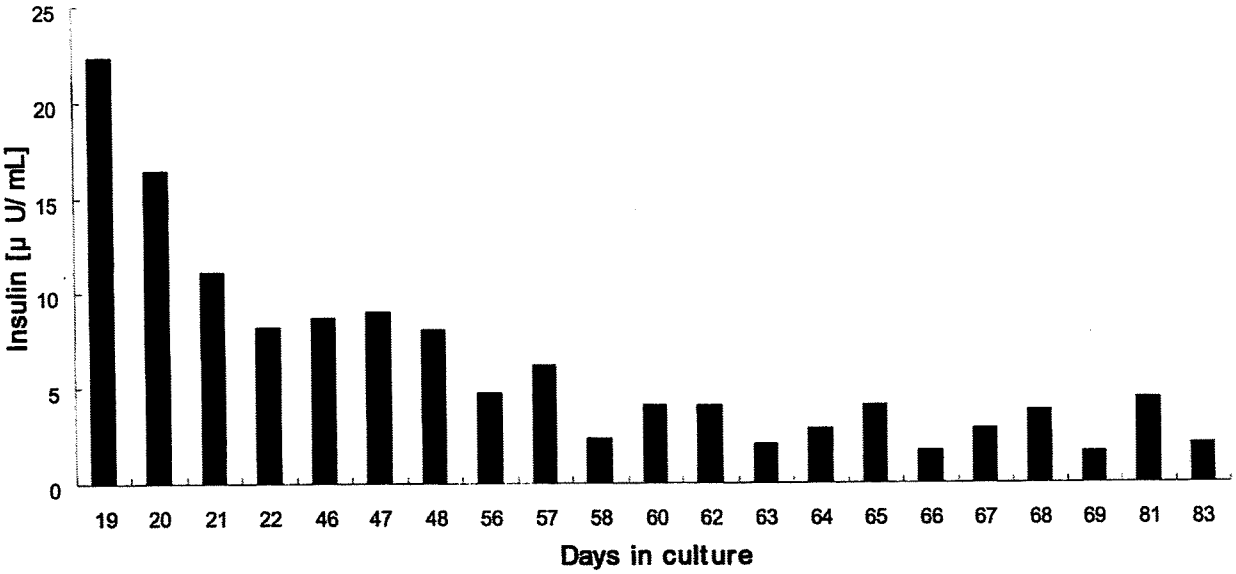

Figure 4. Insulin accumulation in the mixed culture medium of CSI-BAP over 83 days. The insulin concentration showed a tendency to decrease, but the decline was mild. Islets in the CSI-BAP were capable of secreting insulin throughout the observation period, indicating that insulin was released from the islets in CSI-BAP in diffusion manner.

implanted islet cells in islet transplantation. These drugs have serious side effects, including myelosuppression, nephrotoxicity, increased risk of infection, and increased risk of development of certain malignant diseases (e.g., lymphomas) (19). Furthermore, studies indicate that the function of islet cells may deteriorate because these treatments are directly toxic to beta cells (26).

If the donor islets can be fabricates covered with the recipient's tissue, the transplanted islets may not be recognized as nonself. This concept is called immunodelusion, namely the concept of recognizing tissue as if it is the recipient's own tissue. Although immunodelusive bioartificial pancreas (BAP) belongs in the category of immunisolated BAP, it is a new concept of BAP. The CSI-BAP in the present study is different from the conventional BAP because of the use of the chondrocytes (recipient cells) instead of artificial materials. Although both devices allow the passage of smaller molecules by means of diffusion, this CSI-BAP is recognized as self by the host immune cells, and prevents the penetration of immunocytes.

Table 1. Insulin Secretion Into the Mixed Culture Medium Over 24 h Measured by a Microparticle Enzyme Immunoassay

Days in Culture	Insulin Secreation (μU/ml)	Rate of 100% Conversion
10	279.7	100.0%
11	185.7	66.4%
12	141.2	50.5%
13	98.1	35.1%
14	74.1	26.5%
15	77.1	27.6%
16	59.9	21.4%

Insulin release of CSI-BAP on day 16 markedly decreased to 21.4% of the insulin secretion level of day 10, which was the starting day of the measurements.

In order to create the immunodelusive BAP, a cell sheet engineering technique (9,29,30) is utilized in this study. With this technology, the cell sheets are prepared using temperature-responsive polymer (PIPAAm) pattern-grafted dishes. Temperature-responsive polymers are covalently grafted onto the dishes, allowing various types of cells to adhere and proliferate at 37°C. The cells spontaneously detach from the plate when the temperature decreases to below 32°C without the need for proteolytic enzymes. The confluent cells are noninvasively harvested as contiguous cell sheets with intact cell–cell junctions and deposited ECM. Because the ECM associated with the basal side of the cell sheets shows adhesion, the harvested cell sheets can be stratified to reconstruct thicker or more complex tissue architectures. Using this cell sheet engineering, it is possible to manufacture the totally different concept of chondrocytes sheeting immunodelusive immunoisolated bioartificial pancreas.

