year after transplantation. Additional PCR for CMV or BKV was performed if viremia was detected or clinically indicated. All patients received trimethoprim/sulfamethoxazole (80/400 mg) daily for 6 months as a prophylaxis for Pneumocystis jirovecii pneumonia (PCP).

In our ABO-incompatible pancreas transplant patients desensitization with rituximab (200 mg) and plasmapheresis were performed like ABO-incompatible kidney transplantation. As an immunosuppressant, thymoglobulin induction (>4 mg/kg), and maintenance immunosuppressants with tacrolimus with trough level of 10 ng/L, mycophenolate mofetil (MMF), and steroids were used.

As prophylaxis, sulfamethoxazole-trimethoprim is medicated for 1 year and perioperative antibiotic with unacin for 5 days and antiviral agent with acyclovir (400 mg BID) for 1 month.

Japan

Desensitization for the patients from ABO-incompatible donors was achieved according to our protocol for an ABO-incompatible kidney transplantation. Mycophenolate mofetil (MMF) was administrated for 4 weeks before transplantation. Out of 437 patients who underwent pancreas transplantation for 20 years from 2000 to 2019, 27 patients underwent LDPTs including 7 ABO-incompatible cases. Splenectomy was done 14 days before transplantation, followed by double filtrated plasmapheresis (DFPP) at 6, 4, 2 days before transplantation and plasma exchange (PEX) at 1 day before transplantation. 200 mg of cyclophosphamide hydrate was administrated daily during 20 days after transplantation in addition to tacrolimus, MMF, methylprednisolone,

and basiliximab. For the second and third cases, we did not use cyclophosphamide hydrate and MMF was administrated for 28 days before transplantation, and tacrolimus and methylprednisolone were given for 10 days before transplantation. The schedule of splenectomy, DFPP, and PEX was the same as in the first case. From the fourth case, rituximab was introduced at a dose of 200 mg 14 days before transplantation in place of splenectomy. The anti-A and anti-B antibody titers were measured before desensitization by splenectomy or an administration of rituximab, and every day for 7 days before transplantation. 32 folds or less both IgM and IgG in the antibody titers were required to perform transplantation. Immunosuppression was achieved using the same protocol.

Donor

See the Living Donor chapter.

Postoperative Management and Follow Up

Recipient

General

Most of the post-operative management is the same as the Living Donor chapter.

Currently, triple-drug immunosuppression (now with Tacrolimus and MMF) has remained the gold standard for maintenance therapy in pancreas transplantation. In the late 1990s, in selected pancreas recipient categories, triple immunosuppression for maintenance therapy was sometimes abandoned by steroid withdrawal or avoidance. The principles of maintenance therapy for pancreas recipients are the same as for other solid organ recipients. But, because of the high immunogenicity of (especially solitary) pancreas transplants, the amount of immunosuppression required is more than for kidney, liver, or heart transplants.

Korea

Most of the postoperative management and follow-up are illustrated in Chapter 13.

In ABO-incompatible kidney or pancreas transplantation, antibody screening is crucial until postoperative 1 week. If the anti-ABO antibody titer is increasing more than 1:16, postoperative plasmapheresis is recommended. After 1 week after operation significance of changing titer, value is less in terms of clinical management.

Due to strong immunosuppressants in ABO-incompatible transplantation, post-operative prophylactic antibiotic by sulfamethoxazole-trimethoprim is used for 12 months instead of 6 months in ABO-compatible transplantation. Anticandidial prophylaxis with fluconazole is recommended for 2 weeks immediately after operative period.

In pancreas transplantation, anti-ABO antibody titer measuring for 2 weeks is the same as kidney transplantation. Maintenance immunosuppressants are tacrolimus with a trough level of 10 ng/L in early postoperative period and then 7 ng/L, mycophenolate mofetil (MMF), and steroids. In SPK, early steroid withdrawal is tried within 1 week. Antibiotic with unacin for 5 days and sulfamethoxazole-trimethoprim is recommended for 1 year. CMV and BK are monitored for 1 year postoperative period by PCR method. If CMV DNA titer is more than 4 log, valganciclovir treatment is recommended for 2 weeks at least. If BK PCR became positive, a decrease of MMF dosage or leflunomide replacement is recommended.

Japan

In addition to the general care and graft function evaluation which was the same as those in ABO-compatible LDPT (See chapter 17.C), we should be careful of the development of venous thrombus and antibody-mediated rejection (AMR) because vascular thrombus related to AMR was observed in ABOi KT. Besides a Doppler US, contrast-enhanced ultrasonography (CEUS) was performed every day for 7 days after transplanta-

tion. When the thrombus was detected in the splenic vein of the pancreatic graft, the dosage of heparin was increased, and observed the size of the thrombus. In case of size-up of the thrombus or the formation near the anastomosis, a thrombectomy should be performed by interventional radiology or open surgery. For the monitoring of AMR, the antibody titers were measured once a day for 10 days after transplantation. The diagnosis of AMR was achieved by the needle biopsy of the kidney graft. As the rejection therapy for AMR, PEX, IV-IG, rituximab in addition to a steroid pulse therapy were used. Hemodialysis was indicated to the patient who showed oligouria and anuria due to kidney graft rejection.

Prophylactic agents are essential because postoperative infection was considered to be more frequent in ABOi KT as compared to ABO-compatible KT. Penicillin or cephem antibiotics were intravenously given for 7 days after transplantation as bacterial prophylaxis. Antifungal agent, fluconazole, was also given for 1 week after transplantation. Sulfamethoxazole-trimethoprim was administered for 1 year to prevent Pneumocystis pneumonia (PCP) infection. CMV was monitored with antigenemia or PCR assay twice a week for 1 month, once a week for the next 2 months, and once a month after 3 months after transplantation. For all ABOi LDPT patients, CMV prophylaxis (ganciclovir or valganciclovir) was administered for 6 months.

Donor

See the Living Donor chapter.

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Outcome

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General

In the University of Minnesota series, three patients received ABO-incompatible pancreas grafts. In two living donor recipients, preemptive protocols were used; the third recipient (accidentally) received an ABO-incompatible cadaver graft. In the first case, a blood group B white female received a pancreas and kidney from a living unrelated blood group A2B female friend. Pretransplant recipient's anti-A2 IgM titer was 1:64 and IgG 1:32. The recipient underwent pretransplant plasmapheresis, reducing her IgM and IgG titers to 1:4. During the first posttransplant week, the recipient underwent plasmapheresis on a daily basis to maintain low anti-A2 IgM and IgG titers. Posttransplant, induction immunosuppression consisted of a 5-day course of Thymoglobulin (SangStat Corp, Fremont, CA) and five doses of Zenapax (Roche Pharmaceuticals, Nutley, NJ); maintenance immunosuppression was with tacrolimus, mycophenolate mofetil, and prednisone. Anticoagulation was initiated immediately posttransplant with heparin, then coumadin (DuPont Pharma, Wilmington, DE) for 6 months. The recipient was successfully treated for biopsy-proven rejection at 4 months posttransplant. At 3.5 years posttransplant, she had excellent kidney and pancreas graft function. In the second case, a 37-year-old blood group 0 white male received a pancreas and kidney from his blood group A2 33-year-old sister. The recipient's anti-A2 IgM titer was 1:32 and IgG 1:128. The immediate pretransplant titers were 1:8. Posttransplant, plasmapheresis was continued for 6 days, at which time the recipient's anti-A2 IgM titer was 1:8 and IgG 1:16. Posttransplant, IV Ig and plasmapheresis were discontinued on the same day. Induction therapy included a 7-day course of Thymoglobulin and five doses of Zenapax. Anticoagulation was initiated immediately posttransplant with heparin, then Coumadin for 6 months. The recipient was successfully treated for kidney rejection at 2 and 6 months posttransplant. However, he subsequently developed chronic kidney rejection while maintaining good pancreas graft function 2 years posttransplant. In the third case, a 25-year-old blood group 0 male PAK recipient received a blood group A2 cadaver donor graft. By accident, the donor's blood group was initially reported as O. The error was noted after dissection in the recipient was completed but before the graft was implanted. Given the good match and the good quality of the graft,

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the family decided to proceed with the transplant; they were first informed of the potential risk of humoral rejection. Posttransplant, the recipient underwent plasmapheresis and IV Ig transfusion for 10 days to achieve anti-A2 IgM titers of 1:8. At 7 months posttransplant, he has excellent pancreas graft function and his serum creatinine level is within normal range. These three cases illustrate that ABO-incompatible transplants can be safely performed in selected pancreas recipients. Humoral rejection can be avoided with plasmapheresis and IV Ig if the antibody levels pre- and early posttransplant are low.

Korea-KT

Between February 2009 and July 2013, we performed 182 ABO-incompatible kidney transplantation in AMC (Fig. 1) [1]. We analyzed the first 85 patients for postoperative infectious complications in a cross-sectional cohort of patients (group 1, n = 85) who had received an ABO-incompatible kidney transplant under the initial desensitization protocol (Fig. 2) and, in light of the results, amended the pre-conditioning regimen (lower dose of rituximab, selective use of calcineurin inhibitors, anti-metabolite reduction, and prophylactic strategy) given to a prospective cohort (group 2, n = 97). The characteristics of the two groups did not differ significantly. Infectious complications decreased significantly in group 2, including cytomegalovirus (antigenemia 64.7% vs 27.8%, $P < .001$) and BK viremia (35.2% vs 18.6%, $P = .008$). The acute rejection rate and death-censored graft survival were similar in both groups. Notably, with the modified protocol, there were no deaths (8.2% vs 0.0%, $P = .03$) (Fig. 3, Tables 1, 2, and 3).

Pre-conditioning for ABO-incompatible kidney transplantation is a prerequisite for a successful outcome. In ABO-incompatible renal transplantation, postoperative morbidity and mortality were affected by desensitization protocol. Its drawbacks can be limited with the use of a modified immunosuppressive strategy. If immunosuppression is modified according to host conditions, ABO-incompatible kidney transplantation can be performed safely with a successful graft outcome [1, 2].

In an extended study of 4000 consecutive patients who underwent KT at our institution from January 1990 to February 2015, we analyzed clinical outcomes in ABOi and flow-cytometric crossmatch (FCXM) positive KT in a subgroup analysis. This was a retrospective, observational study using data extracted from

