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Pancreas transplantation

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The article presents the literature review on pancreas transplantation (Tx), describes the history of the issue, discusses advantages and disadvantages of various Tx types, long-term outcomes. The issue of islet transplantation has been briefly outlined.

Keywords: diabetes mellitus, pancreas transplantation, kidney transplantation, deceased donor, living donor.

Introduction

Currently the treatment of diabetes mellitus (DM) and its complications prevention is one of the most pressing problems. According to the World Health Organization, DM is the 8th leading cause of death. The world population suffering from diabetes made 171 million in 2000, and this figure is predicted to reach 366 million in 2030.

Cardiovascular diseases are the leading cause of death from diabetes, and the diabetic patients die from cardiovascular diseases 2-4 times more often than the rest of the world population. DM is the main cause of the end-stage chronic renal disease in many countries [1].

Hyperglycemia is a major risk factor for the development of diabetic retinopathy.

Foot ulcers as a result of diabetic neuropathy affect about 15% of patients.

Pancreas tramsplanmation (Tx) is the only definite surgical treatment for DM. Pancreas Tx is not a life-saving surgery like liver, heart or lung Tx, but it can significantly reduce the risk of diabetic complications and improve the patients life quality.

According to IPTR (International Pancreas Transplant Registry), more than 30,000 pancreas Tx were performed worldwide from December 16, 1966, to December, 31, 2008, including 22,000 transplants in the United States and more than 8,000 in other countries. The most frequent during the period 2004-2008 was the procedure of simultaneous pancreas-kidney (SPK) transplantation Tx (73%) [2].

According to IRODaT (The International Registry of Organ Donation and Transplantation), in 2009 the world leading place in pancreas transplants belongs to the USA by the number of solitary pancreas Tx (325 Tx) and the United Kingdom by the number of such procedures per 1 million population (3.4); the amount of SPK transplants was the greatest in the USA (724 Tx), and in Norway when assessed per 1 million of population (3.3). Thus in 2009 the world leaders in pancreas transplants were the USA by the total number of pancreas Tx procedures (1049 Tx), and Norway by the number of pancreas Tx procedures per 1 million of population (6.6).

Historical background

Experimental studies on pancreas Tx began long before the insulin discovery. In 1891, a subcutaneous transplantation of autologous pancreatic fragments was performed in the dog after pancreatectomy [3]. Further experiments in pancreas Tx to the spleen were not successful because of

transplant necrosis. The first pancreas xenotransplantation was performed in London in 1893: a 15-year-old boy underwent subcutaneous implantation of the sheep pancreatic slices. The surgery was performed 20 minutes after the animal's death. The recipient died 3 days after surgery in diabetic coma. P.W. Williams who had performed the surgery suggested that Tx should be performed with the donation from a living donor [4]. In 1916, the transplantation of human pancreas slices was performed in 2 patients, but the grafts were completely absorbed.

The world's first successful pancreas transplantation was performed by W. Kelly and R. Lillehei in Minneapolis on December 17, 1966. They transplanted a duct ligated segmental pancreas graft simultaneously with a kidney from a deceased donor into a 28-year-old female recipient with type 1 diabetic nephropathy [5].

In the same year, R. Lillehei performed the whole pancreas Tx with duodenum extraperitoneally to the left iliac fossa in a 32-year-old recipient [5].

On November 24, 1971, M.Gliedman for the first time used the native ureter for pancreas secret transplant drainage in its Tx [6]. In 1973, F.Merkel reported on segmental solitary pancreas Tx using end-to-side duodenoenterostomy [7].

In 1983, H.Sollinger described the pancreatic graft segment drainage technique via bladder which later became the most widely used for pancreas secret draining [8].

Subsequently D. Nghiem and R. Corry presented good results in whole pancreaticoduodenal transplantation with duodenocystostomy [9].

In 1984, Starzl et al. modified the technique of enteric drained pancreaticoduodenal transplant [10].

During 1980-1990 a bladder drainage technique of pancreatic secretion became the most common since monitoring of the urine amylase activity could be used as a nonspecific rejection marker.

In the 1990 enteric drainage was applied again especially for SPK Tx. It is a more physiologic and the advances in antibiotics and immunosuppressive therapy allowed reducing inflammation and rejection. The frequency of conversion from bladder to enteric drainage reported to be 10% to 15%.

In 1992 L. Rosenlof et al. and M.Shokouh-Amiri et al. reported the portal drainage technique for enteric drained grafts revascularization [11]. Thereafter the large series of cases was reported [12].

Segmental pancreas Tx from living donor was first performed in Minneapolis in 1970s where later in 2001 laparoscopic distal pancreatectomy from a living donor was performed [13].

The world's first robot-assisted pancreas Tx was performed by U. Boggi at Pisa University Hospital in 2011. There were pancreas Tx alone (PTA, n=1), pancreas-after-kidney Tx (PAK, n=1), and SPK Tx (n=1) of 3, 5, and 8 hours duration, respectively [14].

Indications for pancreas transplantation

The most pancreas Tx recipients have type 1 DM, however, 7.7% of pancreas transplants are reported to be performed in type 2 DM patients [15]. Previous total pancreatectomy is considered to be an indication for pancreas Tx. Most literature reports demonstrated good long-term outcomes of pancreas Tx in type 2 DM compared to those in type 1 DM.

Tx benefits become apparent when the risk of diabetic complications overdraws that of immunosuppression side-effects. This is especially

concerns of patients with hypoglycemia episodes and a poor tolerance to exogenous insulin.

The indication to immediate pancreas Tx is the progression of secondary DM complications leading to end-stage renal disease (ESRD), amputations, and blindness which are reported to be observed in 15% of patients. There was established the pancreas Tx significantly improves the life quality in these patients.