Cartilage tissue, which lacks blood vessels, lymphatic

tissue, and nerves, exchanges nutrients (e.g., glucose and amino acids) and waste as well as gas (e.g., O_2 and CO_2) by diffusion. Therefore, it is impossible for leukocytes to invade normal cartilage (6). Chondrocytes in cartilage are surrounded with ECM, which is produced by the chondrocyte itself. Moreover, because an auricular cartilage is an elastic cartilage, it is easily collected from the patient. In addition, deformation of the ear after the excision of the auricular cartilage is rarely observed (12) in clinical plastic surgery field. Therefore, the collection of auricular cartilage as the source of immunoisolation material is acceptable for clinical application cosmetically. In addition, the chondrocytes can vastly expand and a sufficient number of cells can be obtained by continuous culture. Moreover, it was found that cell yield per gram of an ear cartilage is twice that of an articular cartilage (27), and chondrocytes of ear cartilage proliferated faster than articular cartilage. Although, articular cartilage has been frequently used for cartilage tissue engineering research, ear cartilage was used in this study because it is easy to harvest with less donor site morbidity (27). These results demonstrate that elastic cartilage can be used as a perfect and versatile membrane for immunoisolation, if the chondrocytes can be harvested as a shape of membrane and cover the graft cells perfectly.

There was only one previous study that used living cells for encapsulation of islets (17). This study used articular chondrocytes and polyglycolic acid polymer. They harvested chondrocyte membranes physically with a cell scraper when the chondrocyte culture reached confluency, which may weaken the membrane itself and its ECM. They observed that some of the single layered chondrocyte capsules were imperfect and were damaged by penetrating polymer fibers, which may cause host immune attack. The macroncapsulated materials used in their study were not simply living cells from recipients, because they utilized artificial polymer with the recipient cells.

In the current study, the CSI-BAP was developed by using cell sheet engineering to create a multilayer chondrocyte membrane, and its long-term function was evaluated. Histological analysis indicated that islets within the CSI-BAP produced insulin and were completely encapsulated with the chondrocyte sheets. It is possible that the reduction of insulin secretion was due to contamination of the exocrine cells in an early stage after the CSI-BAP was manufactured. Proteolytic enzymes released from the contaminated exocrine cells may impair the islet structure and/or chondrocytes of the CSI-BAP and diminish the endocrine function of CSI-BAP.

The major advantage of this CSI-BAP may be the interaction of the islets and the chondrocytes. The chondrocytes protect the pancreatic islets by providing ECM and avoiding disaggregation, which diminishes its function. This may provide an environment similar for the islets in the pancreas before isolation. In the normal pancreas, a complex network of collagen, proteoglycans (e.g., glycosaminoglycans, glycoproteins), and elastin (28) is present, which is very similar to auricular cartilage. Insulin released from the islets directly acts on chondrocytes as a growth factor. The importance of the ECM for islet function was confirmed in a previous study (3,8,14). It was found that the islets did not survive more than 14 days in the standard culture media (11). By contrast, when overlaid with collagen, monolayers of human islet cells underwent a gradual and complete reorganization into a three-dimensional islet-like structure with striking reinforcement of their secretory activity (11). It is thought that the islets in a CSI-BAP were capable of secreting insulin for a prolonged period compared to the standard culture conditions.

The application of CSI-BAP technology to other endocrine cells, such as parathyroid tissue and thyroid tissue, is also possible. Furthermore, genetically engineered cells that provide a source of erythropoietin, dopamine, or human growth factor, and the creation of an artificial liver using hepatocytes covered with chondrocytes sheets are being considered.

This study is the first report of a CSI-BAP, and there are several factors that require further investigation. The optimal number of layers of chondrocyte sheets must be determined. It is possible to layer the chondrocyte sheets to more than 10 sheets, because of extremely low metabolism of chondrocytes (data not shown). And an evaluation of an immunoisolation test of CSI-BAP both in vivo and in vitro should be performed in the near future. Furthermore, the optimal transplant site is a major issue. Because the CSI-BAP is extremely thin, the surface of the liver, the surface of the pancreas, or the surface of the abdominal wall are therefore all considered to be possible transplant sites.

The results of this study may therefore lead to a new strategies of allo- and xenotransplantion without using immunosuppressive drugs in islet transplantation.

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Clinical islet transplantation in Japan

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Abstract
Introduction The results of clinical islet transplantation in Japan are, here in, reported and discussed its efficacy and problems.
Methods Since the first islet transplantation was performed in 2004, 65 islet isolations and 34 islet transplantations to 18 type 1 diabetic patients have been performed in Japan.
Results Following islet transplantation, patients experienced decreased insulin requirements and lower hemoglobin A1C levels, and positive serum C-peptide levels. All patients achieved stabilized blood glucose levels and the disappearance of hypoglycemic unawareness. Although three patients achieved insulin independency for a limited period, persistent islet graft function was difficult to maintain. Overall islet graft survival was 86.5% at 6 months, 78.7% at 1 year, and 62.9% at 2 years after the first islet transplantation. In our institution, we carried out 23 islet isolations and six islet transplantations to four patients. Although insulin independency was not achieved, all patients showed a disappearance of hypoglycemic unawareness.
Conclusions Using data from the Japanese Trial of Islet Transplantation, the effectiveness of islet transplantation was shown even when using the pancreata from non-heart-beating donors. Although there are a number of problems to be solved and further improvement is needed, we can state that the introduction of clinical islet transplantation offers hope for type 1 diabetic patients.