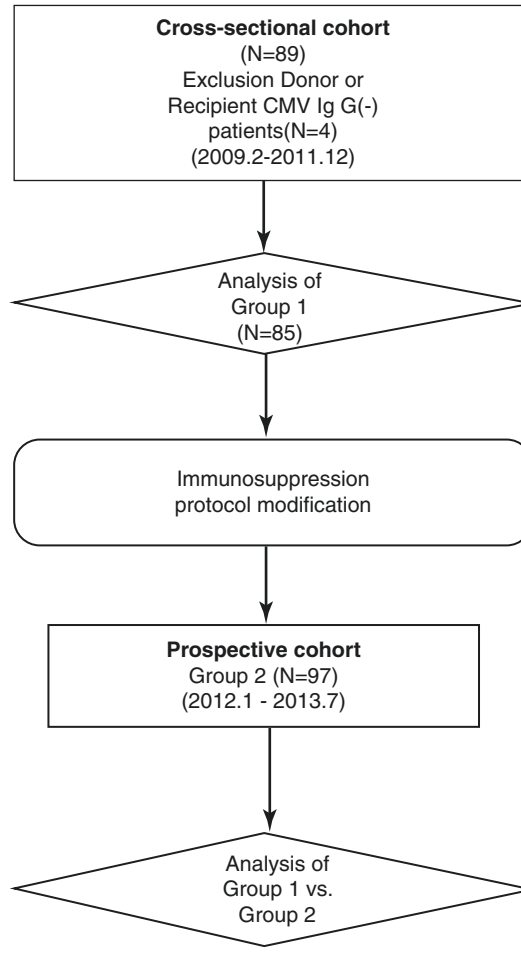


Fig. 1 Schematic flow of the study

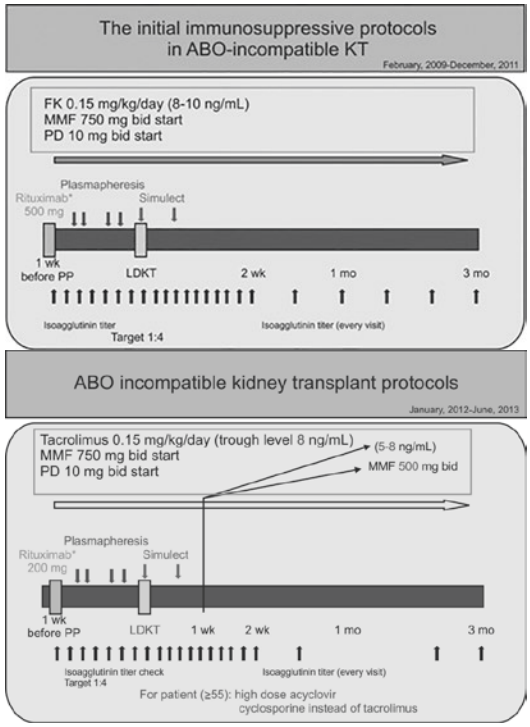


Fig. 2 Immunosuppressive protocols of ABOi KT

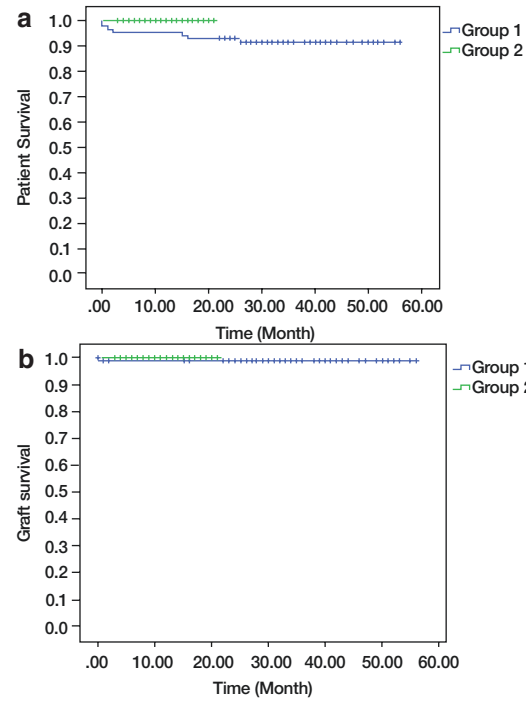


Fig. 3 (**a**) Survival curves of patients in group 1 and group 2. (**b**) Death censored graft survival curves in groups 1 and 2

medical records. Kidney transplantation across immunological barriers such as ABO-incompatible (276 cases, 6.9%), FCXM positive (97 cases, 2.4%), and positive complement-dependent cytotoxicity (CDC) XM KT (16 cases, 0.4%) were included. From a Kaplan-Meier analysis, overall patient survival (PS) rates after KT at 1, 5, 10, and 20 years were 96.9%, 95.1%, 92.0%, and 88.9%, respectively. The overall graft survival (GS) rates after KT at 1, 5, 10, and 20 years were 96.3%, 88.9%, 81.2%, and 67.4%, respectively. Our subgroup analysis suggested that overall PS, GS, death-censored GS, and rejection-free GS in ABOi KT showed no significant differences in comparison with ABO-compatible KT if adequate immunosuppressive treatment was performed. The overall PS rate in patients who underwent FCXM positive KT did not differ significantly from that of the control group during the 3-year follow-up (P = 0.34). The overall GS, death-censored GS, and rejection-free GS also did not differ significantly between the FCXM KT and control groups (P = 0.99, 0.42, and 0.88) [3] (Fig. 4).

However, in comparison with ABO-compatible 260 kidney transplantation, 79 ABOi kidney transplantation under modified desensitization protocol showed still higher post-operative morbidity than that of ABO-compatible KT [4] (Table 4, Fig. 5).

Currently, we evaluated the clinical outcomes of KT stratified by ABO and HLA incompatibilities and identified the factors associated with the clinical outcomes [5]. Recipients who underwent living-related KT between 2012 and 2017 were included and classified into four groups: ABO-compatible and HLA-compatible (ABOc/HLAc), HLA-incompatible (ABOc/HLAi), ABO-incompatible (ABOi/HLAc), and ABO-incompatible and HLA-incompatible (ABOi/HLAi). Out of the 1732 patients who underwent

Table 1 Deaths in the cross-sectional cohort patients (Group 1)

	Sex/age (years)	Rituximab dose (mg)	CNI	CMV anti-genemia	Preceding condition	Cause of death	Postoperative survival duration (days)
Case 1	M/58	200	Tacrolimus	Positive	Scedosporium infection	Infective endocarditis	457
Case 2	F/62	200	Tacrolimus	Positive	DJ removal	Urinary tract sepsis	82
Case 3	M/65	500	Tacrolimus	Negative	T-flow XM(+)	Myocardial infarction	25
Case 4	F/62	200	Tacrolimus	Positive	Fungal infection, T-flow XM(+)	Multi-organ failure	67
Case 5	F/61	200	Tacrolimus	Positive	Pneumonia	Multi-organ failure	54
Case 6	F/54	500	Tacrolimus	Positive	T-flow XM(+)	Aspergillus pneumonia	39
Case 7	M/63	200	Tacrolimus	Positive	Liver abscess, cholangitis	Myocardial infarction	814

Abbreviations: *CNI* calcineurin inhibitor, *CMV* cytomegalovirus, *DJ* double "J" stent, *T-flow XM(+)* T-flow cytometry cross-matching test positive

Table 2 Subgroup analysis of the infection-related death and survival groups in the cross-sectional cohort (Group 1)

	Survival cases (n = 80)	Mortality cases (n = 5)	P value
Median age, years ± SD	43.4 ± 11.7	59.4 ± 3.4	.003
Sex, male	48 (60.0%)	3 (60.0%)	1.00
Blood type			.45
A	19 (23.8%)	0 (0%)	
B	28 (35.0%)	2 (40%)	
O	33 (41.3%)	3 (60%)	
PRA class I or II			.004
<20%	68 (85.0%)	1 (20%)	
≥20%	12 (15.0%)	4 (80%)	
T-flow XM(+)	19 (23.8%)	2 (40%)	.59
Hepatitis (B or C)	9 (11.3%)	0 (0%)	.63
Pneumonia	8 (10.0%)	3 (60%)	.014
UTI	10 (12.5%)	2 (40%)	.12
CMV anti-genemia	50 (62.5%)	5 (100%)	.16

Abbreviations: *PRA* anti-HLA class I and II panel-reactive antibody test determined with the use of the Luminex method (cutoff value: median fluores-positive), *UTI* urinary tract infection, *CMV* cytomegalovirus

KT, the ABO/HLAi group showed the lowest 5-year graft survival rate (91.7%). Death-censored graft survival was not significantly different among the groups. The mortality rate from infections was significantly higher in the ABOi/HLAi group (7.5%) than in the other groups.

Antibody-mediated rejection-free graft survival was the lowest in the ABOi/HLAi group, with significant differences compared with the ABOi/HLAc group (P = 0.02) and the ABOc/HLAi group (P = 0.03). ABOi/HLAi (hazard ratio [HR], 2.63; 95%confidence interval [CI], 1.04–6.65; $P < 0.01$) and combined infection (HR, 1.91; 95% CI, 1.45–2.51; $P < 0.01$) were significant risk factors for acute rejection. Therefore, patients with both ABO and HLA incompatibilities showed inferior rates of overall patient and graft survival due to infectious complications. Infection was a prominent risk factor of acute rejection following KT after

Table 3 Postoperative clinical outcome of the cross-sectional cohort (Group 1) and the prospective cohort (Group 2) of ABO-incompatible kidney transplantation patients and the clinical outcome of patients in both groups after excluding T-flow cytometry-cross-matching–positive patients (sensitized patients)

	Group 1 (n = 85)	Non-sensitized Group 1 (n = 64)	Group 2 (n = 97)	Non-sensitized Group 2 (n = 86)	P value[a]	P value[b]
Lymphocele	4 (4.5%)	3 (4.7%)	4 (4.1%)	3 (3.5%)	1.00	.70
Death	7 (8.2%)	4 (6.3%)	0 (0.0%)	0 (0.0%)	.03	.03
Rejection						
ACR	6 (7.1%)	5 (7.8%)	6 (6.2%)	6 (7.0%)	1.00	1.00
AMR	0 (0%)	0 (0.0%)	3 (3.1%)	3 (3.5%)	.25	.26
UTI	12 (14.1%)	10 (15.6%)	10 (10.3%)	8 (9.3%)	.50	.31
Pneumonia	11 (12.9%)	7 (10.9%)	5 (5.2%)	5 (5.8%)	.07	.36
Herpes-related disease (Zoster, esophagitis, etc.)	12 (14.1%)	9 (14.1%)	9 (9.3%)	8 (9.3%)	.36	.44
CMV anti-genemia-positive	55 (64.7%)	40 (62.5%)	27 (27.8%)	24 (27.9%)	<.01	<.01
>50	14 (16.5%)	12 (18.8%)	7 (7.2%)	6 (7.0%)	.06	.04
CMV disease or syndrome	3 (3.5%)	1 (1.6%)	1 (1.0%)	1 (1.2%)	.34	1.00
BK virus						
PCR-positive	30 (35.2%)	25 (39.0%)	18 (18.6%)	15 (17.4%)	.01	.005
≥4 logs	10 (11.8%)	9 (14.1%)	7 (7.2%)	5 (5.8%)	.32	.10
BK nephropathy	3 (3.5%)	3 (4.7%)	2 (2.1%)	1 (1.2%)	.67	.31

Abbreviations: *ACR* acute cellular rejection, *AMR* antibody-mediated rejection, *UTI* urinary tract infection, *CMV* cytomegalovirus, *BK ≥ 4 logs* ≥4 logs of BK viral loads detected in blood by means of PCR

[a]*P* value between group 1 (n = 85) and group 2 (n = 97)

[b]*P* value between non-sensitized group 1 (n = 64) and non-sensitized group 2 (n = 86)

adjusting for possible confounders including ABO and HLA incompatibility [6] (Tables 5 and 6) (Fig. 6).

In addition, we evaluate the impact of isoagglutinin titer on clinical outcomes as well as factors that may influence isoagglutinin titers. In 95 ABO-i KT patients, preoperatively rituximab administration and plasmapheresis were performed until the titer was reduced to 1:4. Retrospective analysis included blood group; timing and dosage of rituximab; isoagglutinin titer; number of plasmapheresis; and clinical outcomes including graft survival and serum creatinine. Graft survival was 95.8% (n = 91) and average serum creatinine at 1- and 1.5-year post-ABOi-KT was 1.3. Three patients died of sepsis. The identified predictors of titer-rebound after transplant were short intervals (<7 days) between rituximab and first plasmapheresis; high initial titer (1:256); low titer-reduction rate; and blood group O. One patient who experienced a rebound developed antibody-mediated rejection. With low-dose (200 mg) rituximab, the change in isoagglutinin titer-rebound was not significant and the infection rate was significantly decreased [7].