Pancreas transplant recipients may be classified into those who have the ESRD requiring also a kidney Tx, and those who have not yet developed a diabetic nephropathy. The best option is SPK Tx from one deceased donor. Predialysis simultaneous Tx from a living donor may be also performed to avoid dialysis and achieve a non-insulin dependent state through a one-stage surgery with a low rejection rate.

Donor selection criteria

Deceased donor selection criteria

The selection criteria for the majority of pancreatic grafts is the organ donation after brain death (DBD). Pancreas grafts donation after cardiac death donors (DCD) has also been described, but such practice is extremely rare.

In contrast to ABO group compatibility and negative crossmatch, HLA matching is not essential for SPK Tx from deceased donor. Meanwhile for PTA the degree of match is a significant prognostic factor for graft survival.

The donor age is one of the crucial criteria since he is over 45 years old the risk for vascular thrombosis and other complications is expected to be much higher. Acceptable donor body weight is 30 kg or above [16].

A careful selection should be applied to donors who died as a result of cerebrovascular events. The attention should also be paid to the history of hyperglycemia. In most cases centers slight hyperglycemia is not considered to be an absolute contraindication to pancreas Tx without a past medical history of diabetes.

In modern era of preservation solutions pancreas Tx can be done up to 30 hours after procurement. However, prolonged cold ischemia time contributed to the vascular thrombosis.

The donor obesity is a relative contraindication to pancreas Tx since pancreas grafts with fatty degeneration have a higher risk of posttransplant pancreatitis and thrombosis but such grafts are suitable for islet Tx.

Living donor selection criteria

Currently living donor PTA is performed in highly sensitized recipients with low probability of receiving a cadaver graft, intolerance to high-dose immunosuppression or with presence a identical twin or sibling without DM or past medical history of gestational diabetes.

Pancreas specific laboratory workup includes serum amylase and lipase, glycated hemoglobin (HbA1c) determination and oral glucose tolerance tests.

Advantages and disadvantages of various pancreas transplant types

Deceased versus living donor

Organ Tx from a living donor has become an integral part of modern transplantation. Kidney transplant outcomes have demonstrated the potential of living related donor Tx to increase the number of annually performed transplant procedures and also to improve significantly graft survival rates. Besides, the surgery can be scheduled to be safely performed despite the incompatibility problem either by the influence on the recipient's immune system, or through the organ share programs between donor-recipient pairs, as it is practiced in kidney Tx ("kidney paired donation") [17]. In Russia, the "domino" principle (a "paired donation" or "chain" program) has not been widely practiced. However, a living related donor at Tx is subjected to all the typical risks of surgery-related specific postoperative complications [18, 19]. This limits significantly a widespread implementation of living donor pancreas Tx, despite the fact that pancreas was the first extrarenal organ to be successfully transplanted, and a related donor is the only graft source in highly sensitized recipients. This is confirmed by the fact that of all the pancreas transplants in the world since 1966, less than 1% have been the living donor transplant procedures [19]. Only two pancreas transplants have been performed from a living donor for the recent 10 years in the USA [20]

Benefits and limitations of a living donor pancreas Tx were stated by U. Boggi et al. [21]. The benefits of a living donor pancreas Tx may be summarized as follows:

1. The better HLA-match that is quite essential at pancreas Tx alone, especially if the recipient is highly sensitized or can not tolerate a high-dose immunosuppression.

2. Lower rate of delayed graft function (DGF) that is associated with better graft survival rates.

3. The possibility to take precautions for the recipient that make ABO- and crossmatch-incompatible transplants possible.

4. Avoidance of a high-dose immunosuppression in patients with severe comorbidities (e.g., a cancer history).

5. Shortening the waiting times (especially, important for simultaneous pancreas-kidney Tx), thus decreasing the complication rates associated with the disease progression and dialysis.

6. Expansion of the donor pool.

Occasianally a living segmental pancreas graft is used for pancreatic islet cell transplantation [22]. Some authors have reported that a half of a living pancreas is required to obtain a sufficient number of graft islet cells for transplantation to achieve a complete insulin independence in a patient with type 1 DM [22].

The Vancouver Forum convened under the auspices of the EC and The Transplantation Society (TTS) in Canada in 2005 had the goal to approve international guidelines for living lung, liver, pancreas and intestinal donor management [18].

Vancouver Forum provided the ethics statement and medical recommendations worked out by study groups for each transplanted organs [18].

According to the mentioned recommendations a pancreas donor medical assessment should begin with endocrinologic work-up. If metabolic test results are satisfactory the risk of diabetes in donor is expected to be less than 3%.

Avoidance of obesity and overweight is an important factor to reduce the risk of long-term diabetes in donor.

The death risk of living donor can not be accurately estimated due to a limited of Tx reported in literature, but this rate cannot be expected to be lower than that in living kidney donation.

Donor segmental pancreas graftectomy can be done using either open or laparoscopic approach. A hand-assisted laparoscopic technique has all benefits of minimally invasive surgery, and is likely to become a predominant. All donors should obtain a vaccination against pneumococcus, hemophilus influenza type B and meningococcus two weeks prior to surgery.

The incidence of surgical specific complications in living donors are expected to be in 5% of patients [18].

Pancreas Tx alone vs. simultaneous pancreas-kidney Tx

Most often simultaneous pancreas Tx is performed with a kidney transplant especially a simultaneous Tx of these organs from a deceased donor is beneficial, although deceased donor pancreas Tx with living donor kidney Tx or living donor SPK can be performed [13]. The number of SPK Tx has not increased since 1995, but the number of PTA has quadrupled [23].