Keywords Clinical islet transplantation · Complication · Human islets · Islet isolation · Long-term graft survival

Introduction

Pancreatic islet transplantation has the potential to become the most physiologically advantageous and minimally invasive procedure for the treatment of type 1 diabetes mellitus. Since the first clinical islet transplantation was performed at the University of Minnesota in 1974 [1], results have been far from ideal, despite an improvement in the islet isolation technique introduced by Ricordi et al. [2–4]. The introduction of the Edmonton Protocol, which is associated with a highly improved rate of insulin independency, encouraged us to promote clinical islet transplantation [5, 6]. In 1997, we organized a Working Group under the Japanese Society for Pancreas and Islet Transplantation for the purpose of starting a clinical islet transplantation program in Japan. The first task of the Working Group was to establish a system for clinical islet transplantation in Japan including registration of patients, procurement of pancreas for islet isolation, and transplantation of the isolated islets. Thereafter, various problems concerning the initiation of clinical islet transplantation

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were discussed, guidelines were drawn up [7], and a manual [8] for clinical islet transplantation in Japan was completed. Adhering to these guidelines, the first islet isolation from a human pancreas was performed in September 2003, and the first islet transplantation was performed in April 2004 [9–11]. Sixty-five islet isolations and 34 islet transplantations were performed in Japan between 9 September 2003 and 31 March 2007.

Herein, we report the process for starting clinical islet transplantation, and its current status in Japan. In addition, we also describe the results of islet isolations and transplantations in our institution and discuss the problems and future of islet transplantation in Japan.

Current status of islet transplantation in Japan

Process to start a clinical islet transplantation program in Japan

A non-official meeting was held in Tokyo in 1996 to discuss the initiation of a clinical islet transplantation program in Japan. The meeting was conducted by S. Teraoka and T. Asano, with participants from Tokyo Women's Medical College, Chiba University, Tsukuba University, and Sakura National Hospital. This group was officially authorized as the Working Group for islet transplantation of the Japanese Society for Pancreas and Islet Transplantation. The Working Group first developed a system for procuring pancreata for islet isolations after negotiating with the Japan Organ Transplant Network and the Ministry of Health, Labour and Welfare. Because islet transplantation was classified as tissue transplantation, the procurement of the pancreas for islet transplantation is now regulated by the Japanese Tissue Transplant Network. In Japan, nearly all of the pancreata for islet transplantation are procured from non-heart-beating donors because pancreata from brain-dead donors are used mostly for pancreatic organ transplantation, according to the rules of the Japan Organ Transplant Network. Indications for the donor were agreed as shown in Table 1. The pancreas is procured by the procurement team from the islet isolation and transplantation centers authorized by the Japanese Society for Pancreas and Islet Transplantation (Table 2). The pancreas is preserved in University of Wisconsin (UW) solution or by a two-layer method designed by Kuroda et al. [12–18], and is transported to the islet isolation center. Islet isolation is performed immediately at each center. When the results of the isolation fulfill the criteria for fresh islet transplantation: (1) yield: ≥5,000 IEQ/kg (recipient body weight); (2) purity: ≥30%; (3) final cell pellet: ≤10 ml; (4) viability: ≥70%; and (4) endotoxin: ≤5 EU/kg (recipient body weight), a recipient is selected from the recipient pool by the Working Group according to the rules for recipient selection (Table 3). The patients were registered with the Working Group at each transplantation center according to the indications of recipients for islet transplantation in Japan (Table 4).

Table 1 Indications for the donor in islet transplantation in Japan [8]

1. Age: ≤70 years
2. Warm ischemic time: ≤30 min
3. No infectious disease, and no history of diabetes mellitus
4. Preservation solutions: University of Wisconsin solution or the two-layer method [12–18]

Table 2 Japanese islet isolation and transplantation centers authorized by the Japanese Society for Pancreas and Islet Transplantation (April 2008)

1. Tohoku University
2. Fukushima Prefecture University
3. Chiba-East National Hospital
4. Kyoto University
5. Osaka University
6. Kobe University
7. Fukuoka University

Table 3 Rules for recipient selection from the recipient pool in Japan [8]

1. Recipients must be registered with the islet isolation center
2. ABO blood type
3. Second or third transplantation
4. Waiting days

Table 4 Indications for the recipient of islet transplantation in Japan [8]

(1) Indications
a. Insulin-dependent diabetes mellitus (serum C-peptide level: <0.1 ng/ml)
b. Unstable blood glucose levels even under the treatment by a diabetologist
c. Age: <75 years old (preferable)
d. Sufficient informed consent obtained from the patient, family, and family doctor
(2) Contraindications
a. Severe heart disease or severe liver disease
b. Alcoholism
c. Active infectious disease
d. Malignancy
e. Severe obesity
f. Untreated retinopathy
g. Others

Results of islet isolation and islet transplantation in Japan

Sixty-five islet isolations were performed at the islet isolation and transplantation centers from December 2003 to March 2007. Only one isolation was performed using the pancreas from a brain-dead donor and the other 64 isolations were performed using the pancreata from non-heart-beating donors. Thirty-four successful isolations (53.1% of 64 isolations from non-heart-beating donors) fulfilled the fresh islet transplantation criteria and were transplanted to 18 patients. Analysis of factors influencing the results of islet isolation demonstrated that donor age and a warm ischemic time did not affect the results. In contrast, the total ischemic time was significantly shorter in successful isolations in comparison to unsuccessful isolations [8]. All 18 recipients were type 1 diabetic patients with a history of diabetes lasting from 6 to 37 years. The age of the recipients ranged from 16 to 61 years (36.2 ± 10.9 years) and there were 5 males/13 females. Six patients underwent three sequential islet transplantations and four patients underwent two sequential islet transplantations. Out the four patients with three islet transplantations, one patient showed insulin independency, and two out of six patients with two islet transplantations achieved insulin independency. However, all of these patients returned to insulin dependency 2 weeks to 6 months after obtaining insulin independency.