Korea PT

From 1992 to Dec 2019, 23 LDPT were performed among 739 pancreas transplantation from 14 centers in Korea. Among these, two cases of ABO-incompatible LDSPK were performed in two center each. One ABO-incompatible LDSPK patient was performed in 40-year-old female IDDM patient. The recipient, daughter, blood type was B and the donor, father, blood type was A. As a preconditioning regimen, the recipient received a single dose of rituximab (200 mg) 1 week before plasmapheresis; plasmapheresis was performed four

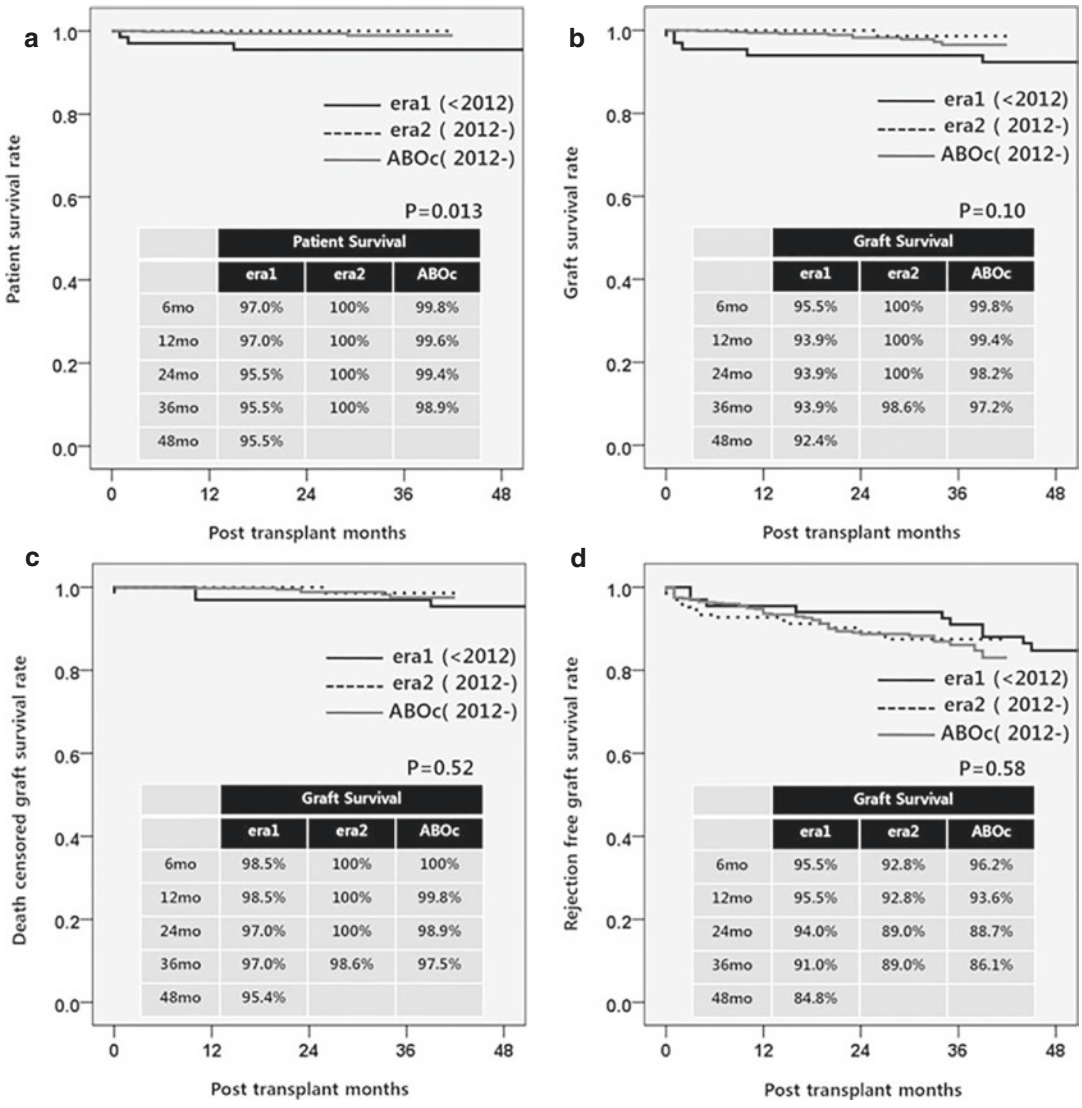


Fig. 4 Long-term patient and graft survival in ABOi kidney transplantation. (**a**) Patient survival, (**b**) Graft survival, (**c**) Death censored graft survival, and (**d**) Rejection free graft survival

times. After preconditioning, the isoagglutinin titer of anti-A antibody fell from 1:256 to 1:2. After SPK, the function of the kidney and pancreas graft was maintained without rejection for 42 months and then a low dose of insulin (10 u/day) requirement was needed with normal functioning renal allograft. The other ABO-incompatible LDSPK patient was performed in 38-year-old male IDDM patient. The blood type of the recipient was O and that of donor was A. For preconditioning, the recipient received a single dose of rituximab (500 mg) 1 week before plasmapheresis. Plasmapheresis was performed totally two times before the transplant. Initial isoagglutinin titer of anti-A antibodies was 1:16, and after preconditioning, it fell to 1:4. After a transplant, function of the pancreas and kidney graft remained stable for 89 months.

Table 4 Binary logistic regression analysis of pooled infectious complications[a]

	Univariate			Multivariate		
Variable	HR	95% CI	*P*-value	HR	95% CI	*P*-value
ABO-status (incompatible)	1.788	1.053–3.034	0.031	1.742	0.986–3.079	0.056
Female sex	1.758	1.091–2.834	0.020	2.207	1.313–3.709	0.003
Body mass index (≥25 kg/m^2)	1.253	0.712–2.207	0.434	–	–	–
Age (≥60 year)	2.339	1.140–4.799	0.021	2.503	1.165–5.380	0.019
HLA antigen mismatch (>3)	1.626	1.012–2.612	0.045	1.400	0.837–2.342	0.200
Previous transplant	1.207	0.440–3.312	0.714	–	–	–
Rejection episode	2.178	1.159–4.090	0.016	2.281	1.164–4.467	0.016
Surgical complications	5.810	1.746–19.338	0.004	4.635	1.305–16.464	0.018
Thymoglobulin induction	0.784	0.302–2.036	0.617	–	–	–
CNI (tacrolimus)	1.021	0.632–1.651	0.932	–	–	–
Cause of ESRD (DM)	1.011	0.557–1.835	0.971	–	–	–
HBV or HCV	0.983	0.395–2.449	0.970	–	–	–
Cold ischemic time (≥60 min)	1.573	0.911–2.718	0.104	1.558	0.874–2.778	0.133

CI confidence interval, *HR* hazard ratio, *HLA* human leukocyte antigen, *CNI* calcineurin inhibitor, *ESRD* end-stage renal disease

[a]All variables are categorical variables (yes/no)

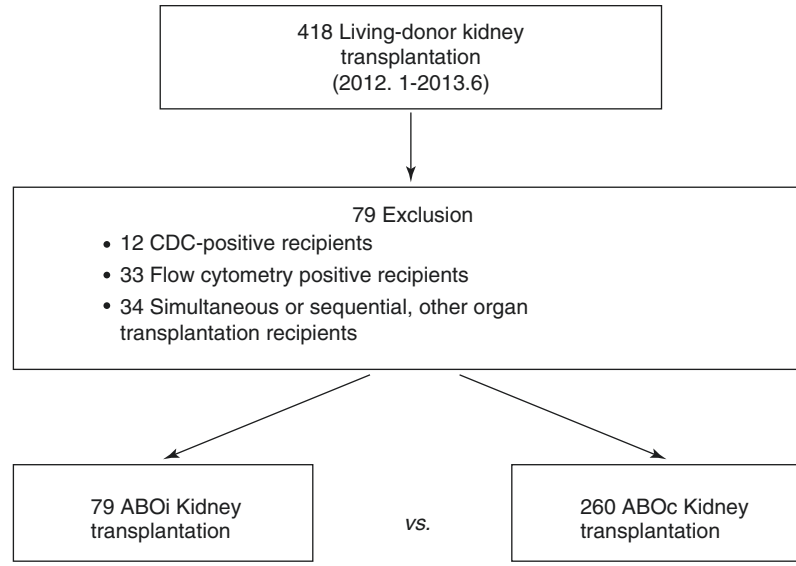


Fig. 5 Selection of the study cohort

Japan-KT

In Japan, the frequency of living donor kidney transplantation (LDKT) exceeds 90% of kidney transplantation. Since the first successful ABOi KT was introduced in 1989 [8–11], ABOi KT has increased year after year and ABOi KT was over 30% among all KT recently. 6246 ABOi KTs were performed from 1989 to 2019, which was 20.0% of 31,231 LDKTs in Japan. In the first decade from 1989 to 2001, 441 ABOi KTs were performed in Japan. Immunosuppressive therapy was achieved by (1) extracorporeal immunomodulation to remove serum anti-A, anti-B antibodies before transplantation, (2) pharmacotherapy (pharmacological immuno-

Table 5 Clinical outcomes at 1 year after transplantation. Values are presented as numbers of patients (%)

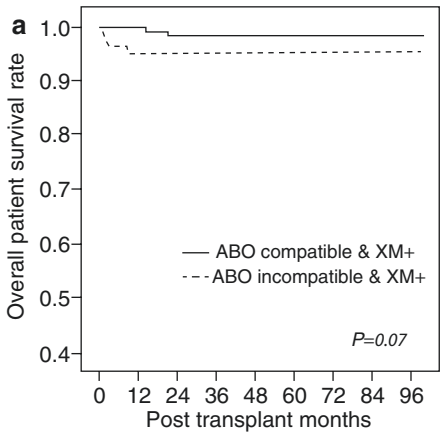
	ABOc/XM+	ABOI/XM+	*P*-value
Number of patients, XM+	176 (66.9)	87 (33.1)	
Overall rejection	21 (11.7)	25 (25.5)	<0.01
ACR only	5 (2.8)	6 (6.1)	0.17
AMR with or without ACR	16 (8.9)	19 (19.4)	0.01
Number of patients, CDC+	14 (63.6)	8 (36.4)	
Overall rejection	0 (0.0)	5 (62.5)	<0.01
ACR only	0 (0.0)	0 (0.0)	—
AMR with or without ACR	0 (0.0)	5 (62.5)	<0.01
Number of patients, FCXM+	162 (67.2)	79 (32.8)	
Overall rejection	21 (13.0)	17 (21.5)	0.09
ACR only	5 (3.1)	4 (5.1)	0.48
AMR with or without ACR	16 (9.9)	13 (16.5)	0.14
Mortality	0 (0.0)	4 (4.6)	<0.01
Bacterial infection			0.14
Urinary tract infection	39 (21.7)	12 (12.1)	
Pneumonia	14 (7.8)	7 (7.1)	
Biopsy proven BKVN	1 (0.6)	1 (1.1)	0.61
Surgical complications			0.30
Bleeding	10 (5.6)	2 (2.0)	
Urinary complications	3 (1.7)	3 (3.1)	

Table 6 Factors associated with acute rejection during the first year after transplantation

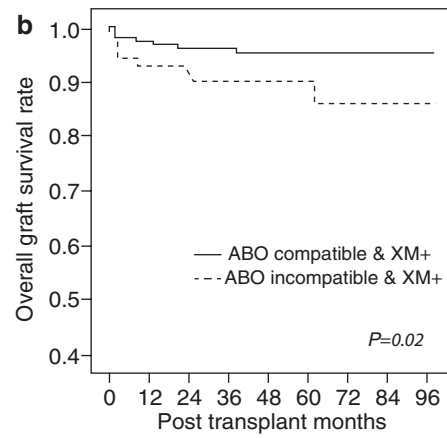
	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Female vs. male sex	1.91 (1.00–3.63)	0.05	2.27 (1.10–4.72)	0.03
Cyclosporin vs. Prograf	1.15 (0.45–2.91)	0.78		
Basiliximab vs. ATG	1.87 (0.84–4.16)	0.78		
CDC positive vs. FCXM positive	1.00 (0.39–2.57)	0.99		
PRA class I	1.00 (0.99–1.00)	0.24		
PRA class II	1.00 (0.99–1.02)	0.13		
DSA class I (MFI/1000)	1.08 (1.00–1.17)	0.05	1.10 (1.01–1.20)	0.03
DSA class II (MFI/1000)	1.10 (1.03–1.16)	<0.01	1.10 (1.03–1.18)	<0.01
XM+ and ABOi vs. XM+ and ABOc	2.59 (1.36–4.93)	<0.01	2.38 (1.21–4.72)	0.01