Considering deceased donor organ deficiency the alternative way compared to SPK Tx for type I diabetes recipients with ESRD is a deceased donor pancreas Tx prior or after a living donor kidney Tx. A. Andren-Sandberg at Karolinska Institute (Sweden) retrospectively analyzed the results of SPK Tx and pancreas after kidney (PAK) Tx from a living donor. They compared patient, kidney allograft, and pancreas allograft survivals. Of

11,966 patients who received a kidney allograft, 807 patients underwent a living donor PAK Tx and 5580 underwent SPK transplantation. The mean waiting time to pancreas Tx after kidney Tx ammounted 336 days. The average hospital stay for SPK Tx recipients was 13±15 days, whereas for PAK Tx recipients it was 6±4 days and 10±8 days for kidney and pancreas, respectively. After all factors were analyzed, the authors estimated that the patients who received PAK transplant had higher patient survival rate (HR 0.52; 95% confidence interval 0.39 to 0.70), and higher kidney allograft survival (HR 0.48; 95% confidence interval 0.39 to 0.60), but they had worse pancreas allograft survival (HR 1.37; 95% confidence interval 1.16 to 1.62) compared to recipients of SPK Tx. Thus, PAK Tx was associated with better patient survival and kidney allograft survival, but worse pancreas allograft survival and a longer hospital stay [24]. Additionally PTA recipients are less tolerable to immunosuppression.

Bladder-drained versus enteric-drained pancreas transplantation

Pancreas secretion drainage in pancreas Tx has been a debatable issue so far. There are various options, including ligation of the main pancreatic duct, duodenostomy, enteral or bladder drainage. The main bemefit of the bladder drainage in PTA or PAK Tx is the ability to diagnose in time an early rejection that is evidenced by the decrease in the concentration of urine amylase levels prior to irreversible hyperglycemia. Thrombosis rates after PTA or SPK Tx with bladder drainage are almost similar (5.0-7.2%), however, in case of enteric drainage, thrombosis incidence increases (5.5-11.6%). This can be the most reasonably explained by a growing number of unrecognized graft rejections in the cases of enteral drainage manifesting themselves as graft thrombosis.

An anastomotic leak that often requires a surgical treatment for septic complications makes one of the most difficult problems with enteral drainage. The risk of this complication is related to anastomotic technique: a manual or apparatus suture. In case of a bladder drainage, anastomotic leaks can be managed conservatively by the placement of a urinary catheter. Some surgeons prefer to construct the pancreas graft anastomosis with a Roux-en-Y small bowel loop to prevent anastomotic leaks.

Bladder drainage disadvantages include acidosis (due to bicarbonate deficiency), urinary symptoms, upper urinary tract infections, hematuria, and dysplasia. The incidence of graft reflux pancreatitis can reach 50%. It is associated with a urinary retention and cystitis causing the activation of pancreatic enzymes by enterokinase in the graft duodenal mucosa.

In some authors' opinion, the diagnosis of a neurogenic bladder should not be the reason to refuse from the bladder drainage in all cases. Up to 25% of recipients with the bladder drainage require a conversion to the enteral drainage within 10 years, and even in this case, the graft may be lost [25].

Until 1995, the bladder drainage had been used in 85% of SPK Tx. However, until 2005 the rate had decreased to 20%. This pancreas secretion drainage is still widely used for PTA.

According to both retrospective and prospective studies, neither bladder, nor enteral drainage make any significant benefits for the recipient and transplant survival [26].

Systemic versus portal vein drainage

The portal venous drainage is usually performed in recipients of the enteric drained pancreas transplant to obtain a physiological insulin passage through the liver responsible for 50% of insulin metabolism. The systemic venous drainage may induce systemic hyperinsulinemia. Hyperinsulinemia de novo predisposes the patient to an accelerated development of atherosclerosis but there is no direct relation between this phenomenon and pancreas Tx. There was no difference in carbohydrate metabolism between the recipients after SPK Tx and non-diabetic recipients of KTA [27]. A systemic drainage increases blood concentrations of low-density lipoproteins, and apolipoprotein B, while with a portal venous drainage their blood concentrations are reduced as well as those of free cholesterol and very low density lipoproteins. A negative feature of portal drainage is an elevated blood pressure in the portal vein system compared to that in the inferior vena cava that results in an increased risk of pancreas allograft vascular thrombosis associated with a portal venous drainage despite its metabolic advantages.

Complications after pancreas transplantation

The pancreas allograft vascular thrombosis is the main problem in pancreas transplantation. It usually leads to a graft loss and affects an immediate outcome. This complication occurs in 10-20% of pancreas graft recipients; and the incidence is 3 times higher than that in PTA recipients compared to SPK Tx. Thrombosis usually occurs within the first postoperative week, but can occur as early as within the first 24 hours in patients with a good allograft function. It may be caused by a decreased blood flow to the allograft (due to a specific anatomy, etc.), a reperfusion

injury, acute rejection, hypovolemia, hypotension, or pancreatitis. Other contributing factors associated with allograft thrombosis include a longer cold ischemia time, an older donor age, or donor death due to cardiac or cerebrovascular events [28]. The assessment for pancreas allograft thrombosis in the immediate postoperative period includes the monitoring of serum electrolytes, glucose, and diagnostic imaging.

There are venous and arterial allograft thrombosis. Venous thrombosis generally presents with swelling of the graft, pain, increased serum glucose and amylase levels. This complication is practically irreversible. Measures to prevent graft thrombosis include a bed rest, anticoagulation, and Doppler imaging. A thrombectomy followed by an anticoagulation therapy is indicated.

Arterial thrombosis may involve the splenic artery or the superior mesenteric artery. The superior mesenteric artery thrombosis results in a duodenal necrosis; there is a rise in the serum glucose, and the serum amilase decreases. The patient presents with gray urine color and a urine leak from the duodenum can be observed. There is no abdominal pain. In this case surgery is required for removal of the duodenal segment, and the pancreatic graft is anastomosed to the bladder. If the splenic artery is thrombosed, the body and tail of the pancreas may necrotized which is followed by the development of a pancreatic fistula into the peritoneal cavity or fluid collections. There is no treatment for allograft thrombosis with a rare exception of partial venous thrombosis.