The islet transplantation technique was performed according to the Edmonton Protocol. The isolated islets were transplanted into the portal vein using an angiocatheter via an ultrasonography guided puncture. A steroid-free immunosuppressive regimen was used with sirolimus, tacrolimus, and anti-CD25 antibody according to the Edmonton Protocol [5]. As shown in Fig. 1, serum C-peptide levels were 0.5 ± 0.4 ng/ml after the first, 0.4 ± 0.2 ng/ml after the second, and 0.8 ± 0.4 ng/ml after the third islet transplantation. Positive insulin secretion from the islets, as indicated by serum C-peptide levels, resulted in decreased insulin requirement; 39.7 ± 18.0 U/day before transplantation, 24.2 ± 110 U/day after the first, 21.4 ± 11.5 U/day after the second, and 21.0 ± 7.7 U/day after the third islet transplantation. In addition, hemoglobin A1C levels decreased from 8.8 ± 1.8% before transplantation to 7.5 ± 1.4% after the first, 6.5 ± 1.4% after the second, and 6.2 ± 1.2% after the third islet transplantation. All patients obtained stabilized blood glucose levels, which resulted in the disappearance of hypoglycemic unawareness [19]. Overall islet graft survival, defined as a serum C-peptide level of >0.3 ng/ml according to the criteria of the International Trial of the Edmonton Protocol [20], was 86.5% at 6 months, 78.7% at 1 year, and 62.9% at 2 years after the first islet transplantation (Fig. 2) [19].

Results of islet isolation and islet transplantation in our institution

From September 2003 to April 2007, 23 islet isolations were performed from the pancreata of non-heart-beating donors in our institution [GMP grade Bio-clean Cell Processing Center (CPC), Clinical Research Center, Chiba-East National Hospital]. The age of the donors ranged from 10 to 69 years (37.5 ± 18.0 years), and there

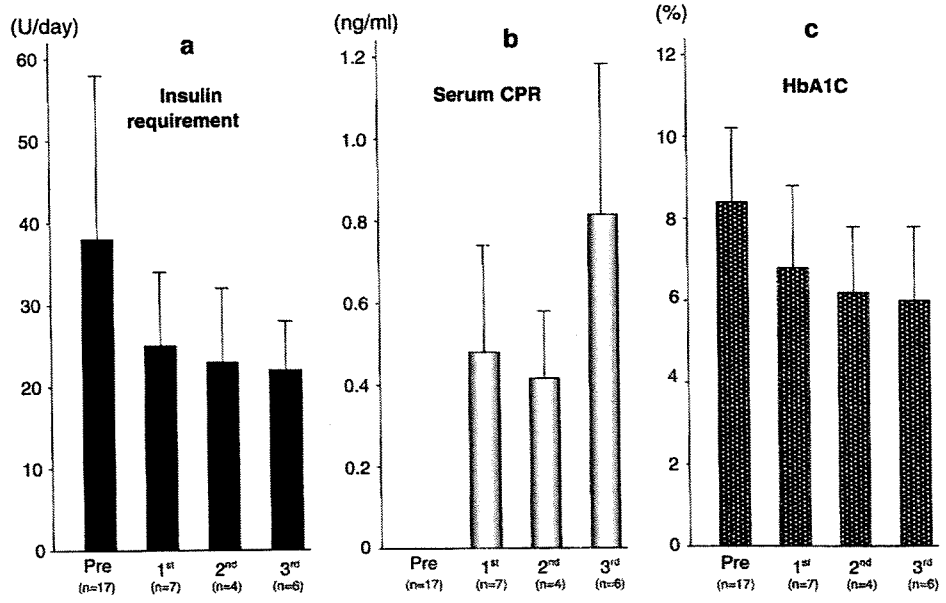

Fig. 1 Outcomes of clinical islet transplantation in Japan. **a** Insulin requirement decreased after the first (*1st*), the second (*2nd*), and the third (*3rd*) islet transplantation. **b** Serum C-peptide (*CPR*) levels became positive after islet transplantation, especially after the third islet transplantation (serum CPR = 0.8 ± 0.4 ng/ml). **c** Hemoglobin A1C decreased after islet transplantation due to stabilization of blood glucose levels

were 13 males/10 females. The causes of death were cerebrovascular disorder (10 cases), hypoxia (7 cases), trauma (5 cases), and 1 brain tumor. After cardiac arrest,

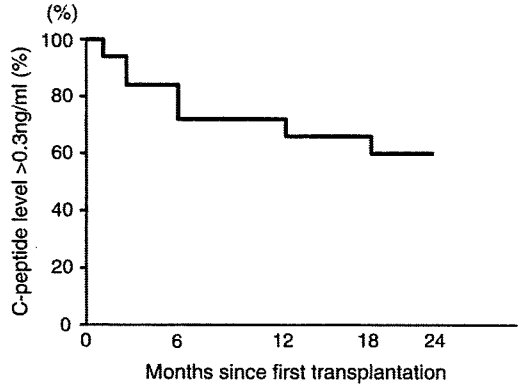

Fig. 2 Overall islet graft survival (defined as CPR >0.3 ng/ml) was 86.5% at 6 months, 78.7% at 1 year, and 62.9% at 2 years after the first islet transplantation