Abbreviations: *ATG* antithymocyte globulin

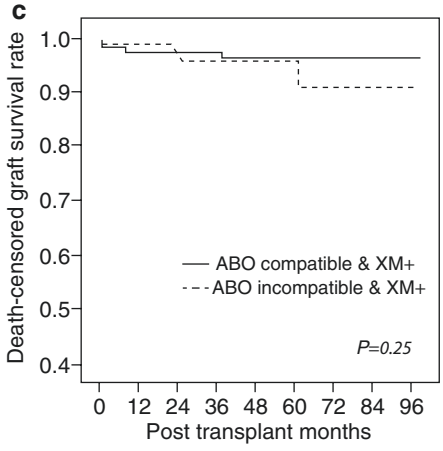
suppression), (3) splenectomy, and (4) anticoagulation therapy. Extracorporeal immunomodulation for antibody removal was plasmapheresis and immunoadsorption. Immunoadsorption with Biosynsorb® (Unicom Corporation, Tokyo, Japan) was carried out in 51 of 441 patients [12, 13]. As production of Biosynsorb® was discontinued, plasmapheresis was used to remove antibodies before transplantation. Splenectomy, one of the major organs producing anti-A, anti-B antibodies was performed in 433 (98%) of 441 patients. The eight patients who did not undergo splenectomy were children in whom the operation was considered unfeasible or patients who were B-incompatible with a low antibody titer. Because AMR after transplantation is considered local (intrarenal) disseminated intravascular coagulation (DIC) [13, 14], anticoagulation therapy was prophylactically administered in 60% of the transplant centers. After transplantation, 223 patients (51%) received anticoagulation therapy. The



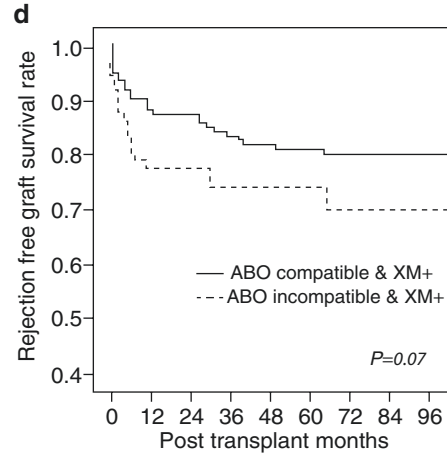
Survival rate % (N.at risk)	1yr	3yr	5yr
ABOc/XM+ (N=176)	100.0(154)	98.6(96)	98.6(72)
ABOi/XM+ (N=87)	95.3(71)	95.3(41)	95.3(34)



Survival rate % (N.at risk)	1yr	3yr	5yr
ABOc/XM+ (N=176)	97.7(150)	96.3(119)	95.5(88)
ABOi/XM+ (N=87)	93.0(69)	89.9(55)	89.9(44)



Survival rate % (N.at risk)	1yr	3yr	5yr
ABOc/XM+ (N=176)	97.7(150)	97.7(119)	96.8(85)
ABOi/XM+ (N=87)	98.8(69)	95.6(55)	95.6(44)



Survival rate % (N.at risk)	1yr	3yr	5yr
ABOc/XM+ (N=176)	87.7(136)	83.3(109)	80.9 (95)
ABOi/XM+ (N=87)	77.2(54)	74.0(46)	74.0 (42)

Fig. 6 Long-term survival after kidney transplantation. (**a**) Patient survival, (**b**) Graft survival, (**c**) Death censored graft survival, (**d**) Rejection free graft survival

patients given anticoagulation therapy received a target dose of 250–300 mg/day of nafamostat mesylate (FUT), a short-acting anticoagulant, by 24-h continuous infusion for 3–7 days after transplantation. After the patients' general condition had stabilized, oral platelet aggregation inhibitor (ticlopidine or aspirin) was given continuously as long as the graft remained viable. Overall patient survival rates at 1, 3, 5, 7, and 9 years after ABOi KT were 93%, 89%, 87%, 85%, and 84%, respectively. Corresponding overall graft survival rates were 84%, 80%, 71%, 65%, and 59%. After ABOi KT, graft survival rates were significantly higher in younger years (<30) and in patients who received anticoagulation therapy. There were no significant dif-

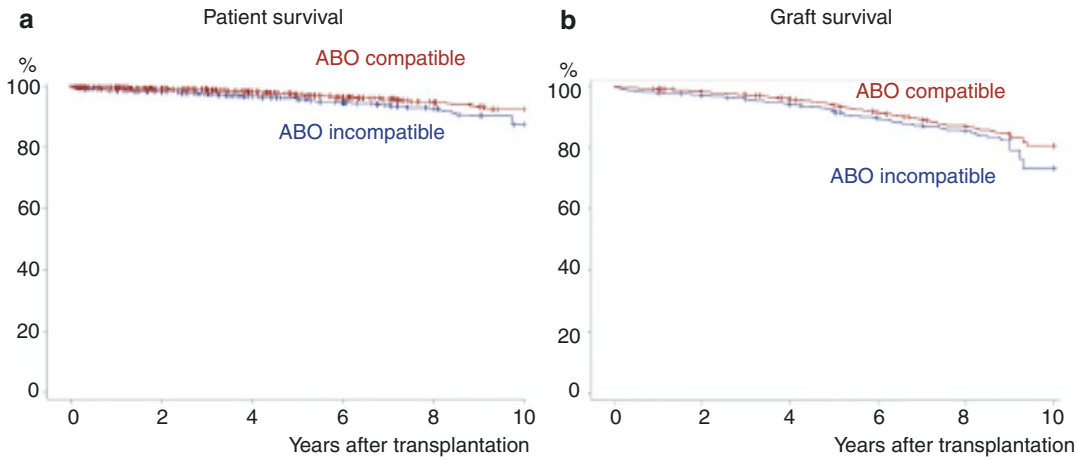


Fig. 7 Patient (**a**) and graft survival (**b**) in Japan(2010–2018)

ferences between A-incompatible and B-incompatible recipients with respect to clinical outcomes. The long-term outcome in recipients of ABOi KT was excellent. Thereafter the use of rituximab and MMF became available in Japan, and a multicenter prospective clinical study was performed [15]. Patient and graft survivals were both 100% after 1 year and no severe adverse effect by this protocol was seen. Also, in my own experiences concerning ABOi KT in the initial period in Chiba-East National hospital, an excellent outcome was obtained [16]. Twenty-one ABOi KTs were performed from 2004 to 2007. Pretransplant immunosuppression and desensitization protocol were performed with splenectomy, administration of mycophenolate mofetil, tacrolimus, methylprednisolone, double filtration plasmapheresis (DFPP), and plasma exchange (PEX). Both IgM and IgG titers were maintained at lower levels (≤fourfold) for 7 days after transplantation in all patients. Cytomegalovirus antigenemia was observed in 11 patients (52.4%). One patient (4.8%) developed a PCP and the formation of lymphocele was observed in one patient (4.8%). Total patient survival at 3 years was 95.2%, and graft survival at 3 years was 90.5%, which were almost equal to those in the patients who underwent ABO-compatible kidney transplantation.

Furthermore, the recent outcome including long-term patient and graft survivals using the national data was analyzed [15]. As shown in Fig. 7, patient and kidney graft survivals were similar between the ABO-compatible and incompatible groups. However, both long-term patient and kidney graft survivals at 8 years or later was significantly higher in ABO-compatible group than those in ABOi group.

Japan-PT

Based on the excellent outcome of ABOi KT in my experience and national data, we have introduced the first ABOi LDPT in 2006. The patient was a 32-year-old woman and her blood type was O. She was diagnosed as type 1 diabetes when she was 10 years old and underwent intensive insulin therapy. Because of diabetic nephropathy, her serum creatinine levels became more than 6.0 mg/dl. Her mother, a 58-year-old woman, was the donor. Her blood type was A (A1). LDPT was successfully performed and both donor and the recipient were discharged without any complications. Thereafter, we performed six consecutive ABOi LDPTs. Characteristics both of the donor and the recipient were shown in Table 7. All recipients were

Table 7 Characteristics both of the donor and the recipient of ABO-incompatible living donor pancreas transplantation in Asia (2006–2020)

Variables	#1	#2	#3	#4	#5	#6	#7	#8
Recipient								
Age (years)	32	30	30	25	29	40	37	38
Gender	Female	Female	Male	Female	Male	Female	Female	Male
Body mass index (kg/m^2)	19.0	20.9	24.6	24.5	21.0	20.9	22.71	28.70
Blood type	O	B	O	O	A (A1)	O	B	O
Primary disease	T1DM	T1DM	T1DM	T1DM	T1DM	T1DM	T1DM	T1DM
History of diabetes (years)	23	31	20	16	21	23	14	18
Insulin amounts (units/day)	42	32	24	32	38	25	24	64
H bA1c (%)	8.1	6.8	9.1	7.4	7.0	7.6	6.4	6.9
Serum C-peptide (ng/ml)	0.24	<0.03	0.28	<0.03	<0.03	<0.03	0.10	2.30
Donor								
Age (years)	58	55	60	53	53	42	60	31
Gender	Female	Female	Female	Female	Female	Male	Male	Female
Relation to the recipient	Mother	Mother	Mother	Mother	Mother	sibling	Father	Spouse
Body mass index (kg/m^2)	17.7	20.4	23.6	23.1	24.7	24.8	24.6	26.9
Blood type	A (A1)	AB	A (A1)	B	AB	A (A1)	A (A1)	A (A1)
HLA mismatch to the recipient	3	0	3	2	3	2	1	4

type 1 diabetic patients with a long history of diabetes ranging from 16 to 31 years. In spite of intensive insulin therapy (four times injection per day), all the recipients showed frequent hypoglycemic unawareness. The donors were 5 mothers and 1 sibling of the recipient. Four cases were A incompatible and the other two were B incompatible. Subtypes of blood type A were all A1 in one recipient and two donors. The donors fulfilled both ethical and medical criteria. All recipients underwent SPK. In the first case (Case#1), desensitization and immunosuppression were done by splenectomy 14 days before transplantation, DFPP at 6, 4, 2 days before transplantation, and PEX at 1 day before transplantation. 200 mg of cyclophosphamide hydrate was administered daily for 20 days after transplantation in addition to tacrolimus, MMF, methylprednisolone, and basiliximab. In the second and third cases (Case#2,3), cyclophosphamide hydrate was not used and MMF was administered 28 days before transplantation and tacrolimus and methylprednisolone were given 10 days before transplantation. In the latter three cases (#4,5,6), rituximab was administered at a dose of 200 mg 14 days before transplantation in place of splenectomy.

Both IgM and IgG antibody titers decreased in all cases less than 32-folds at the time of transplant (Fig. 8). All six recipients achieved both withdrawals of insulin treatment and hemodialysis immediately after transplantation. All the recipients became free from hypoglycemic unawareness and maintained normal blood glucose levels, serum C-peptide, and normal HbA1c levels for 3 years after transplantation. Also, 75g-OGTT revealed a good endocrine function in all cases (Fig. 9). Kidney graft loss from chronic rejection occurred at 35 months after transplantation in one patient (Case#1). Although serum C-peptide was in the normal range, insulin therapy was restarted in two patients (Case #3,4) at 7.1 years and 8.2 years after transplantation. According to the data at 10 years follow-up, the patient survival was 100% and the pancreas graft survival (fasting serum C-peptide levels; >0.3 ng/ml) was 100%, which were better than ABO compatible LDPT (Fig. 10).