The results of a retrospective cohort study in pancreas transplantation were reported in 2010. The study included patients in whom the pancreas Tx was performed in the period from 1998 to 2006 (n=216 recipients) who were then followed up until July 2008 [29]. Data regarding infectious

complications, graft rejection, prophylactic antibiotics, graft survival, absolute lymphocyte counts, and recipient survival were analized. SPK Tx, PTA, and PAK Tx were performed in 42, 67, and 107 patients, respectively. The mean average age of recipients was 47, 41, and 44 years, respectively. Overall, 63% had a severe infection during the median follow-up of 6.4 years. The mean number of infectious episodes was 2.3 (1 to 12) with mostly bacterial infections and were most often observed within the first 3 months after Tx. The bladder exocrine drainage was associated with a significantly higher risk of infection. Infectious complications within the first 3 months after transplantation were related to a higher mortality; the absolute leukocyte count was the predictor of infection development.

Pancreatitis appears one of the most common complications after pancreas Tx. Pancreatitis that occurs in the immediate postoperative period results from the pancreas damage during cold ischemia or from an excessive traction of the pancreas during surgery. This process is usually self-limiting. The pancreatitis that occurs in the later postoperative period is most likely due to the reflux of urine into the pancreatic duct of a bladder-drained pancreas. Endocrine function is usually not affected. Reflux pancreatitis requires the treatment with a bladder drainage.

Blocking the pancreatic exocrine secretions with such chemotherapy drugs as cisplatin or 5-fluorouracil has been proposed as a therapy to prevent the post-transplant pancreatitis [30]. However, this method has a disadvantage of hampering the tissue regeneration that might affect anastomosis.

Other complications which may occur during the post-transplant period include a urinary tract inflammation, pancreatic abscesses, and anastomotic leaks.

Long-term results of pancreas transplantation

It is quite difficult to draw conclusions based on available data on pancreas Tx as recipients of SPK Tx are commonly non-comparable with those of KTA by age and the stage of the disease.

Based on literature, a 1-year survival rate among pancreas transplant recipients exceeds 95%, and a 3-year survival is 90%. Meantime, a 1-year graft survival makes up to 85% after SPK Tx and 79% after PTA [2].

The use of younger donor organs and shorter ischemia time significantly reduces the risk of graft loss [2]. With modifications in immunosuppressive and anticoagulatory therapies, a 1-year graft survival for living donor pancreas recipients have reached more than 85%. Living donor transplants increase the number of organs available for transplantation and decrease the number of patient deaths while on the waiting list. Meanwhile, a meticulous donor evaluation is a key factor for minimizing the complication rate in these cases.

Among 119 pancreas Tx performed in Asan Medical Center (Seoul, Korea), there were 42 (43.7%) cases of PTA, 10 (8.4%) PAK Tx, and 67 (56.3%) SPK Tx. Deceased donor and living donor Tx were 108 and 11, respectively. The bladder drainage of pancreatic secretions was performed in 69 (58%) recipients and the enteric drainage was performed in 50 (42.0%). Overall pancreas graft survival rates at 1, 5, 10 years were 81.6%, 63.4%, and 57.1%, respectively, and recipient survival rates were 93%, 86%, and 86%, respectively; a median follow-up period was 39 months [31].

According to UNOS (United Network for Organ Sharing) and IPTR (International Pancreas Transplant Registry), a 1-year patient, kidney graft, and pancreas graft survival rates in SPK Tx recipients were 95%, 91% and

86%, respectively. SPK Tx in diabetic patients is associated with significantly improved patient and kidney graft survival rates compared to KTA [32]. A 1-year pancreas graft survival following PAK Tx and PTA makes 78-83%.

Another study demonstrated that a pancreas Tx after living related donor kidney Tx significantly improved recipient and kidney allograft survival rates compared to living KTA during the follow-up period of 8 years [33].

In a retrospective study, the mortality rates were analyzed in patients with DM who were older than 50 years compared with recipients younger than 50 years. The majority were SPK Tx. Despite data from USA clinics suggesting a significantly increased risk of mortality in recipients older than 45 years compared to younger, the study showed that carefully selected patients with DM who are older than 50 years can undergo successful pancreas Tx with patients and allograft survival rates similar to those observed in younger patients [34].

Among SPK Tx performed at the University of Minnesota from March 1994 to August 2000, there were 32 living donor transplants. When compared to the group of SPK Tx from deceased donors, one-year patient survival rates were 100%, and 96%, the allograft survival rates were 86%, and 81%, respectively [35].

Whether a pancreas Tx offers a survival benefit in patients with diabetes still remains debated [36]. Some authors reported 15-year survival rates for recipients and allografts that were 56% and 36% for SPK Tx, 42% and 18% for PAK Tx, 59% and 16% for PTA, respectively. The most common causes of pancreatic allograft loss 10 years after Tx were the recipient death (53%) and chronic rejection (33%).

G. Tyden et al. reported a 60% increased survival for SPK transplant recipients compared to kidney transplant recipients in comparable age groups of diabetic patients at 10 years after Tx (80% vs. 20%), but these data were not consistent for living related kidney Tx recipients [37]. More recently, S.G. Rayhill et al. reviewed the results of more than 600 Tx, and obtained similar data for Tx from a living donor. The latter results were better when compared to those of deceased Tx [38].

The analyzed results of 13,000 kidney Tx in type 1 diabetic patients demonstrated the 10-year patient survival rates were 67% for a SPKTx, 65% for a living donor KTA, and 46 % for deceased KTA, the difference being statistically significant ($p<0.05$) [39]. The expected remaining life years were 10 years longer in the recipients of SPK Tx compared to that in diabetic recipients of deceased KTA (23.4 years vs 12.9 years); however, there was no survival benefit in SPK Tx recipients of 50 years and older [39]. When kidney was transplanted from a living donor, the patient survival among pancreas transplant recipients was higher, and the pancreas graft survival increased by 20%. The review of over 5,000 kidney Tx showed that the SPK Tx contributes to a kidney transplant survival as compared to deceased Tx in diabetic patents, despite the increased acute rejection rate (15% vs. 9%) [40].