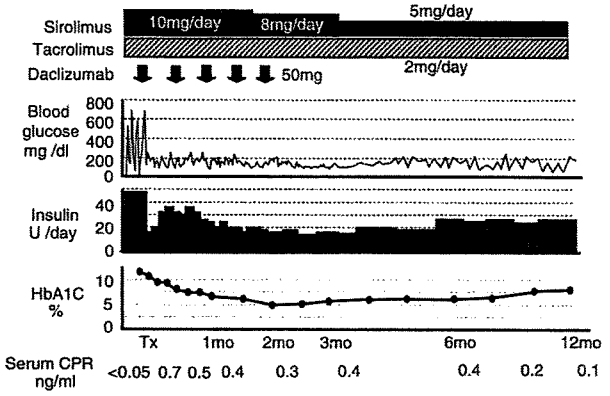

Fig. 3 Post-transplant course of patient #1 (Department of Surgery, Chiba-East National Hospital): stabilization of blood glucose levels and a decrease in insulin requirements were obtained due to the positive serum CPR. However, serum CPR decreased gradually after islet transplantation

pancreata were procured using our in situ perfusion technique [21]. In 9 of the 23 donors, permission to insert a catheter into the aorta for systemic heparinization before cardiac arrest was not given, which resulted in a prolonged warm ischemic period. The pancreata were preserved using a two-layer method [12–18] or a simple cold storage in UW solution and were transported to our CPC.

Islet isolation was performed according to the Edmonton Protocol, with some modifications [22–29]. Briefly, the pancreas was distended with a cold liberase solution (Liberase HI, Roche Diagnostics, Indianapolis, IN) by a ductal injection. Thereafter, the distended pancreas was cut into several pieces and put into a Ricordi chamber and digested using a closed automated system at 37°C. Shaking of the Ricordi chamber was performed either by hand or using a shaker. The pancreatic digests were collected in a flask on ice and were purified on a Euro-Ficoll discontinuous solution using a COBE 2991 cell processor. When the results of the isolation fulfilled the criteria for fresh islet transplantation in Japan, the islets were immediately transplanted to the recipient.

Our technique of islet transplantation follows the same procedure as in the Edmonton Protocol. The immunosuppression protocol was a triple therapy using sirolimus, tacrolimus, and anti-CD25 antibody. Four patients underwent six islet transplantations. All patients were type 1 diabetic patients (1 male, 3 females) complaining of frequent hypoglycemic unawareness and showing undetectable serum C-peptide levels (<0.03 ng/ml). The patient ages ranged from 16 to 33 years old. Two patients underwent two sequential islet transplantations.

The islet yield was 400–491,040 IEQ (mean 148,511) and the final purity was 1–70% (mean 35.3). The stimulation index of static incubation was 1.38–11.69. Six isolations were used for transplantation because they fulfilled the Japanese criteria (success rate: 26.1%). All

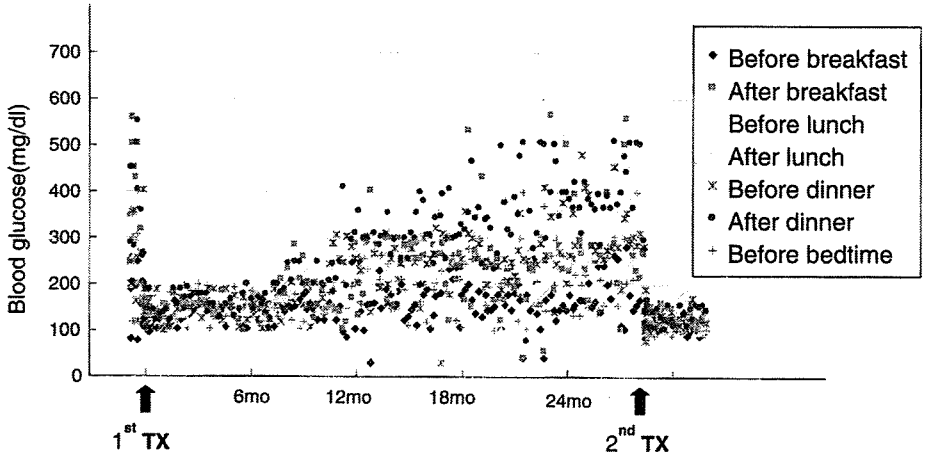

Fig. 4 Changes in blood glucose levels after islet transplantation in patient #1: control of the blood glucose levels became poor 12 months after transplantation. However, blood glucose levels were again stabilized by a second islet transplantation

patients, including two cases of single transplantation, showed a positive serum C-peptide level (0.4–0.8 ng/ml) immediately after transplantation. Although insulin independency was not achieved, all patients experienced stabilization of their blood glucose levels, a reduction in the amount of insulin required, and the disappearance of hypoglycemic unawareness. Hemoglobin A1C levels were significantly decreased from 9.4 ± 3.1% to 6.4 ± 0.6% at 4 months after transplantation. Although stomatitis and diarrhea, side effects of sirolimus, were observed in 2 patients, severe complications did not occur. In patient #1, serum C-peptide levels decreased gradually after transplantation (Fig. 3). Blood glucose levels were, however, again stabilized after the second islet transplantation (Fig. 4).

Discussion

Encouraged by the successful results of the Edmonton Protocol, a Working Group began preparations for a clinical islet transplantation program in Japan, and the first human islet isolation was performed at our institution on September 12, 2003. The first human islet transplantation for a type 1 diabetic patient was performed by the Kyoto group [9–11].

In Japan, pancreata from non-heart-beating donors are used for islet isolation since the pancreata from brain-dead donors are usually used for pancreas or pancreas/kidney transplantation. A respirator is rarely withdrawn from a patient, even though the donor is diagnosed as brain dead. Moreover, the donors usually are not examined to diagnose brain death; therefore, cannulation into the abdominal aorta with a double balloon catheter via the femoral artery and systemic heparinization are not permitted before a cardiac arrest. Under the present conditions in Japan, viability of the pancreata may decrease before procurement, thus often resulting in a poor yield and a low purity of the islet isolation.