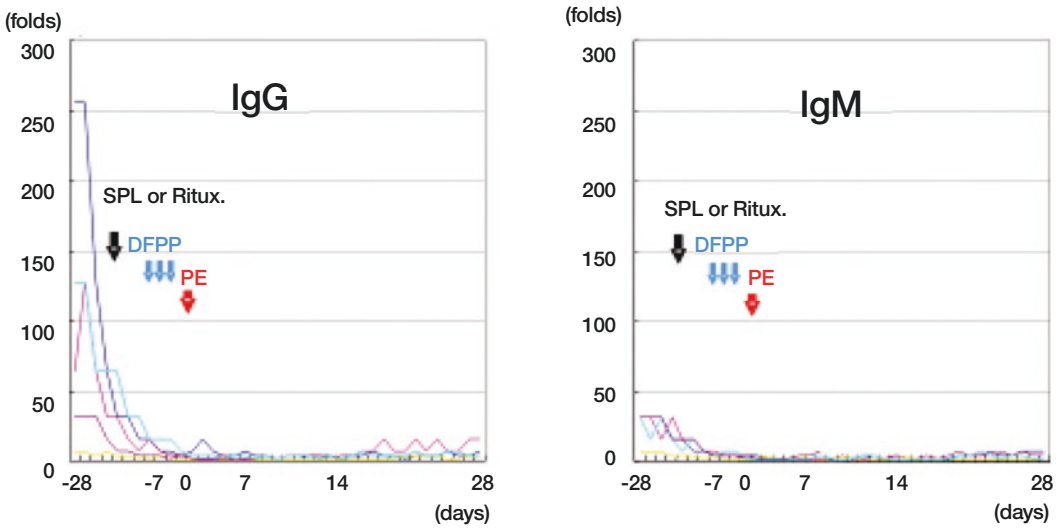


Fig. 8 Change in anti-A, B antibody titer in ABOi living donor pancreas transplantation

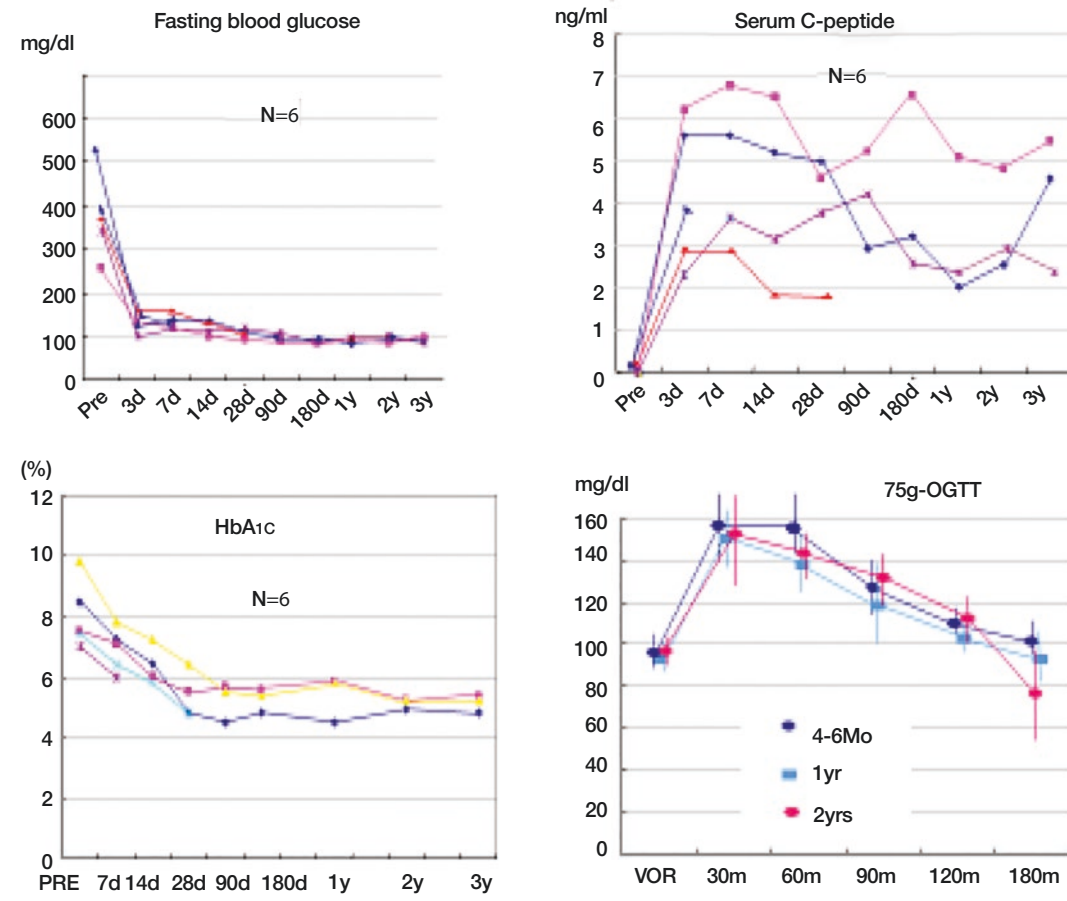


Fig. 9 Changes in blood glucose, serum C-peptide, HbA1C, and 75 g OGTT after living donor pancreas transplant

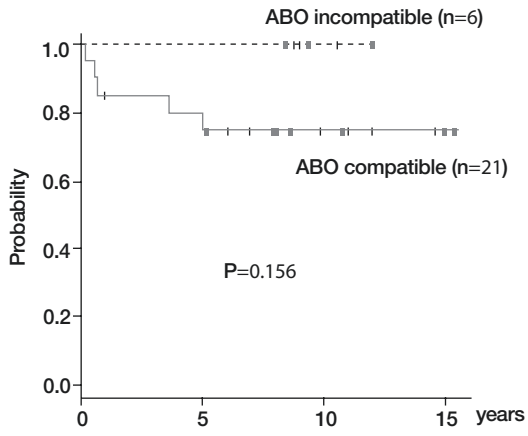


Fig. 10 Comparison of death censored graft survival depending on ABO compatibility

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Complication

Duck-Jong Han, Takashi Kenmochi, and Young Min Ko

Recipient

Korea

One recipient experienced minor pancreas juice leakage from graft pancreas but recovered with conservative treatment. Pancreas graft was well maintained for 42 months but a low dose of insulin (10 u/day) was required for keeping the normoglycemia.

There were no postoperative ABO-related or allograft rejection in both patients.

Japan

Postoperative complications in ABOi LDPT were similar to those in ABO compatible LDPT. AMR due to ABO incompatibility was not experienced in these six recipients. Although two patients (33.3%) showed a positive study in CMV antigenemia, the patients converted to negative after conservative therapy using ganciclovir. One patient (16.7%) developed post-transplant lymphoproliferative disorder (PTLD) and needed chemotherapy using rituximab. One patient developed a chronic rejection of kidney graft. Despite steroids, the kidney graft loss occurred 35 months after transplantation. However, the pancreas graft remained stable and maintained insulin-free status.

Donor

Korea

There was no donor-related clinically significant complication except one minor pancreatic juice leakage developed and treated conservatively.

Japan

Although one donor developed minor leakage of pancreatic juice from the cut surface of residual pancreas, all donors were discharge from the hospital 7–21 days after the operation. In the 10 years follow-up, the development of diabetes and renal dysfunction has not been observed.

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Part IV

Islet Transplantation

Islet Transplantation

Yuumi Akashi, Takayuki Anazawa, Junji Fujikura, and Chung Gyu Park

Clinical Islet Transplantation

History of Clinical Islet Transplantation in Japan (Akashi, Kenmochi)

The first islet transplantation in Japan was an autologous pancreatic tissue transplant performed by Watanabe K. et al. at Chiba University in 1979. After that, many basic research works were conducted by Yasunami Y. (Fukuoka University) [1], Nakagawara G. (University of Fukui) [2], Motoki R. (Fukushima Medical University) [3], Kubota S. (St. Marianna Medical University) [4], Kuroda Y. (Kobe University) [5] and Gotoh M. (Osaka University) [6]. After Kenmochi T. returned to Chiba University from studying abroad at UCLA from 1992 to 1995 [7], Yamaura A., Asano T. and Kenmochi T. obtained research funding from the Ministry of Education, Culture, Sports, Science and Technology in Japan, and started to prepare for clinical islet transplantation in Japan.

In 1997, the Islet Transplantation Working Group (ITWG) was organized in the Japanese Pancreas and Islet Transplantation Association (JPITA). ITWG was led by Dr. Takehide Asano of Chiba University. To date, ITWG has conducted feasibility studies for clinical islet transplantation in Japan, and determined donor indication criteria for islet transplantation, the criteria of islet isolation/freezing/transplantation institution, recipient indication criteria, determination and registration of recipients, and establishment of islet transplantation system. ITWG published "Guidelines for Islet Transplantation" (1998), "Do You Know Islet Transplantation?" (1999), "For the Recipient of Islet Transplantation" "About Islet Donation" (1999), "Outline of Islet Transplantation" (1999), and "Islet Transplantation Agreement" (2000). The essence was to carry out clinical islet transplantation in a national unified team to improve the results. In 2002, the first edition of the "Manual for Clinical Islet Transplantation in Japan" was published and functioned as a bible for performing clinical islet transplantation in Japan.

In 2003, the first islet isolation and cryopreservation in Japan was carried out by Kenmochi T. at the Sakura National Hospital, and the first islet transplantation was carried out by Tanaka K. and Matsumoto S. at Kyoto University in 2004, marking the start of islet transplantation in Japan [8].

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After that, islet transplantation using a DCD donor was performed using the Edmonton protocol introduced by Shapiro A.M. of the University of Alberta [9]. Although the Edmonton protocol was the standard immunosuppressive method at that time, the long-term graft survival was not successful. In our clinical study, the 5-year islet graft survival rate was only 22% [10, 11].

In 2007, FDA in the US temporarily suspended the islet transplant program because it was found that bovine brain extract was used in the process of collagenase production. Following this, the Japanese Ministry of Health, Labor and Welfare also suspended the islet transplant program in Japan. The ITWG confirmed the effectiveness of the new collagenase that was free from bovine brain extract in experiments using pigs, and in 2012, islet transplantation in Japan was resumed.

On resuming islet transplantation in Japan, ITWG verified the outcome and suspected that the causes of poor long-term graft survival were as follows: (1) Using a cardiac arrest donor, (2) Inadequate immunosuppressive therapy. The use of DBD donor pancreas for islet transplantation was finally realized in 2013 through negotiations with the Japan Society for Transplantation, the Ministry of Health, Labor and Welfare, and the Japan Organ Transplant Network. The newly designed immunosuppressive protocol was introduced by Hering BJ of the University of Minnesota in 2005 [12]. In this protocol, induction therapy using r-ATG (Thymoglobulin) and Etanercept was essential in addition to the use of maintenance immunosuppressive agents including calcineurin inhibitor and mycophenolate mofetil. The utility of this protocol was confirmed from the data of multicenter clinical trials named CIT protocol [13]. Therefore, we designed a new immunosuppressive protocol, CIT-J, based on the CIT protocol.

In Japan, however, clinical islet transplantation has not been covered by insurance and has been conducted for a long time as a multicenter clinical trial supported with research funding. Although the islet transplantation seemed to be proceeding smoothly, the number of cases was small and the results are inferior to those of pancreas transplantation. These were the main problems in islet transplantation in Japan. In addition, pancreatic islet transplantation has been performed in the category of tissue transplantation, but unlike other tissue transplantations, the procurement of pancreas was the same process as organ transplantation, and in situ perfusion of the pancreas was required. Thus, islet transplantation seemed to be a delicate standing position in Japan. This also affected the relationship with related academic societies. When the Japanese Society for Transplantation dealt with islet transplantation, it was treated as organ transplantation, and the Japanese Society of Tissue Transplantation treated it as tissue transplantation. However, thanks to the steady efforts of the ITWG members, we have continued the clinical practice of islet transplantation. Recent results using the CIT-J protocol have improved dramatically and were also supported by the Japan Diabetes Society, Japan Transplantation Society, and Japan Tissue Transplantation Society. Clinical islet transplantation was finally achieved to obtain insurance coverage on April 1, 2020. Recent clinical islet transplantation was led by Anazawa T. (Kyoto University) [14] and Kodama S. (Fukuoka University) [15].

