Global Health & Medicine. 2020; 2(6):360-366.

MINI-REVIEW

DOI: 10.35772/ghm.2020.01069

Pancreas transplantation for type 1 diabetes in Japan: past, present and future prospects

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Abstract: In Japan, the first pancreas transplantation was performed in 1984 from a brain-dead donor; subsequently, however, the concept of brain death became a social issue. Thereafter, the "Organ Transplant Act", which enables brain-dead transplantation, was enacted in 1997, and then revised in 2010 so that donation after brain death became possible only with the consent of the family. Under the recipient selection and registration system developed after the enactment of the "Organ Transplant Act", more than 400 pancreas transplants have been carried out at facilities certified for brain-dead pancreas transplantation in Japan. Of the 410 total cadaveric pancreas transplants performed by the end of 2019, the patient survival and pancreatic and kidney graft survival rates were considered to be comparable to those in the United States and Europe despite the high frequency of marginal donors. Minimally invasive allogenic islet transplantation came to be covered by national health insurance in 2020 following good outcomes of a recent trial. Furthermore, to overcome the serious donor shortage in Japan, development of xenogeneic islet transplantation and regenerative medicine using stem cells is in progress, with xenotransplantation using porcine islets appearing particularly promising.

***Keywords*:** pancreas transplantation, simultaneous pancreas and kidney transplantation (SPK), pancreas after kidney transplantation (PAK), pancreas transplantation alone (PTA), islet transplantation, xenotransplantation

Introduction

Insulin-depleted patients with type 1 diabetes (T1D), even those receiving intensive insulin therapy, such as multiple daily injections (MDI) and insulin pump (continuous subcutaneous insulin infusion [CSII]), suffer from severe glycemic lability, which frequently causes life-threatening severe hypoglycemia and diabetic ketoacidosis. In addition, these conditions often force patients to undergo emergency transport or hospitalization, resulting in poor quality of life (QOL). Furthermore, complications of diabetes also progress, and renal failure often leads to dialysis treatment. Such patients are candidates for transplantation medicine, and pancreas transplantation or pancreatic islet transplantation is thus considered.

Pancreas transplantation is divided into the following three categories: simultaneous pancreas and kidney transplantation (SPK), pancreas transplantation after kidney transplantation (PAK), and pancreas transplantation alone (PTA). Among these categories, SPK not only improves the QOL due to blood glucose stabilization and insulin withdrawal, but also substantially improves the life prognosis; consequently, more than 80% of Japanese pancreas transplants have been performed as SPK. Allogenic islet transplantation, which is minimally invasive, recently came to be covered by the national health insurance system in Japan based on positive results of a clinical trial.

We herein review the history, current status, and challenges of pancreas transplantation, as well as discuss future prospects concerning diabetes transplantation medicine in Japan.

Brief history of pancreas transplantation in Japan

Since the first pancreas transplant was performed at the University of Minnesota in 1966, more than 50,000 pancreas transplantations have been performed worldwide so far (*1*). In Japan, although the first pancreas transplant was performed in 1984 from a brain-dead donor, the concept of brain death subsequently

became a social issue, and thereafter 14 cases of pancreas transplants were performed using circulatory-death donors. With the introduction of the "Organ Transplant Act", which enables brain-dead transplantation, in October 1997, the Central Coordination Committee of Pancreas Transplantation and the sub-committees were organized in Japan. These organizations comprised three Japanese medical associations: the Japanese societies for Diabetology (the Japan Diabetes Society), Nephrology (the Japanese Society of Nephrology) and Transplantation (the Japan Society for Transplantation and the Japan Society for Pancreas and Islet Transplantation).

These committees operate under the following two policies: participation in an Expert Medical Board of two diabetologists and two nephrologists, set up in the seven local regions of Japan, whose mission was to evaluate pancreas transplantation candidates; and participation in an Expert Surgeon Board, composed of experienced transplantation surgeons, an expert on immunosuppressive therapy, a diabetologist and a nephrologist.