J.M. Venstrom et al. reported lower survival rate among the patients with a preserved renal function after PTA compared to diabetic patients received a standard treatment while awaiting for Tx [36]. SPK Tx was associated with a 1.5-times poorer survival within initial 3 months post-Tx mainly due to a larger extent of surgical intervention. This risk is significantly higher: 2.27-times in pancreas Tx alone, and 2.89-times in

pancreas-after-kidney Tx. However, four years later the risk increased in the recipients of SPK Tx [36].

R.W. Gruessner et al. according to UNOS data reported that 12% of patients were listed for Tx in different centers and were irrationally distributed for treatment [41]. Those waiting for a certain intervention could have received a different treatment. Ten percent of patients waiting for a SPK Tx could have received PAK Tx or KTA. Another study of UNOS data underestimated the mortality of patients awaiting for a pancreas Tx [41]. Recipient survival rates at 1 year after SPK Tx, PAK Tx and PTA appeared higher compared to patients on the waiting list, particularly in specialized centers (Fig.2). Over 50% of those listed for a SPK transplant died while being on the waiting list for over 4 years [23].

Recurrence of Type 1 diabetes followed by pancreas transplantation

The occur of type 1 DM de novo in patients followed by pancreas Tx was documented by D.E. Sutherland in the 1980s [42]. This phenomenon was observed in pancreas tail living transplant recipients from HLA-identical twins (5 cases) and HLA-identical siblings (5 cases) in the absence of immunosuppression 4–8 weeks after transplantation. A relatively rapid return to hyperglycemia without pancreatic rejection was consistent with the recurrence of autoimmunity that was confirmed by histological signs of insulitis with a mononuclear cell infiltrate and a selective β-cell destruction. This was the evidence supporting the concept of cellular immunity as a key pathogenic mechanism of type 1 diabetes mellitus in humans.

R.K. Sibley et al. subsequently examined tissues obtained by a biopsy, graftectomy, and autopsy from 100 pancreas recipients. Autoimmune diabetes recurrence was not noted in patients who received

immunosuppression and who underwent pancreas Tx from non-HLA-identical related donors.

No cases of a post-transplant recurrence of diabetes were reported in deceased pancreas transplant recipients. No anti-islet humoral immune responses were observed in this group as demonstrated by an islet cell antibody assay that today remains a highly sensitive and predictive test to identify individuals at risk of developing diabetes. The above data supported that the immunosuppression effectively prevented the recurrence of the disease that is directly dependent on HLA-matching between donor and the recipient (the recurrent diabetes would only occur if there is high HLA matching, such as identical twins or HLA-identical close relatives).

Since HLA matching could theoretically contribute to the emergence of autoimmune processes, it is important to remember that the recipients of full HLA-matched grafts received either a low-dose immunosuppression or no immunosuppression at all. Thus, a direct comparison of the likelihood of recurrent autoimmunity in HLA-matched and HLA-unmatched donor–recipient pairs cannot be performed.

This concept was challenged by E. Bosi et al. who published a study of 23 pancreas Tx recipients (22 simultaneous with kidney) and noted a 2-fold increase of islet cell antibody (ICA) titers in 7 patients [43]. Seven of the 9 ICA-positive patients experienced a graft failure 2–35 months after the ICA detection. Since these patients were HLA mismatched, the above study provided the evidence that the recurrence of ICA may take place in this recipient population as well. Moreover, it should be noted that all patients received three- or four-component immunosuppression.

Other studies have also confirmed the increase in ICA titers and the pancreas allograft function loss in HLA-mismatch recipients. Thus,

immunosuppression does not prevent the recurrence of humoral autoimmune response of the ICA production. R. Santamaria et al. reported an unusual case of a SPK transplant patient who experienced a reenhanced autoimmunity after receiving organs from a living HLA-identical sibling, despite the immunosuppression with azathioprine and prednisone [44]. Worthwhile to note that diabetes recurred 8 years after transplantation.

Another study reported the recurrence of type 1 DM in recipients of deceased SPK Tx, where pancreas allograft biopsies demonstrated a selective destruction of β-cells [45]. In these series, the recipients received a triple immunosuppression therapy. Meanwhile, these patients had diverse cross-match results.

S. Braghi et al. reported results of a retrospective study where they analyzed a cohort of 110 SPK transplant cases and followed 75 of these patients for up to 11.2 years [46]. Pancreas graft survival was not affected by the presence of GAD/IA2 antibodies before the transplant. A total of 59% (n=44) of the patients remained antibody negative at follow-up, 17% (n=13) had stable antibody levels, 17% (n=13) had declining levels and 7% (n=5) had increasing levels. Of the latter five, four lost the allograft function after 0.7–2.3 years of follow-up. No data were available on the presence of autoreactive T cells in these patients, nor on the lesion in the graft investigated by means of pancreatic allograft biopsies. Other investigators reported the presence of type 1 diabetes-associated autoantibodies in SPK Tx recipients.

During 2005-2007, 3 SPK Tx from a living donor were performed at A.A.Shalimov National Institute of Surgery and Transplantology NAMS of Ukraine [47]. The first patient (female) is alive with a functioning graft. The

other two recipients died from severe sepsis on the 50th and 13th postop days.