Indication for Islet Transplantation (Fujikura)

Indication of Recipient

Based on the favorable outcomes of a recent trial of clinical islet transplantation in Japan (CIT-J003), allogeneic islet transplantation was approved for coverage by the national health insurance of Japan from 2020. Following the insurance coverage, indication criteria for islet transplantation were re-developed through collaboration with the Japanese Pancreas and Islet Transplantation Association (JPITA) and the Japan Diabetes Society (JDS). According to the statement, islet transplantation is recommended for insulin-deficient diabetic patients with severe glycemic variability and fear of intractable hypoglycemia despite optimal treatment by a diabetologist certified by the JDS. As above, basic principles for the indication of islet transplantation are the same as for pancreas transplantation

Table 1 Eligibility criteria and exclusion criteria for allogeneic islet transplantation in Japan

Eligibility criteria
1. With the informed consent of the patient for islet transplantation
2. Age from 20 to 75 years old (at the time of consent acquisition)
3. Insulin-dependence for >5 years
4. Severely reduced endogenous insulin secretion (ad libitum serum C-peptide <0.2 ng/mL)
5. Poor glycemic control despite treatment efforts by a certified diabetologist
6. Cases approved by the expert medical board of diabetologists in JPITA, having a difficulty in glycemic control due to such factors as anti-insulin antibody and autonomic neuropathy, even if requirement number 4 is not met.
Exclusion criteria
1. Obesity (BMI ≥ 30 kg/m^2)
2. Severe ischemic heart disease or heart failure
3. Severe liver dysfunction
4. Severe kidney dysfunction (eGFR < 30 mL/min/1.73 m^2), an individual evaluation is required for renal transplant patients.
5. Unstable preproliferative or proliferative retinopathy (excluding blindness)
6. Alcohol or drug abuse
7. Active or latent infection that may be exacerbated under immunosuppression after transplantation.
8. Active foot ulcer or gangrene
9. Malignancy
10. Any other conditions unsuitable for transplantation

alone. The details of the criteria are described in Table 1. With regard to obesity, BMI > 30 was used as an exclusion criterion in the CIT Consortium Protocol 07 (CIT-07) trial, which showed satisfactory results (Diabetes Care 2016; 39:1230–1240).

The CIT Consortium Protocol 07 (CIT-07) trial showed islet transplantation was an effective treatment for subjects with impaired awareness of hypoglycemia and intractable severe hypoglycemic events (Diabetes Care 2016; 39:1230–1240).

Allocation of Donor Pancreases

At present, donated pancreases are preferentially allocated to pancreas transplantation. The organs are offered for islet transplantation only after they have been turned down for use as a whole organ transplant for reasons such as elderly donor, obese donor, pancreatic fatty infiltration, and a prolonged cardiopulmonary arrest time.

Methods of Islet Transplantation (Anazawa)

Islet Isolation

Transplantation of a sufficient amount of highly viable pancreatic islets is essential to achieve better glycemic control after islet transplantation. Tremendous progress has been made in the standardization of islet isolation in the last 30 years.

In Japan, a ductal injection which protects the pancreatic ducts by injecting preservation solution from the main pancreatic duct immediately after procurement of the pancreas is often performed [16]. Cold storage methods are simple immersion storage with UW solution or the two-layer method [17, 18]. In the two-layer method, perfluorodecalin is placed in the lower part of the container and UW or ETK solution is placed in the upper part, so that more than two-thirds of the pancreas is immersed in the perfluorodecalin. An analysis of islet isolation results from donors after cardiac death in Japan showed better results with the two-layered method than with simple immersion in UW, and storage time of less than 5 h may be desirable [19], but the evaluations in other countries are inconsistent.

The brief islet isolation methods are as follows (Fig. 1): The procured and cold-preserved pancreas was distended with cold enzyme solution through the main pancreatic duct in the Cell Processing Unit. The distended pancreata were digested at 35–37 °C using the semiautomated method [20]. In the pancreas digestion step, the islets must be damaged by hypoxia, warm ischemia, activated proteolytic enzymes released from the acinar cells, mechanical stress, and oxidative stress. Research efforts should focus on understanding the detailed molecular ultrastructure of the pancreatic islet–exocrine matrix in the full range of donors [21], and on developing clinical-grade enzyme (recombinant) blends [22] that can be efficiently used on all donor pan-

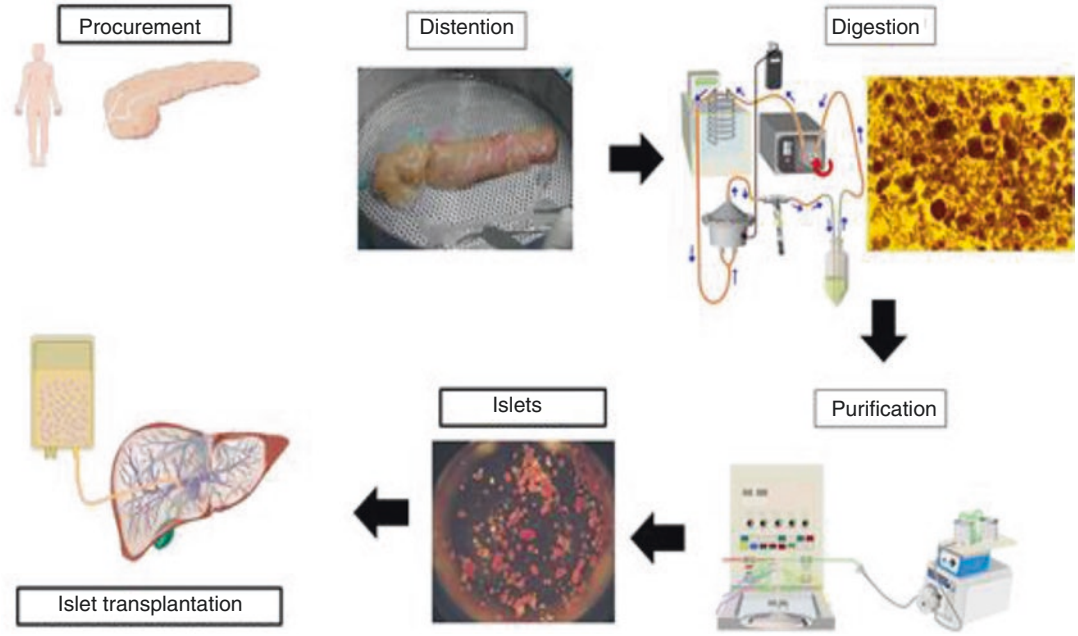

Fig. 1 Scheme of human islet isolation procedure—Cell Processing Center, Kyoto University

creata. The pancreatic digest was purified by continuous density gradient on a COBE 2991 cell processor under cold conditions. Since the specific density of the tissue varies according to the state of the pancreas and the state of digestion, confirming the density of the islets and acinar calls before purification will contribute to the success [23]. Isolated islets were cultured for a short time, and the islets were transplanted if the releasing criteria (islet mass ≥5000 IE/kg [recipient body weight], islet purity ≥30%, membrane-integrity viability ≥70%, packed-tissue volume <10 mL, negative Gram stain, and content ≤5 endotoxin U/kg [recipient body weight]) were met.

Islet Transplant and Engraftment

The isolated islets are transplanted from a catheter placed in the portal vein percutaneously under local anesthesia by infusing the product suspended in the transplant media by gravity. General anesthesia and laparotomy are unnecessary, and transplantation is completed in a short time. The intrahepatic portal vein is punctured by interventional radiology under ultrasonographic and fluoroscopic guidance, and then, a 4Fr brite tip sheath is placed. A Seeking catheter was then placed in the main portal vein and DSA was performed. Once it is confirmed that the catheter is properly positioned and begin islet transplantation. After islet transplantation is completed, remove the sheath while filling the puncture route with local hemostatic agents (Fig. 2).

If this approach is not possible, such as in cases of large hepatic hemangioma, the portal vein system can be accessed surgically by limited laparotomy with intravenous infusion following catheterization of the mesenteric vein.

Immunosuppressive Protocol

In 2000, the "Edmonton Protocol" was seen as a great success in islet transplantation when all first seven patients treated achieved and maintained insulin independency [24]. In Japan, islet transplants have been performed initially on an immunosuppressive protocol following the Edmonton protocol. The glucocorticoid-free regimen comprised sirolimus/tacrolimus plus anti-interleukin-2 receptor antagonist antibody (basiliximab) induction for islet transplant alone recipients or the continuous immunosuppressive regimen for islet after kidney recipients basilix-

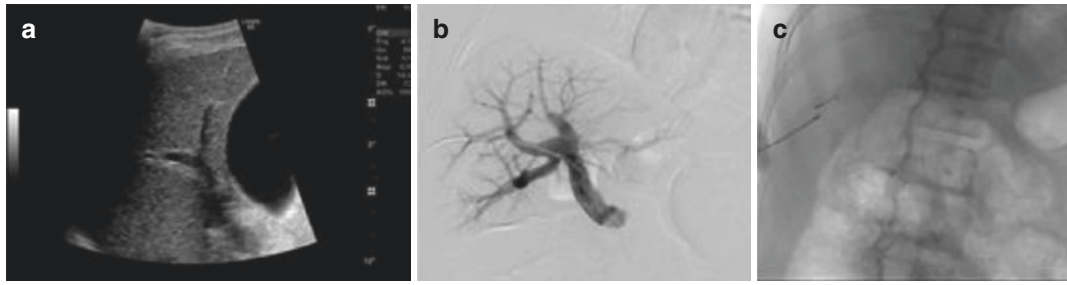

Fig. 2 Process of islet transplantation (**a**) portal vein puncture under ultorasonography, (**b**) catheter insertion and transplantation into the portal vein, (**c**) catheter removal—Kyoto University hospital

imab induction at the time of islet transplantation. Two doses (20 mg) of basiliximab were administered intravenously within 2 h before and 4 days after transplantation. Sirolimus was administered daily to achieve a target trough level of 12–15 ng/mL during 3 months after transplantation, after which the target level was decreased to 7–12 ng/mL. Tacrolimus was administered twice daily to achieve a target trough level of 3–6 ng/mL. When significant proteinuria or other side effects related to sirolimus administration developed, the immunosuppressive regimen was switched to tacrolimus plus mycophenolate mofetil (MMF) at the dose of 1–1.5 g/day.

University of Minnesota group introduced refinements in induction immunosuppressive therapy using T-cell-depleting antibody (rabbit antithymocyte globulin: rATG) that increased the proportion of subjects maintaining insulin independence with a single-donor islet transplantation [25]. Since the use of T-cell-depleting antibody for induction immunosuppressive therapy has become mainstream, the T-cell-depleting protocol was also introduced in clinical trials conducted in Japan.

The rATG dose of 0.5 mg/kg (patient body weight) was administered intravenously for at least 12 h before the initial islet transplantation. Islet transplantation should be performed after the completion of this initial dose. This initial dose should be followed by three cool doses of rATG at 1.83 mg/kg every 24 h (one cool dose should be administered over 12 h). The total dose of rATG is 6.0 mg/kg. Induction immunosuppression consisted of rATG for the first transplant, with basiliximab replacing rabbit antithymocyte globulin at subsequent transplants. A soluble TNF-alpha receptor (etanercept) 25 mg is administered subcutaneously 1 h before islet transplantation. In addition, etanercept 25 mg is administered subcutaneously on islet transplant Day 3, Day 7, and Day 10, respectively. Maintenance immunosuppression was initiated with tacrolimus with doses adjusted to a target trough level of 10–12 ng/mL at 3 months, 8–10 ng/mL at 3 months to 6 months, and 6–8 ng/mL thereafter. MMF at the dose of 0.5–1.5 g/day is also used as maintenance immunosuppression.