In 2010, to increase the number of brain-dead donors, the "Revised Organ Transplant Act" was enacted, wherein donation after brain death is possible with only consent of the family. Subsequently, a roughly 5-fold increase in the number of brain-dead donors was noted and around 30-40 cases of pancreas transplantation were performed annually (*2*). By the end of 2019, more than 400 pancreas transplants have been carried out at facilities certified for brain-dead pancreas transplantation (currently 18 facilities) since introduction of the "Organ Transplant Act".

Indication and registration system in Japan

Considering the risk of long-term immunosuppression-related adverse events, surgical risk and donor shortage, it has been reported that the traditional indications of pancreas transplantation include T1D patients with end-stage renal failure or nonuremic patients with glycemic lability experiencing problematic hypoglycemia such as severe hypoglycemia (SH) and impaired awareness of hypoglycemia (IAH), despite optimal diabetes management. Correspondingly, in Japan, T1D with renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73m^2) is an indication for SPK or PAK; the former has been offered mostly to patients on dialysis therapy and the latter to those who already underwent kidney transplantation and were taking immunosuppressive therapy. In contrast, T1D with severe glycemic lability despite optimal treatment by a diabetologist certified by the Japan Diabetes Society is an indication for PTA. Glycemic lability is evaluated by continuous glucose monitoring (CGM) data as well as self-monitoring of blood glucose values and the incidence of problematic hypoglycemia. Furthermore, in Japan, mainly because of extreme donor shortage, type 2 diabetes (T2D) is never considered an indication for transplant, and patients must be in an insulin-depleted status, defined by a serum C-peptide level ≤ 0.3 ng/mL while fasting and ≤ 0.5 ng/mL when glucagon (or meal)-stimulated (when renal failure is present, ≤ 0.3 ng/mL change in stimulated C-peptide levels from fasting) based on the data of fulminant T1D patients (FT1D). FT1D, originally identified in Japan, is an independent T1D subtype showing a markedly rapid onset of hyperglycemia with ketoacidosis and absence of insulin secretion capacity, even at disease onset (*3*). In practice, however, patients who meet these criteria may be excluded if they have a history of malignant disease, progressive proliferative retinopathy, or a condition that may be aggravated by surgery; of note, while there is no contraindication regarding age, ≤ 60 years old is desirable.

After examination by the Expert Medical Board set up in seven local regions of Japan, all recipient candidates are registered with the Japan Organ Transplant Network (JOTN), and recipient selection is performed based on the following conditions: blood type must be compatible, and the direct crossmatch test must be negative. Recipients on the waiting list are prioritized for selection as follows: *i*) the order of the recipients is arranged based on the number of human leukocyte antigen (HLA) mismatches, with priority given to cases involving fewer HLA mismatches; *ii*) cases are then prioritized in the order of SPK, PAK, and PTA; *iii*) priority is then given according to the length of the waiting period duration; and *iv*) cases are then prioritized in ascending order according to the estimated transport time, with priority given to cases with a shorter estimated transport time (*4*).

Results of pancreas transplantation in Japan

Numbers of pancreas transplantation

The Japan Society for Pancreas and Islet Transplantation has been registering all pancreas transplant cases in Japan since 2006 with the aim of improving pancreas transplant results in Japan. Of the 437 patients who underwent pancreas transplantation by the end of December 2019 since the first case in April 2000 after the introduction of the "Organ Transplant Act", the 410 cadaveric pancreas transplants (407 under brain-death and 3 under circulatory-death) included 344 SPK (83.9%), 48 PAK (11.7%) and 18 PTA cases (4.4%). The remaining 27 cases were living pancreas transplants, which have not been performed since 2014 (Figure 1). The donors' and recipients' background characteristics, immunosuppressive regimen, and outcomes of the above 410 cases of cadaveric pancreas transplantation (*2*) are described as follows.

Donors' background characteristics

The male to female ratio was 234:176, and the median body mass index (BMI) was 21.8 kg/m^2. The median donor age was 43 years old. Figure 2A shows the distribution of the donor age: the majority were in their 40s (27.8%), followed by 50s (22.0%) and 30s (18.3%), and donors ≥ 40 years old accounted for 56.3%. Among the 410 cases, 208 (50.7%) had brain death caused by cerebrovascular accidents, and 190 (46.3%) had episodes of cardiopulmonary arrest during the course. A total of 201 cases (49.0%) were hemodynamically unstable at the time of procurement. The median HbA1c of donors was 5.4%. The total cardiac arrest time was 36 min (range: 2-282). As a result, 291 donors (71.0%) exceeded the Pittsburgh's marginal donor criteria defined as they were *i*) > 45 years of age; *ii*) hemodynamically unstable requiring high dose dopamine (> 10 mg/kg/min) or more than 2 vasopressors; or *iii*) non-heart-beating donors (*5*).