In our experience, the results of islet isolation from non-heart-beating donors (yield and purity) were extremely varied. We analyzed the outcomes of 23 human islet isolations performed in our CPC and compared the factors of successful isolation (fulfilling the fresh islet transplantation criteria) and unsuccessful isolation. Donor age, gender, warm ischemic time, and in situ perfusion solution were not different between the two isolation groups. Only the cold ischemic time was significantly shorter in the successful isolations than that in the unsuccessful isolations. Moreover, the use of the two-layer method improved the outcome of islet isolations in comparison to the use of UW solution, though not to a significant degree. The two-layer method is considered to be advantageous for the preservation of the pancreata for islet isolation and transplantation [12–18]. However, Caballero-Corbalán et al. recently reported that the two-layer method had no beneficial effect in comparison to the use of UW solution on human islet isolation and transplantation [30].

Six isolations were successful and were used for fresh islet transplantation, even from non-heart-beating donors. These results demonstrate that the Edmonton Protocol is indicated for islet isolation from a damaged pancreas with some modifications. We used a two-step digestion technique as previously reported. Our previous data using a two-step digestion technique demonstrated that the islets were protected from digestion damage, resulting in a higher yield and purity using both porcine and human pancreas [24]. Further improvement of islet isolation is needed, especially from the pancreata of non-heart-beating donors in Japan. The Kyoto group developed a modified two-layer preservation method and improved the islet yields in human and porcine islet isolation [31, 32].

The major advantage of islet transplantation is that it is a safe procedure in comparison to pancreas transplantation. The complications often caused by the organ transplantation procedure were not observed in the six islet transplantations in our institution. Blood pressure and portal pressure, which was monitored during transplantation showed no significant change in any of the patients. The infusion of the islet suspension required only 15–20 min. Stomatitis and diarrhea, side effects of sirolimus, occurred in two patients and were the only complications observed after transplantation. Both patients recovered from these complications with a reduction of the sirolimus dose (patient #1) or a change from sirolimus to mycophenolate mofetil (patient #2).

The islets isolated from the pancreata of non-heart-beating donors functioned immediately after transplantation in all four patients. These patients were free from hypoglycemic unawareness and obtained stabilized blood glucose levels. All patients showed a positive serum C-peptide level and a reduced insulin requirement. These data demonstrate that the islets isolated from damaged pancreas with ischemia functioned as well as those from brain-dead donors.

Many problems remain to be solved in clinical islet transplantation. The most essential problem is the difficulty in maintaining persistent islet graft function. In particular, long-term insulin independency after islet transplantation is rarely observed, both in international trials of the Edmonton Protocol [20] and in the Japanese trial. A number of factors are considered to cause declining islet function over time. Selection of the immunosuppressive regimen is an important key for islet graft survival. A steroid-free immunosuppressive regimen was introduced for islet

transplantation because of the β-cell toxicity and the diabetogenic effect of this agent [5]. A steroid-free immunosuppressive regimen was also recently indicated for kidney and liver transplantation [33–35]. This steroid-free immunosuppressive regimen was also effective for islets after kidney transplantation [36, 37]. However, an mTOR inhibitor, sirolimus, which is used as the main agent in the steroid-free immunosuppressive regimen of the Edmonton Protocol, has a number of side effects including renal toxicity and severe ulceration of the small bowel [38, 39]. Further improvements in the immunosuppressive regimen after islet transplantation are needed.

Another important factor for persistent islet graft function is the promotion of islet engraftment after transplantation. We reported the efficacy of nicotinamide and 15-deoxyspergualin on the engraftment of mice islet isografts [40]. In addition, in a clinical study, 15-deoxyspergualin promoted the engraftment of unpurified islet transplantation [41]. A recent report by Yasunami et al. demonstrated the efficacy of inhibition of proinflammatory cytokines on islet engraftment in mice [42]. This agent may have a promising role to play in clinical islet transplantation in Japan.

From the data of the Japanese trial of islet transplantation promoted by the Working Group, the effectiveness of islet transplantation was shown, even when using pancreata from non-heart-beating donors. The patients showed positive C-peptide levels and stabilization of blood glucose levels. In particular, the disappearance of hypoglycemic unawareness led to a prominent improvement in the patient's quality of life. Although there are a number of problems to be solved, including further improvement of islet isolation, transplantation technique, and long-term graft survival, we can state that the start of clinical islet transplantation provides a reason to hope for type 1 diabetic patients.

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Living donor pancreas transplantation in Japan

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Abstract
Background/purpose Living-donor pancreas transplants (LDPs) were introduced at Chiba-East National Hospital in 2004, and 12 LDPs have been performed at this institution to date. Based on the outcome of these 12 LDPs, the efficacy and safety of LDPs are herein discussed.
Methods Twelve diabetic patients underwent LDPs; ten had simultaneous pancreas and kidney transplants from living donors, one had pancreas transplant after a kidney transplant from a living donor, and one had a pancreas transplant alone from a living donor. The donors were parents or brothers and the ABO blood types were incompatible in three LDPs. The procedures for the donor and recipient operations were performed according to the technique established by the University of Minnesota. Bladder drainage was used in 11 recipients and enteric drainage was used in one patient. Tacrolimus, basiliximab, mycophenolate mofetil, and prednisone were used for induction and immunosuppressive treatment. A splenectomy, double-filtered plasmapheresis, and plasma exchange were added in the ABO-incompatible LDPs.
Results No complications were observed in the donors during hospitalization. The 1-year survivals of the patients, kidney grafts, and pancreas grafts were 100, 100, and 100%, respectively. The 3-year survivals were 91.7, 90, and 91.7%, respectively. Three patients developed leakage of pancreatic juice and one patient required a surgical procedure. Cytomegalovirus antigenemia was detected in five patients (42%).
Conclusions Based on the excellent outcome of the LDPs at this institution, LDPs is therefore expected to become a promising option for the treatment of patients with severe diabetes.