Outcome of Islet Transplantation (Fujikura, Anazawa)

Islet Transplantation Using Donors After Cardiac Death Between 2004 and 2007 in Japan

In Japan, donors after cardiac death (DCD) are not deemed suitable for whole-organ pancreatic transplantation, and can provide a source of the pancreas for islet transplantation. Between 2004 and 2007, 65 islet isolations were performed for 34 transplantations in 18 patients with type 1 diabetes mellitus, including two patients who had prior kidney transplantation [19]. All but one donor (64/65) was DCD at the time of harvesting. Of the 18 recipients, 8, 4, and 6 recipients received 1, 2, and 3 islet infusions, respectively.

Overall graft survival (defined as a C-peptide level of ≥0.3 ng/mL) was 72.2%, 44.4%, and

22.2% at 1, 2, and 5 years, respectively, whereas the corresponding graft survival after multiple infusions was 90.0%, 70.0%, and 30.0%, respectively [26]. Three of these recipients achieved insulin independence in 14, 79, and 215 days. HbA1c levels and the requirement of exogenous insulin were improved before the loss of graft function. All recipients became free of severe hypoglycemia unawareness, however, at least 5 of 14 patients who had graft failure experienced a recurrence of severe hypoglycemia after the loss of graft function. Islet transplantation employing DCD can ameliorate severe hypoglycemic episodes, significantly improve HbA1c levels, sustain significant levels of C-peptide, and achieve insulin independence after multiple transplantations. However, islets from DCD may be associated with reduced long-term graft survival. Further improvements in the clinical outcome by modification of islet transplantation protocols are necessary to establish islet transplantation using DCD.

Long-Term Follow-Up of Islet Transplantation Performed Between 2004 and 2007 in Kyoto University Hospital, Japan

Kyoto University transplantation team investigated the 10-years efficacy and safety of Edmonton Protocol-based islet transplantation (ITx) conducted between 2004 and 2007 in their hospital compared with intensive insulin monotherapy (IIT) [27]. Seven ITx patients were compared with age-matched 26 IIT patients. HbA1c improvements and elevated C-peptide levels were significant in ITx at 2 years post-transplantation. No significant differences were found in liver and kidney functions at 10 years between ITx and IIT. The occurrence of severe hypoglycemia was 14% vs 31% (relative risk 0.46, $P = 0.64$), that of infectious disease was 43% vs 12% (relative risk 3.71, $P = 0.09$) and digestive symptoms was 43% vs 7.7% (relative risk 5.57, $P = 0.05$) in ITx vs IIT, respectively. No patient died in either group within the cohort. The study shows ITx contributes to the reduction of hypoglycemia and better glycemic control with tolerable risks over a period of 10 years.

Reduced Glycemic Variability and Flexible Graft Function After Islet Transplantation

The CIT Consortium Protocol 07 (CIT-07) trial showed islet transplantation was an effective treatment for subjects with impaired awareness of hypoglycemia and intractable severe hypoglycemic events [28]. Kyoto University transplantation team reported a case of an IAK patient whose intermittently scanned continuous glucose monitoring (isCGM) sensor glucose data (mean±SD) showed an improvement of glycemic control and variability: 180 ± 43 mg/dL before transplantation, 98 ± 18 mg/dL at 6 months, 121 ± 19 mg/dL without exogenous insulin at 17 months, and 132 ± 25 mg/dL at 25 months after transplantation [29]. They also detected hypoglycemia-induced elevation of blood glucagon level. This case shows the flexible and multiple graft islet function may contribute to the quality of blood glucose control in the daily life of the recipients.

Future Prospect (Anazawa)

In Japan, a clinical trial of islet transplantation based on an immunosuppressive protocol using ATG has been completed, and the results are expected to be reported soon. Based on these results, the number of patients wishing to undergo islet transplantation and the number of cases is expected to increase.

Currently, islets are transplanted into the portal vein, but the problem is that many of the transplanted islets are compromised by a thrombogenic and inflammatory reaction triggered by the complement/coagulant system and innate immune response, called Instant Blood Mediated Inflammatory Reaction [30]. In addition, the difficulty of biopsy of the graft and the impossibility of removing the graft poses a high safety hurdle in the clinical implementation of the ES/iPS cell-derived pancreatic islet cell transplants and xenografts (porcine islets) that are currently being developed. Several attempts have been made to find a site of efficacy beyond the intrahepatic portal vein. A successful case of a laparoscopic implantation approach in the omental

pouch has been reported [31] and is currently undergoing clinical trial. The development of subcutaneous transplantation is also active, and clinical cases of subcutaneous transplantation using a device that allows oxygenation of transplanted islets have been reported [32]. At present, there are no better transplant outcomes than the intrahepatic portal vein, but it is hoped that islet transplantation will be further developed as new scientific solutions to the problems of the alternative transplant site.

Experimental Islet Transplantation: Xeno Islet Transplantation

Chung-Gyu Park

Comparison of Islet Destruction by IBMIR or Acute Rejection During Early Transplantation Period in Various Immunosuppressive Regimens After Adult Porcine Islet to Nonhuman Primate Xenotransplantation

Abstract

Objective: Porcine islet xenotransplantation has been widely studied in the NHP diabetic model over two decays to apply clinical trial due to an unlimited supply of donor islet. However, there are still obstacles to overcome such as instant blood mediated inflammatory reaction (IBMIR), acute humoral and cellular rejection, and chronic rejection to be more acceptable to clinical study. In this study, we analyzed islet destruction by IBMIR and acute rejection during an early time period after pig to NHP islet xenotransplantation in various immunosuppressive regimens.

Materials and methods: Various immunosuppressive regimens were used such as mainly CD154 group (five NHPs), CD40 + TAC group (five NHPs), and clinically applicable immunosuppressive group (seven NHPs) and historical control group (three NHPs). Levels of porcine C-peptide measured to analyze IBMIR at 15 min, 1 or 2 h, and 4 h after porcine islet transplantation, infused glucose during 24 h and porcine C-peptide/fasting glucose ratio (CP/G) and SUITO index at 7 days after porcine islet transplantation were calculated.

Results: The levels of porcine C-peptide tend to be higher in the order of historical control group, CD40 + TAC group, clinically applicable immunosuppressive group, and CD154 group. Infused glucose dose, *CP/G, and SUITO index* were higher in the CD154 group with the longest mean survival day compared to other groups.

Conclusions: Longer survival group showed lower levels of porcine C-peptide during 4 h, higher CP/G and SUITO index at 7 days, and higher infused glucose dose during 24 h *after porcine islet to NHP xenotransplantation compared to those of shorter survival group*.

Keywords

Acute rejection; Porcine islet transplantation; Nonhuman primate; IBMIR; Islet destruction

Introduction

Human islet allotransplantation has been the final therapeutic option for type 1 diabetes patients who have hypoglycemic unawareness [33]. Nevertheless, due to the donor organ shortage, porcine islet xenotransplantation has been considered an attractive alternative [34]. Since the close homology between human and porcine insulin, porcine islets are considered the implantable candidates for clinical applications [35]. Our group has endeavored to achieve long-term porcine graft survival in a pig to nonhuman primate (NHP) model so far. Our group has shown long-term control of diabetes with the anti-CD154 monoclonal antibody (5C8) based immunosuppressive regimen [36], anti-CD40 monoclonal antibody (2C10R4) based immunosuppressive regimen [37], and with a clinically applicable immunosuppressive regimen in pig to NHPs islet xenotransplantation [38]. Collectively, those results revealed the potential impact of the porcine islet donor and offered promise that an unlimited source of transplantable beta cells may be possible. However, several hurdles remained to be overcome. The main hurdles are the instant blood mediated inflammatory reaction (IBMIR)

and acute humoral and cellular rejection since those are more problematic in islet xenotransplantation compared to islet allotransplantation due to species-specific incompatibilities in the early period after islet transplantation [39]. The objective of this study was to analyze porcine islet loss during IBMIR and the early time period after pig to NHP islet xenotransplantation in our different immunosuppressive regimens.

Materials and Methods

Group Design, Animals, and Immunosuppressive Regimen

We used our three published articles which were pig to NHP islet xenotransplantation using various immunosuppressive regimens such as mainly CD154 group (five NHPs) [36], CD40 + TAC group (five NHPs) [37], clinically applicable immunosuppressive group (seven NHPs) [38], and historical control group (three NHPs) which was not published and was shown early graft failure of the porcine islet to NHP xenotransplantation to analyze IBMIR and early graft rejection and briefly summarized in Table 2. A detailed description of the immunosuppressive regimen and usage of IS were described in upper mentioned references.

All procedures that affected the handling and care of the animals were in compliance with the guidelines set forth in the Guide for the Care and Use of Laboratory Animals prepared by the Institute of Laboratory Animal Resources and published by the US National Institutes of Health (NIH Publication No. 86-23, revised 2011) and they were approved by the Seoul National University Institutional Animal Care and Use Committee.

Measurement of Porcine C-Peptide and Blood Glucose Level

Blood glucose concentrations were measured using a small electrode-type blood glucose meter (Accu-Chek™; Roche Diagnostics, Seoul, Korea). For measuring serum C-peptide concentrations, blood samples were collected in a serum separating tube. Blood samples were centrifuged at 2990 × *g* for 20 min at 4 °C, and the separated serum was stored frozen at −80 °C until further use. Porcine serum C-peptide concentrations were determined by an immunoradiometric assay PCP-22K (Millipore, Billerica, MA, USA) or porcine C-peptide ELISA assay kits (Mercodia, Uppsala, Sweden), respectively, according to the manufacturers' instructions.

Table 2 Brief summarization of immunosuppressive regimen to control of IBMIR and T or B cell and mean graft survival day

	IBMIR control	T or B cell control	Mean graft survival day[a] (range)
Historical control group	Heparin, CVF, Aspirin LMWH Heparin	Anti ICAM-1 mAb, Leflunomide Anti ICAM-1 mAb ATG, Bortezomib	6 (5–7)
CD154 group	Plavix, Heparin, CVF or HFH, Humira	ATG, Anti CD154 mAb, Sirolimus	395 (180 to >603)
CD40 + TAC[#] group	Plavix, Heparin, CVF, Humira	ATG, Anti CD40 mAb, Sirolimus, Tacrolimus	68 (3–266)
Clinically applicable IS group	Plavix, Aspirin, Heparin, IVIg, Humira, Anakinra, Tocilizumab	ATG, Belimumab, Abatacept, Tofacitinib, Sirolimus, Tacrolimus	120 (34 to >222)

TAC tacrolimus, *IS* immunosuppression
[a]Graft survival day was defined as the day on which the serum porcine C-peptide fell <0.3 ng/mL or <0.15 ng/mL, as measured by RIA or ELISA

Porcine C-Peptide Measurement to Analyze IBMIR

Sera were collected to measure porcine C-peptide at 15 min, 1 or 2 h, and 4 h after porcine islet xenotransplantation in NHPs.

Calculation of Infused Glucose During 24 Hours After Porcine Islet Transplantation

To prevent hypoglycemia by released insulin from destructed porcine islet due to IBMIR or immune rejection, glucose was intravenously infused to maintain desired target value of the blood glucose level (approximately 100 mg/dL) and infused glucose dose was calculated during 24 h after porcine islet transplantation.

Calculation of Porcine C-Peptide/Fasting Glucose Ratio (CP/G) and SUITO Index

CP/G and SUITO index were measured at 7 days after porcine islet to NHP xenotransplantation in four groups. The SUITO index is suggested by Takita et al. [40] and is designed to assess important endpoints such as insulin independence and reduction of hypoglycemia after islet allotransplantation. This index is 100 for normal healthy humans and 0 for type 1 diabetic patients with no ability to secrete insulin. The formula is as follows: SUITO index = fasting C − peptide level (ng/mL)/[fasting blood glucose level (mg/dL) − 63] × 1500.