Recipients' background characteristics

The male to female ratio was 161:249, and the median BMI was 20.9 kg/m^2. The median recipient age at transplantation was 44 years old (range: 24-69). Figure 2B shows distribution of recipient age: the majority were in their 40s (46.3%), followed by 30s (26.3%) and 50s (22.0%), and 16 recipients were in their 60s (3.9%). The median pre-operative duration of diabetes was 28 years (range: 2-53), and the median pre-operative dialysis period in SPK patients was 7 years (range: 0-29). The median waiting period was 1,395 days (range: 6-5,740). The median HbA1c level at transplantation was 7.6% (range: 4.8-15.2).

Immunosuppressive regimen

In Japan, tacrolimus (TAC)-based immunosuppression,

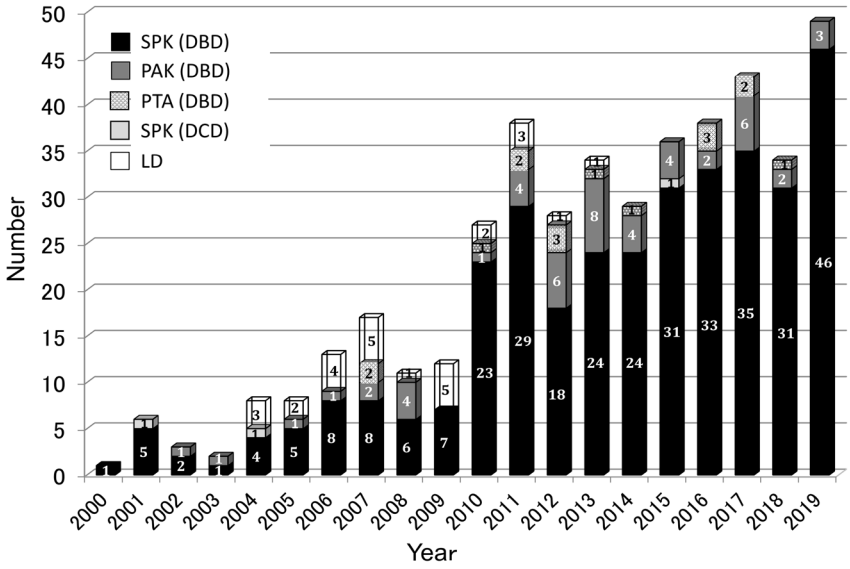

Figure 1. The number of pancreas transplant cases from April 2000 to December 2019 in Japan (*n* = 437) (*2*). DBD, donation after brain-death; DCD, donation after circulatory-death; LD, living donation; PAK, pancreas transplantation after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation.

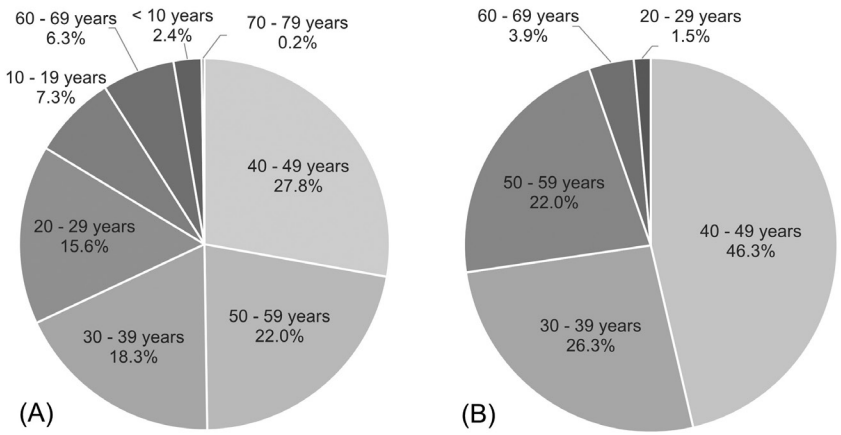

Figure 2. Distribution of the donor age (A) and the recipient age (B) (*n* = 410) (*2*).