The first pancreas transplantation in Russia was performed by Academician V. I. Shumakov in 1987. That was a simultaneous pancreas tail and kidney transplant from a deceased donor [48]. Today 3 centers in Russia make pancreas Tx: Boris Petrovsky's Scientific Center of Surgery Russian Academy of Medical Sciences (RSCS), N.V. Sklifosovsky Research Institute for Emergency Medicine, and V.I. Shumakov Federal Research Center of Transplantology and Artificial Organs (FRC). Until June 2012, 32 pancreas Tx were performed in RSCS in the period from 2005 to 2012. In 2006-2007, 6 pancreas Tx were performed in FRC; no further data on transplant outcomes in this Centre have been available. There were 21 pancreas Tx made in N.V. Sklifosovsky Institute from 2008 to 2012 [49].

Pancreatic islet transplantation

Pancreatic islet cell transplantation is likely to be discussed separately. Therefore, here we will briefly summarize this issue.

In 1967, P.Lacy et al. were the first to describe a collagenase-based method for pancreatic islet isolation [50]. The first successful intraportal islet cell Tx resulting in a complete insulin independence was performed in Pittsburgh in 1990 [51]. In 2000, J. Shapiro reported successful intraportal islet cell Tx in 7 patients. No severe hypoglycemia episodes were observed in any of the post-transplant patients. Two to three donor pancreas were required for one islet cell transplantation; the patients received triple immunosuppression. Since then this treatment has been referred to as Edmonton Protocol [52].

The first islet cell Tx for chronic pancreatitis was performed by D.E. Sutherland at the University of Minnesota in 1977. The patient experienced a significant pain-relief in the posttransplant period, but further he required exogenous insulin therapy [53].

As of 2011, autologous islet cell transplantation is performed only in 10 centers of the worldwide, 7 of which are located in USA [54].

After Edmonton Protocol publication, the number pancreatic islet cell Tx increased. In the period of the Protocol implementation to the clinical practice, the results of clinical islet Tx greatly varied among centres. An international multicenter clinical trial was started to evaluate the Edmonton Protocol useful [55]. However, the results were not favourable: a successful pancreatic islet cell isolation was achieved only in 30-50 % even in specialized centers, with 4 to 6 donor pancreas required to obtain insulin independence.

In 2005, long-term results of islet Tx using Edmonton Protocol were reported [56] demonstrating a retained islet cell viability in 80% of recipients. However, less than 10% of the patients remained insulin independent at 5 years of follow-up after islet Tx.

The necessity of multiple donor pancreas using to achieve an insulin independence in islet cell Tx recepients is a limitation of Edmonton Protocol. Yet the authors from the University of Minnesota demonstrated a potential use of a single-donor pancreas for this purpose. Their immunosuppression protocol included antithymocyte globulin (thymoglobulin) [57]. Subsequently, similar results were shown by other authors.

A pancreas islet cell encapsulation strategy gave no positive results, as was shown by a recent meta-analysis. The evolution of this method will likely be the scope of gene engineering technology.

As for autologous pancreas islet cell Tx, this method is becoming more common in the treatment of chronic pancreatitis associated with severe pain. Islet Tx helps to avoid surgical diabetes after pancreatectomy. This method is also useful when pancreatectomy for benign tumors or pancreatic injury performed.

The results of autologous islet Tx are much better than those of islet allotransplantation due to absent immunoreactivity to recipient's native cells and, therefore, no need in immunosuppression, shorter cold and warm ischemia time, a higher number of islet progenitor cells [58].

A recent meta-analysis demonstrated that pancreatectomy followed by autologous islet cell Tx, the insulin independence retained in 46% of patients at 5 years' follow-up, and in 10% at 8 years [59].

According to the recently published report by D.E.Sutherland et al. on a 30-year experience in the autologous islet cell Tx in more than 400 patients (including 53 children aged 5-18 years), the patient survival was 96% in adults and 98% in children at 1 year, 89% and 98%, respectively, at 5 years. Complications requiring relaparotomy occurred in 15.9% of recipients, including bleeding in 9.5%. Islet function (assessed by C-peptide levels over 0.6 ng/mL) was achieved in 90% of patients. At 3 years, 30% of recipients (25% adults and 55% children) were insulin independent; 33% had a partial function [60].

Conclusions

Pancreas Tx is the treatment for DM. SPK Tx from a deceased donor appeared to be optimal. A living pancreas segment Tx isn't suitable for a donor, as well as for recipient; this surgery could be performed for exceptional cases only. Apparently the advances in pancreas Tx will likely be associated with progress in gene engineering.

References

1. Report of task force team for basic statistical study of Korean diabetes mellitus: diabetes in Korea 2007. Task Force Team for Basic Statistical Study of Korean Diabetes Mellitus: Korean Diabetes Association, Health Insurance Review & Assessment Service. Seoul: Goldfishery, 2008.

2. Gruessner A.C., Sutherland D.E. Pancreas transplant outcomes for United States (US) cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR). *Clin. Transpl*. 2008. 45–56.

3. Minkowski O. Weitere Mitteilungen über den Diabetes mellitus nach Extirpation des Pancreas. *Berl. Klin. Wochenschr*. 1892; 29: 90–96.

4. Williams P.W. Notes on diabetes treated with extract and grafts of sheep's pancreas. *Br. Med. J*. 1894; 19: 1303–1304.

5. Kelly W.D., Lillehei R.C., Merkel F.K., et al. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. *Surgery*. 1967; 61 (6): 827–837.

6. Gliedman M.L., Gold M., Whittaker J., et al. Clinical segmental pancreatic transplantation with ureter-pancreatic duct anastomosis for exocrine drainage. *Surgery*. 1973; 74 (2): 171–180.

7. Merkel F.K., Ryan W.G., Armbruster K., et al. Pancreatic transplantation for diabetes mellitus. *IMJ III Med. J.* 1973; 144 (5): 477–479.