Statistical Analysis

The statistical software GRAPHPAD PRISM5 (GraphPad Software, La Jolla, CA, USA) was used for the one-way ANOVA with Dunnett's post hoc test.

Results

1. Levels of porcine C-peptide by released from destructed porcine islet due to IBMIR or immune rejection during 4 h after porcine islet to NHP xenotransplantation

   The levels of porcine C-peptide tend to be higher in the order of historical control group, CD40 + TAC group, clinically applicable immunosuppressive group, and CD154 group (Fig. 3). Although there were no statistically significant, released porcine C-peptide of CD154 group with the longest mean survival day seemed to the lowest levels of porcine C-peptide.

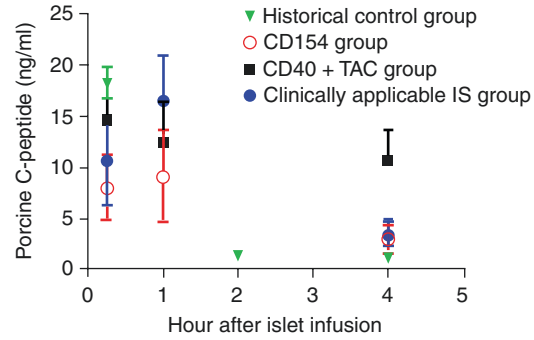

Fig. 3 Levels of porcine C-peptide by released from destructed porcine islet due to IBMIR or immune rejection during 4 h after porcine islet to NHP xenotransplantation in four groups. Although there are no statistically significant, the levels of porcine C-peptide tend to be higher in the order of historical control group, CD40 + TAC group, clinically applicable IS group, and CD154 group. *TAC* tacrolimus, *IS* immunosuppression

2. Infused glucose dose to prevent hypoglycemia

   Infused glucose dose to prevent hypoglycemia by released insulin from destructed porcine islet due to IBMIR or immune rejection during 24 h after porcine islet to NHP xenotransplantation in four groups was statistically higher in CD154 group with the longest mean survival day compared to other groups ($P < 0.05$) (Fig. 4). Infused glucose doses of CD40 + TAC group and the clinically applicable immunosuppressive group were also statistically higher than that of the historical control group with the shortest mean survival day ($P < 0.05$).

3. CP/G and SUITO index were measured at 7 days after porcine islet to NHP xenotransplantation

   CP/G and SUITO index were also showed the same patterns and statistical differences with infused glucose dose in terms of a group of longer mean survival days having higher CP/G and SUITO index compared to group of the shortest mean survival day (Fig. 5).

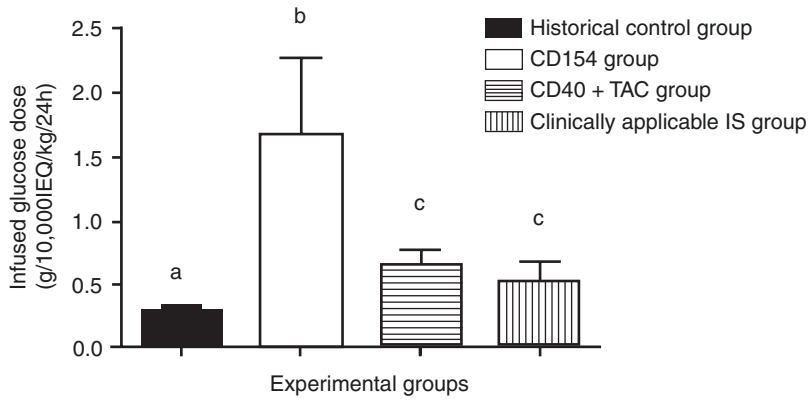

Fig. 4 Infused glucose dose to prevent hypoglycemia by released insulin from destructed porcine islet due to IBMIR or immune rejection during 24 h after porcine islet to NHP xenotransplantation in four groups. One-way ANOVA with Dunnett's post hoc test was used for statistical analysis ($P < 0.05$). *TAC* tacrolimus, *IS* immunosuppression

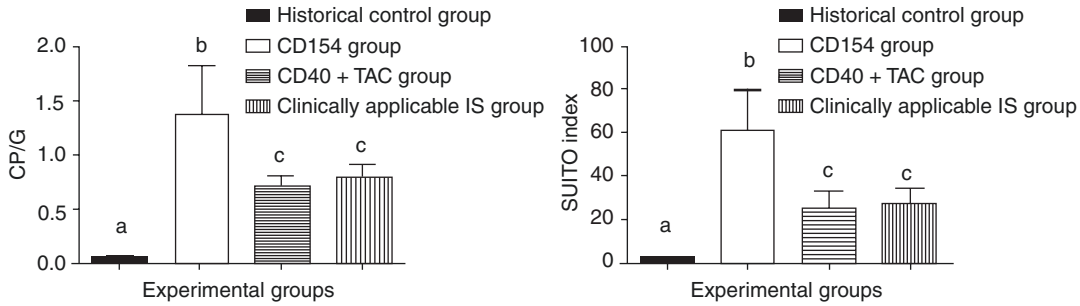

Fig. 5 Porcine C-peptide/fasting glucose ratio (CP/G) and SUITO index were measured at 7 days after porcine islet to NHP xenotransplantation in four groups. One-way ANOVA with Dunnett's post hoc test was used for statistical analysis ($P < 0.05$). *TAC* tacrolimus, *IS* immunosuppression

Discussion

IBMIR is caused by the direct contact of infused islets with the recipient's blood which activated platelet, coagulation system, and subsequent inflammatory reaction resulting in a large amount of early islet loss (estimated about 60–70% and less than 4 h). The complement system and coagulation pathway were activated due to species-specific incompatibility in IBMIR and platelets quickly bind to islet and neutrophils and monocytes are infiltrated [41]. And islets produce pro-inflammatory cytokines due to the isolation stress including HMGB-1, IL-8, TNF-α, IL-1β, and IL-6 [42]. Consequently, the recruited neutrophils and monocytes are activated, and they then infiltrate the islets and release cytotoxic granules which induce lysis of the islet. And these cytokines can activate innate cells. Ultimately, these cytokines and innate cells can stimulate the subsequent adaptive immune responses of T and B cells [43]. In view of acute humoral rejection, isolated pig islet and its own endothelial cell express αGal, Neu5Gc, and B4GALNT2 which induces complement-dependent injury of islets by human antibodies [44]. In terms of acute cellular rejection, human CD4 T cells play a critical role in porcine islet rejection [45]. The acute cellular rejection occurs during the first 24 h to 20 days after transplantation in diabetic primates and a massive infiltration of macrophages and CD4 and CD8 T cells is characterized in the

grafts [43]. Additionally, the T cell-mediated response induces natural killer cell, B cell, and innate responses.

We analyzed porcine C-peptide during 4 h, infused glucose dose during 24 h, and CP/G and SUITO index at 7 days after porcine islet to NHP xenotransplantation to evaluate infused islet destruction from IBMIR and acute humoral and cellular rejection in the four groups of different immunosuppressive regimens. The order of the long survival group was CD154 group, clinically applicable IS group, CD40 + TAC group, and historical control group. The longer survival group showed lower levels of porcine C-peptide during 4 h and higher CP/G and SUITO index at 7 days *after porcine islet to NHP xenotransplantation*. These results showed that a more potent immunosuppressive regimen was more suitable to prevent IBMIR and acute rejection. And the longer survival group showed higher infused glucose dose during 24 h *after porcine islet to NHP xenotransplantation*. *Generally, if the loss of islets was large in IBMIR, infused glucose dose also increased to prevent hypoglycemia* [46]. *However, shorter graft survival group had a lower dose of glucose infusion.* This phenomenon was not easily explained and further study is needed to find out why longer survival of porcine islet needs more glucose infusion to prevent hypoglycemia.

In conclusion, the longer survival group showed lower levels of porcine C-peptide during 4 h, higher CP/G and SUITO index at 7 days, and higher infused glucose dose during 24 h *after porcine islet to NHP xenotransplantation compared to those of shorter survival group*. And the development of a more effective clinically acceptable immunosuppressive regimen to overcome IBMIR and acute rejection is required by a multifaceted approach for porcine islet xenotransplantation.

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Correction to: Outcome

Duck-Jong Han, Byung Hyun Choi, Jun Gyo Gwon, Jongwon Ha, Taihei Ito, Takashi Kenmochi, Myoung Soo Kim, Chang Kwon Oh, Jae Berm Park, Yi-Ming Shyr, Yoshito Tomimaru, and Shin-E Wang

Correction to: Chapter 6 in: D.-J. Han et al. (eds.), Pancreas Transplantation – the Asian Experience, https://doi.org/10.1007/978-981-16-4597-6_6

The chapter was inadvertently published with errors and the following corrections needs to be updated:

Outcome chapter page 104. Fig 17, 18, 19 should be updated as below

Overall patient survivals at 1, 5, 10 years were 96.2%, 93.6%, 90.4% each (Fig. 17). Overall pancreas graft survivals at 1, 5, 10 years were 90.6%, 80.8%, and 75.2% each (Fig. 18). The pancreas graft survivals in SPK, PAK, PTA, and SPLK were 93.6%, 91.6%, 83.7%, and 98.3% respectively at 1 year. Those were 91.0%, 80.2%, 65.9%, and 81.6% at 5 year, and 84.5%, 72.4%, 61.4%, and 81.6% at 10 year respectively which showed the better graft survival in SPK and SPLK in uremic condition compared with PAK or PTA (Fig. 19).

Outcome chapter page 106. Fig 17, 18 and 19 do not match graph and legend or data in box. Fig 17 shows 10yr survival rate of around 92%, however, in box it is 46%. 5yr survival is also wrong. It is also wrong in fig 18. Fig 19 does not match figure title (graft survival) and fig legend (patient survival). Box data is not matched with graph.

In chapter "Outcome" in Part I, one of authors, Jongwon Ha's name presented incorrectly:

It has been changed to **Jongwon Ha**, from Jong Won Ha (as currently shown in the book).

The updated online version of the original chapter can be found at https://doi.org/10.1007/978-981-16-4597-6_6

D.-J. Han et al. (eds.), *Pancreas Transplantation – the Asian Experience*, https://doi.org/10.1007/978-981-16-4597-6_25

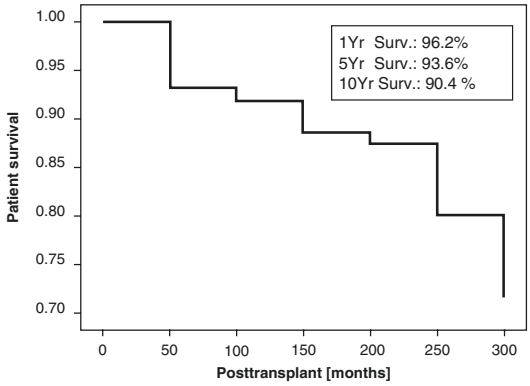

Fig. 17 Patient survival following pancreas transplant in Korea, June 1992–Dec 2020

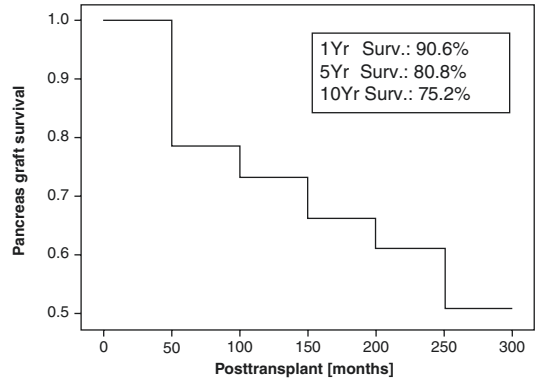

Fig. 18 Pancreas graft survival following pancreas transplant in Korea, June 1992–Dec 2020

Fig. 19 Pancreas graft survival according to operation type in Korea, June 1992–Dec 2020