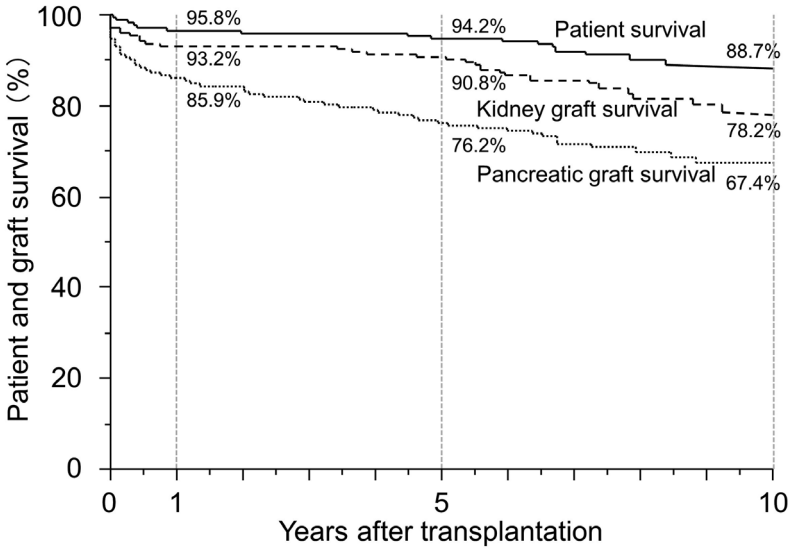

Figure 3. The patient and graft survival after transplantation in Japan (*2*).

in combination with steroids, mycophenolate mofetil (MMF), and anti-IL-2R antibody (basiliximab) was the most frequent regimen, and has been used in 293 cases (71.5%). However, recently, instead of anti-IL-2R antibody, antithymocyte globulin (ATG) has been used in 85 cases (20.7%), and both anti-IL-2R antibody and ATG were used in 6 cases (1.5%). In contrast, a cyclosporine-based combination regimen was only used in 5 cases (1.2%).

The patient survival and pancreas and kidney graft survival

The patient survival and pancreatic and kidney graft survival rates are shown in Figure 3 (pancreatic graft loss was defined as a C-peptide level < 0.3 ng/mL and kidney graft loss as dialysis reintroduction). The patient survival rates at 1, 5, and 10 years after transplantation were 95.8%, 94.2%, and 88.7%, respectively. In addition, the survival rates of pancreas and kidney grafts at 1, 5, and 10 years were 85.9%, 76.2%, and 67.4%, and 93.2%, 90.8%, and 78.2%, respectively. These outcomes were comparable to those observed in other countries (*6*) despite the high frequency of marginal donors as described above. In addition, Ito *et al.* recently reported that the outcomes of pancreas transplantation from ≥ 50-year-old donors were comparable to those from younger donors in their study of 361 cadaveric pancreas transplants in Japan by the end of December 2018 (*4*).

Early and delayed complications of pancreas transplantation

The graft survival rate of pancreata was lower than that of kidneys in every period. Critically, the transplanted pancreas is often abolished early after transplantation. The causes of transplanted pancreas loss were graft thrombosis in 19 cases (5.5%) and patient death in 22 cases (6.4%) among 344 SPK patients; and rejection reaction in 18 cases (27.3%), graft thrombosis in 5 cases (7.6%) among 66 cases of PAK or PTA patients. Since the pancreas is known to be prone to intravascular thrombosis, the high proportion of graft thrombosis may be due in part to the frequent usage of marginal donors. The high frequency of rejection reactions in PAK or PTA may be due to the fact that rejection cannot be monitored by changes in renal function and/or that the current rule does not consider HLA matching in PAK or PTA recipient selection (in SPK, at least one match of HLA-DR is a prerequisite) (*7*). Countermeasures against thrombosis and further improvement in immunosuppressive therapy are therefore imperative. Abolition of the transplanted pancreas due to recurrence of T1D was also observed in 6 (1.5%) of 410 deceased pancreas transplantation patients, another issue that remains to be resolved.