8. Sollinger H.W., Kamps D., Cook K., et al. Segmental pancreatic allotransplantation with high-dose cyclosporine and low-dose prednisone. *Transplant. Proc*. 1983; 15 (4) Suppl. 1, 2: 2997-3000.

9. Nghiem D.D., Corry R.J. Technique of simultaneous renal pancreatoduodenal transplantation with urinary drainage of pancreatic secretion. *Am. J. Surg*. 1987; 153 (4): 405–406.

10. Starzl T.E., Iwatsuki S., Shaw B.W., et al. Pancreaticoduodenal transplantation in humans. *Surg. Gynecol. Obstet*. 1984; 159 (4): 265–272.

11. Rosenlof L.K., Earnhardt R.C., Pruett T.L., et al. Pancreas transplantation. An initial experience with systemic and portal drainage of pancreatic allografts. *Ann. Surg.* 1992; 215 (6): 586–595.

12. Gaber A.O., Shokouh-Amiri M.H., Hathaway D.K., et al. Results of pancreas transplantation with portal venous and enteric drainage. *Ann. Surg*. 1995; 221 (6): 613–622.

13. Gruessner R.W., Kandaswamy R., Denny R.J. Laparoscopic simultaneous nephrectomy and distal pancreatectomy from a live donor. *Am. Coll. Surg*. 2001; 193 (3): 333–337.

14. Boggi S., Signori S., Vistoli F., et al. Laparoscopic Robot-Assisted Pancreas Transplantation: First World Experience. *Transplantation*. 2012; 93 (2): 201–206.

15. Nath D.S., Gruessner A.C., Kandaswamy R., et al. Outcomes of pancreas transplants for patients with type 2 diabetes mellitus. *Clin. Transplant*. 2005; 19 (6): 792–797.

16. Gruessner R.W., Sutherland D.E., Troppmann C., et al. The surgical risk of pancreas transplantation in the cyclosporine era: an overview. *J. Am. Coll. Surg*. 1997; 185 (2): 128–144.

17. Takahashi K., Saito K., Takahara S., et al. Excellent long-term outcome of ABO-incompatible living donor kidney transplantation in Japan. *Am. J. Transplant*. 2004; 4 (7): 1089–1096.

18. Barr M.L., Belghiti J., Villamil F.G., et al. A report of the Vancouver forum on the care of live organ donor: lung, liver, pancreas and intestine data and medical guidelines. *Transplantation*. 2006; 81 (10): 1373–1885.

19. Tan M., Kandaswamy R., Sutherland D., Gruessner R.W. Live donor pancreas transplantation. In: Corry R.J., Shapiro R., eds. *Pancreatic Transplantation*. New York: Informa healthcare, 2007. 55 p.

20. Organ Procurement and Transplantation Network. Available at: http://optn.transplant.hrsa.gov/latestData/rptData.asp

21. Boggi U., Amorese G., Marchetti P., Mosca F. Segmental live donor pancreas transplantation: review and critique of rationale, outcomes, and current recommendations. *Clin. Transplant*. 2011; 25 (1): 4–12.

22. Matsumoto S., Okitsu T., Iwanaga Y., et al. Insulin independence after living-donor distal pancreatectomy and islet allotransplantation. *Lancet*. 2005; 365: 1642.

23 Gruessner R.W., Sutherland D.E., Gruessner A.C. Mortality assessment for pancreas transplants. *Am. J. Transplant*. 2004; 4 (12): 2018–2026.

24. Poommipanit N., Sampaio M.S., Cho Y., et al. Pancreas after living donor kidney versus simultaneous pancreas-kidney transplant: an

analysis of the organ procurement transplant network/united network of organ sharing database. *Transplantation*. 2010; 89 (12): 1496–1503.

25. Sollinger H.W., Sasaki T.M., D'Alessandro A.M., et al. Indications for enteric conversion after pancreas transplantation with bladder drainage. *Surgery*. 1992; 112 (4): 842–845.

26. Stratta R.J., Gaber A.O., Shokouh-Amiri M.H., et al. A prospective comparison of systemic-bladder versus portal-enteric drainage in vascularized pancreas transplantation. *Surgery*. 2000; 127 (2): 217–226.

27. Katz H., Homan M., Velosa J., et al. Effects of pancreas transplantation on postprandial glucose metabolism. *N. Engl. J. Med*. 1991; 325 (18): 1278–1283.

28. Troppmann C., Gruessner A.C., Benedetti E., et al. Vascular graft thrombosis after pancreatic transplantation: univariate and multivariate operative and nonoperative risk factor analysis. *J. Am. Coll. Surg*. 1996; 182 (4): 285–316.

29. Rostambeigi N., Kudva Y.C., John S., et al. Epidemiology of infections requiring hospitalization during long-term follow-up of pancreas transplantation. *Transplantation*. 2010; 89 (9): 1126–1133.

30. Yan S., Ding Y., Sun F., et al. Pretreatment of Cisplatin in Recipients Attenuates Post-Transplantation Pancreatitis in Murine Model. *Int. J. Biol. Sci*. 2012; 8 (3): 298–309.

31. Han D.J., Sutherland D.E. Pancreas Transplantation. *Gut Liver*. 2010; 4 (4): 450–465.

32. McCullough K.P., Keith D.S., Meyer K.H., et al. Kidney and pancreas transplantation in the United States, 1998-2007: access for patients with diabetes and end-stage renal disease. *Am. J. Transplant*. 2009; 9 (4 Pt. 2): 894-906.

33. Sampaio M.S., Poommipanit N., Cho Y.W., et al. Transplantation with pancreas after living donor kidney vs. living donor kidney alone in type 1 diabetes mellitus recipients. *Clin Transplant*. 2010; 24 (6): 812–820.

34. Schenker P., Vonend O., Krüger B., et al. Long-term results of pancreas transplantation in patients older than 50 years. *Transpl. Int*. 2011; 24 (2): 136–142.