Keywords Living-donor pancreas transplantation · Safety for the donor · ABO-incompatible · Insulin independence

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Introduction

Since the first pancreas transplantation was performed at the University of Minnesota by Kelly et al. [1], more than 23,000 diabetic patients have undergone pancreas transplantation [2]. The outcome of pancreas transplantation has improved so that it is almost equivalent to that of kidney transplantation, due to improvements in the surgical techniques and the introduction of an improved immunosuppressive protocol [3]. Pancreas transplantation has now become the most successful physiological treatment for type 1 diabetic patients.

In Japan, the first pancreas transplantation was performed at Tsukuba University in 1984 by Fukao et al. [4] from a brain-dead donor. In Japan, the availability of brain-dead donors for pancreas or other organ transplantations is, however, extremely limited because of the social

circumstances in this country. Therefore, until 1994, most pancreas transplantations were from obtained non-heart-beating donors. The procurement of organs for transplantation from brain-dead donors, however, was officially permitted in 1997 according to the establishment of the law in 1997 in Japan. Subsequently, pancreas transplantation from a brain dead donor was begun again at Osaka University, by Ito et al. [5] and, as of December 2007, 52 patients had undergone pancreas transplants from brain dead donors. Although the outcome of pancreas transplantation from brain-dead donors in this country was excellent, even when using marginal donors [6], 19 patients on the waiting list for pancreas transplantation died of diabetic complications, including hypoglycemic episodes and cardiovascular disease, between 2000 and 2007.

The first extrarenal organ to be successfully transplanted using living donors was the pancreas. The first pancreas transplantation using a living donor was performed on 20 June 1979, at the University of Minnesota [7, 8]. Furthermore, simultaneous pancreas and kidney transplantation from a living donor was introduced in 1994, also at the University of Minnesota [9]. The outcome of the living-donor transplantations performed at the University of Minnesota demonstrated the segmental pancreas to be able to normalize plasma glucose levels and provide insulin independence to patients with severe diabetes. The outcome of the donors was considered to be acceptable when stringent donor criteria concerning endocrine function were used [10].

Based on the severe shortage of deceased donors in Japan and the satisfactory outcome of living-donor pancreas transplantations at the University of Minnesota, living-donor pancreas transplantation was introduced in this country on 7 January 2004 [11]. In Japan, 15 living-donor pancreas transplantations have so far been performed at three institutions (Chiba-East National Hospital, 12; Niigata University Hospital, 2; Osaka University Hospital, 1).

The present article describes the outcomes of both the donors and the recipients of living-donor pancreas transplants (LDPs) at Chiba-East National Hospital, because 80% of LDPs in this country were performed at this institution. In addition, the efficacy and the safety of this procedure is also discussed.

Patients and methods

Recipients

Twelve type 1 diabetic patients underwent living donor pancreas transplantations at Chiba-East National Hospital from January 2004 to June 2008. Ten patients (83%) underwent a simultaneous pancreas and kidney transplant from living donors (LDSPK) because of end-stage renal disease (ESRD). One patient (8.3%) underwent a pancreas transplant after a kidney transplant from a living donor (LDPAK) and the other patient (8.3%) underwent a pancreas transplant alone from a living donor (LDPTA).

Table 1 Characteristics of the recipients and donors of pancreas transplantation from a living donor (Department of Surgery, Chiba-East National Hospital, 2004–2008)

Recipients	
Patient number	12
Age, in years (range)	34.6 ± 5.1 (30–46)
Gender (male/female)	6/6
Age at onset of DM in years (range)	12.8 ± 5.9 (0.9–19)
Duration of DM in years (range)	22.0 ± 4.5 (15–30)
Amount of insulin (units/day)	41.6 ± 19.2 (four times daily)
Anti GAD or IA-2 Abs	Positive 6, negative 6
M value	68.2 ± 14.5
ESRD	Yes 10 (HD 8, preemptive 2), no 2
Donors	
Patient number	12
Age in years	58.8 ± 10.6 (28–72)
Gender (male/female)	4 (3 fathers, 1 brother)/8 mothers
ABO compatibility	Identical, 9; incompatible, 3
75-g-OGTT	Normal pattern
IV-GTT (δCPR, 0–5 min)	6.8 ± 1.7 ng/ml per 5 min
Body mass index	22.9 + 1.87

DM diabetes mellitus, *Ab* antibodies, *ESRD* endstage renal disease, *HD* hemodialysis, *75-g-OGTT* 75-g oral glucose tolerance test, *CPR* C-peptide release

The characteristics of the recipients are shown in Table 1. All patients had type 1 diabetes and the onset of diabetes had been rapid due to diabetic ketoacidosis. All patients showed frequent hypoglycemic episodes despite carrying out four courses of potent insulin injection therapy based on their self-measured plasma glucose levels. Unstable plasma glucose levels resulted in a high *M* value [12] (68.2 ± 14.5). Serum C-peptide levels were undetectable (<0.03 ng/ml) in nine patients and levels were less than 0.1 ng/ml in the other three patients. The peripheral nerve conduction velocity was decreased in 11 of the 12 patients and a head-up tilt test demonstrated an autonomic disturbance by diabetes in 11 patients. No retinopathy was observed in any patients at the time of transplantation.