Future Prospects

The comparison with allogenic islet transplantation and allocation of donor pancreata

In Japan, pancreas transplantation has been covered by the national health insurance system under the "Revised Organ Transplant Act", whereas allogenic islet transplantation was recently covered by the national health insurance system, under the "Act on the Safety of Regenerative Medicine". Pancreas transplantation requires major surgery with relatively frequent complications. In contrast, islet transplantation is a minimally invasive procedure involving infusion

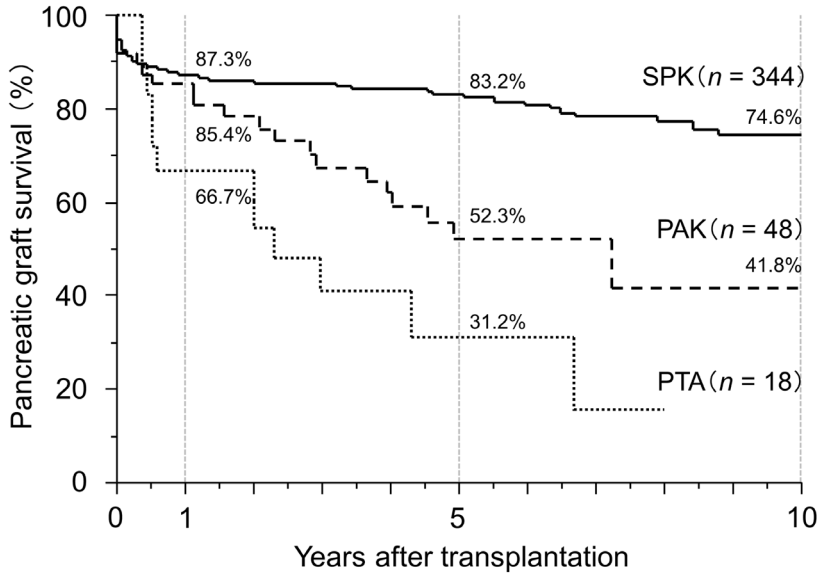

Figure 4. A comparison of the pancreatic graft survival in SPK, PAK and PTA (*2*). PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation.

of purified islets *via* the hepatic portal vein with local anesthesia only, although two or more donor organs are usually required to achieve comparable metabolic results to those of pancreas transplantation. Although the number of brain-dead donors has increased, the donor pool remains very small in Japan. With the start of insurance coverage for islet transplantation, the allocation of donor pancreata to pancreas transplantation versus islet transplantation will become an important issue. So far, brain-dead donor pancreata have been used in preference to pancreas transplantation, but the utilization of pancreata for transplantation is approximately 60%, a lower proportion than that of other organs, and this value is decreasing annually (*8*), probably because pancreas transplants from poorly conditioned donors tend to be avoided. An even stronger trend was reported in the United States (*9*). However, a significant percentage of the pancreata that are not used, for reasons such as old age, obesity and a long cardiopulmonary arrest time, may be useful for islet transplantation.

In patients with end-stage renal failure who are indicated for kidney transplantation, since the benefits of SPK are extremely good, pancreas transplantation should be prioritized over islet transplantation. However, in cases of T1D without renal failure or T1D after kidney transplantation, since the long-term pancreas graft survival rate of PAK and PTA is substantially poorer than that of SPK at present (Figure 4) (*2*), islet transplantation may be considered as the first choice, given the degree of invasiveness and safety. Of note, with regard to PAK, it was reported that immunosuppressive therapy using ATG resulted in a lower incidence of complicated graft rejection and better pancreatic graft survival than not using ATG in 39 cases of PAK in Japan (*10*). Further clinical assessment will be necessary to ensure the proper allocation of donor pancreata.

Alternative approaches

To overcome the shortage of available human pancreata, there have been considerable efforts seeking alternative islets sources, such as xenogeneic islets, human embryonic stem cells (hESCs), and induced pluripotent stem cells (iPSCs). Among them, porcine islets are considered the most advanced and promising sources of islets for transplantation based on the long history of clinical trials and accumulated safety and efficacy data, while hESCs-derived β cells have only limited clinical data, and no clinical data are available regarding iPSCs-derived β cell transplantation (*11,12*).