35. Sutherland D.E., Najarian J.S., Gruessner R. Living versus cadaver donor pancreas transplants. *Transplant. Proc*. 1998; 30 (5): 2264–2266.

36. Venstrom J.M., McBride M.A., Rother K.I., et al. Survival after pancreas transplantation in patients with diabetes and preserved kidney function. *JAMA*. 2003; 290 (21): 2817–2823.

37. Tyden G., Bolinder J., Solders G., et al. Improved survival in patients with insulin-dependent diabetes mellitus and end-stage diabetic nephropathy 10 years after combined pancreas and kidney transplantation. *Transplantation*. 1999; 67 (5): 645–648.

38. Rayhill S.C., D'Alessandro A.M., Odorico J.S., et al. Simultaneous pancreas-kidney transplantation and living related donor renal transplantation in patients with diabetes: is there a diff erence in survival? *Ann. Surg*. 2000; 231 (3): 417–423.

39. Ojo A.O., Meier-Kriesche H.U., Hanson J.A., et al. The impact of simultaneous pancreas-kidney transplantation on long-term patient survival. *Transplantation*. 2001; 71 (1): 82–90.

40. Bunnapradist S., Gritsch H.A., Peng A., et al. Dual kidneys from marginal adult donors as a source for cadaveric renal transplantation in the United States. J. *Am. Soc. Nephrol.* 2003; 14 (4): 1031–1036.

41. Gruessner R.W., Sutherland D.E., Gruessner A.C. Survival after pancreas transplantation. *JAMA*. 2005; 293 (6): 675–676.

42. Sutherland D.E., Sibley R., Xu X.Z., et al. Twin-to-twin pancreas transplantation: reversal and reenactment of the pathogenesis of Type I diabetes. *Trans. Assoc. Am. Physicians*. 1984; 97: 80–87.

43. Bosi E., Bottazzo G.F., Secchi A., et al. Islet cell autoimmunity in Type I diabetic patients after HLAmismatched pancreas transplantation. *Diabetes*. 1989; 38 Suppl. 1: 82–84.

44. Santamaria P., Nakhleh R.E., Sutherland D.E., Barbosa J.J. Characterization of T lymphocytes infiltrating human pancreas allograft affected by isletitis and recurrent diabetes. *Diabetes*. 1992; 41 (1): 53–61.

45. Tyden G., Reinholt F.P., Sundkvist G., Bolinder J. Recurrence of autoimmune diabetes mellitus in recipients of cadaveric pancreatic grafts. *N. Engl. J. Med*. 1996; 335 (12): 860–863.

46. Braghi S., Bonifacio E., Secchi A., et al. Modulation of humoral islet autoimmunity by pancreas allotransplantation influences allograft outcome in patients with Type 1 diabetes. *Diabetes*. 2000; 49 (2): 218–224.

47. Saenko V.F., Kotenko O.G., Skums A.V. Simul'tannaya transplantatsiya podzheludochnoy zhelezy i pochki ot zhivogo rodstvennogo donora. [Simultaneous transplantation of pancreas and kidney from a living related donor]. *Klinichna khirurgiya*. 2005; 11/12: 97. (In Russian).

48. Shumakov V.I., Ignatenko S.N., Petrov G.N., et al. Transplantatsiya pochki i podzheludochnoy zhelezy bol'nym insulinozavisimym sakharnym diabetom. [Kidney transplantation and pancreatic cancer patients with insulin-dependent diabetes mellitus]. *Khirurgiya*. 1991; 7: 3–8. (In Russian).

49. Kaabak M.M., Zokoev A.K., Babenko N.N. Kombinirovannaya transplantatsiya pankreatoduodenal'nogo kompleksa i pochki. [Combined transplantation pancreatoduodenal complex and kidneys]. *Khirurgiya*. 2013; 2: 109–118. (In Russian).

50. Lacy P., Kostianovsky M. Method for the isolation of intact islets of Langerhans from the rat pancreas. *Diabetes*. 1967; 16 (1): 35–39.

51. Tzakis A.G., Ricordi C., Alejandro R., et al. Pancreatic islet transplantation after upper abdominal exenteration and liver replacement. *Lancet*. 1990; 336 (8712): 402–405.

52. Shapiro A.M., Lakey J.R., Ryan E.A., et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-freeimmunosuppressive regimen. *N. Engl. J. Med*. 2000; 343 (4): 230–238.

53. Sutherland D.E, Matas A.J., Najarian J.S. Pancreatic islet cell transplantation. *Surg. Clin. North. Am*. 1978; 58 (2): 365–382.

54. Matsumoto S. Clinical allogeneic and autologous islet cell transplantation: update. *Diabetes Metab J*. 2011; 35 (3): 199–206.

55. Shapiro A.M., Ricordi C., Hering B.J., et al. International trial of the Edmonton protocol for islet transplantation. *N. Engl. J. Med*. 2006; 355 (13): 1318–1330.

56. Ryan E.A., Paty B.W., Senior P.A., et al. Five-year follow-up after clinical islet transplantation. *Diabetes.* 2005; 54 (7): 2060–2069.

57. Hering B.J., Kandaswamy R., Ansite J.D., et al. Single-donor, marginal-dose islet transplantation in patients with type 1 diabetes. *JAMA*. 2005; 293 (7): 830–835.

58. Matsumoto S. Autologous islet cell transplantation to prevent surgical diabetes. *J. Diabetes*. 2011; 3 (4): 328–336.

59. Bramis K., Gordon-Weeks A.N., Friend P.J., et al. Systematic review of total pancreatectomy and islet autotransplantation for chronic pancreatitis. *Br. J. Surg*. 2012; 99 (6): 761–766.

60. Sutherland D.E., Radosevich D.M., Bellin M.D., et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J. Am. Coll. Surg*. 2012; 214 (4): 409–424.