Although porcine islet xenotransplantation for humans has been reported to be less effective than allogeneic islet transplantation (*12*), that has the advantage of providing an unlimited supply of fresh, uniformly quality-controlled islets from medical-grade pigs. Furthermore, porcine insulin differs from human insulin in only a single amino acid residue and was used to treat diabetes in humans for many years before the start of human insulin treatment from the 1980s. Consequently its efficacy and safety are well established. To prevent a xenogeneic immune reaction and instant blood-mediated inflammatory reaction (IBMIR), which also occurs in cases of allotransplantation, without the need for exogenous immunosuppressive therapy, micro- or macro-immune isolation devices are being developed (*9,13*). Indeed, trials of alginate microencapsulated porcine islets (DIABECELL), dubbed "bioartificial islets", are now ongoing.

Conclusion

Insulin pumps and CGM devices are being developed as advanced medical devices for T1D and are gradually becoming popular in Japan. However, given the lag time of both the exogenous insulin effect and the subcutaneous measurement of glucose concentration, it is still an insufficient replacement for pancreatic β-cell function (*9,14*). The superior efficacy of pancreas or islet transplantation is evident with respect to not only the normalization of the blood glucose lability but also IAH and SH avoidance.

In Japan, starting in 2020, allogenic islet transplantation is now covered by the national health insurance system in addition to pancreas transplantation. The continued development of Japanese transplantation medicine, which now enters a new stage 10 years after the introduction of the "Revised Organ Transplant Act", is expected. However, donor shortages remain a serious issue, and only a limited number of patients have been able to benefit from transplantation medicine. As next-generation transplantation medicine, the development of xenogeneic islet transplantation and regenerative medicine using human stem cells (*e.g.* hESCs and iPSCs) has been advancing. In particular, transplantation of "bioartificial islets" using porcine islets appears promising, and clinical translation is expected in the near future.

Acknowledgements

We thank the members of the islet cell transplantation project at the Diabetes Research Center, Research Institute of National Center for Global Health and Medicine. We also thank Dr. Masaaki Watanabe and Dr. Yasuyuki Koshizuka (Hokkaido University Hospital), Dr. Shigehito Miyagi and Dr. Kazuaki Tokodai (Tohoku University Hospital), Dr. Akira Kenjo and Dr. Ryo Okada (Fukushima Medical University Hospital), Dr. Keiichi Kubota and Dr. Yukihiro Iso (Dokkyo Medical University Hospital), Dr. Hiroto Egawa and Dr. Yoshihito Kotera (Tokyo Women's Medical University Hospital), Dr. Shigeyuki Kawachi and Dr. Hitoshi Iwamoto (Tokyo Medical University Hachioji Medical Center), Dr. Toshifumi Wakai and Dr. Takashi Kobayashi (Niigata University Hospital), Dr. Shunji Narumi and Dr. Takahisa Hiramitsu (Nagoya Daini Red Cross Hospital), Dr. Taihei Ito (Fujita Health University Hospital), Dr. Hidetaka Ushigome and Dr. Shuji Nobori (Kyoto Prefectural University Hospital), Dr. Hideaki Okajima and Dr. Takayuki Anazawa (Kyoto University Hospital), Dr. Hirochika Toyama and Dr. Sachio Terai (Kobe University Hospital), Dr. Hideki Ohdan and Dr. Hiroyuki Tahara (Hiroshima University Hospital), Dr. Keiichi Okano and Dr. Minoru Oshima (Kagawa University Hospital), Dr. Keizo Kaku and Dr. Yasuhiro Okabe (Kyushu University Hospital), Dr. Shinichiro Ono and Dr. Tomohiko Adachi (Nagasaki University Hospital), and Dr. Yoshifumi Bekku and Dr. Akira Maki (Saitama Medical Center, Saitama Medical University) for their cooperation with the registry of Japanese pancreas transplantation.

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Received August 6, 2020; Revised September 7, 2020; Accepted September 9, 2020

Released online in J-STAGE as advance publication September 18, 2020.

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