Donors

The donors were the mothers for eight recipients, fathers for three recipients, and a brother for one of the recipients. The donors' ages ranged from 28 to 72 years. ABO blood

type compatibilities to the recipients were identical in nine donors and incompatible in the other three donors. A potential donor first must undergo an interview with the doctors, nurses, transplant coordinators, and medical social workers and must provide voluntary consent. Subsequently, the donor must show negative findings on a flow cross-match examination between the donor's T lymphocytes and the recipient's serum. All donors must fulfill the criteria for living-pancreas transplantation donors, as shown in Table 2.

The evaluation of pancreatic endocrine function includes a normal 75-g oral glucose tolerance test (75 g-OGTT), normal CS1 (first-phase C-peptide secretion calculated from the sum of the C-peptide secretion rates from 0 to 5 min after intravenous glucose tolerance test (IV-GTT) [13] and a normal level of hemoglobin (Hb) A1C. In addition, islet cell autoantibodies (anti-GAD and anti-IA2 antibodies) must be absent, and body mass index (BMI) must be less than 25.

Table 2 Criteria for donors for living pancreas transplantation (Department of Diabetology, Chiba-East National Hospital, 2004)

Age ≤65 years (desirable)
No family history except for the recipient
Normal endocrine function
75-g-OGTT: normal pattern (all plasma glucose levels <180 mg/dl)
IVGTT: normal CS1
HbA1C: ≤5.5%
Negative anti-GAD and IA-2 antibodies
BMI <25
Contraindications
Active infectious disease
HIV (+), HTLV-1 (+), HBs antigen (+), HCV antibody (+)
Malignancy
Abnormal anatomy of the pancreas
Alcoholism

CS1 the first phase C-peptide secretion calculated from the sum of C-peptide secretion rates from 0 to 5 min after glucose injection, *BMI* body mass index

Eleven of the 12 donors completely fulfilled our criteria. One donor did not fulfill the criteria because she was 72 years old. But because her pancreatic endocrine function was excellent and she qualified as a potential donor for LDPTA, the committee for living donor pancreas transplantation and the Institutional Review Board (IRB) at Chiba-East National Hospital finally approved her as a donor after obtaining sufficient informed consent from her and her family members.

The contraindications were almost the same as those for other transplantations. For the safe procedure of the donor operation, the blood vessels of the pancreas and the kidney were evaluated using three-dimensional angiography from dynamic computed tomography (CT Fig. 1). In order to evaluate segmental function of the donor pancreas, ^{11}C-methionine positron emission tomography (PET) was also performed [14] (Fig. 2).

Operative methods and postoperative care

Donors

Procurement of the distal pancreas from the living donor was performed according to the procedure of the Minnesota Group as previously reported [7]. In LDSPK, under an open laparotomy, the left kidney was first excised, followed by a distal pancreatectomy with a splenectomy (Fig. 3). In two recent donors, however, hand-assisted laparoscopic surgery (HALS) was introduced as a less invasive procedure for simultaneous nephrectomy and distal pancreatectomy.

Antibiotics were administrated intravenously for 7 days after the surgery. Gabexate mesilate (600 mg/day) was given for 7 days in order to inhibit the occurrence of residual pancreatitis. Oral intake was resumed 6 days after the surgery. Before being discharged from the hospital, the donors underwent a CT scan to rule out the formation of a pancreatic cyst or abscess. To assess the exocrine and endocrine function of the residual pancreas, serum

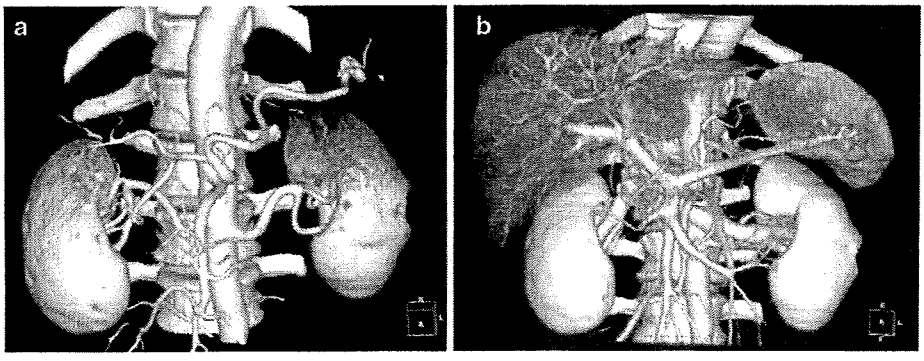

Fig. 1 a, b Images of the blood vessels of pancreas and kidneys of a donor; reconstructed from three-dimensional angiography from a dynamic computed tomography (CT) scan. Department of Radiology, Chiba-East National Hospital

amylase, lipase, trypsin, and plasma glucose levels were determined daily. In addition, the serum C-peptide levels were determined once a week. After discharge, the donors were monitored at the outpatient clinic and their plasma glucose levels, HbA1C, and serum C-peptide levels were measured at 1 and 3 months and every year after the operation. A 75-g-OGTT was performed at 6 months, and then every year after the surgery.

Recipients

In the recipients, the kidney transplantation was performed in the standard fashion as previously described in detail, with vascular anastomoses to the left external iliac vessels and an ureterocystostomy. The segmental pancreatic graft was revascularized by anastomosing the donor splenic artery and vein to the right iliac artery and vein of the recipient. A pancreaticocystostomy was performed using a two-layer technique including the anastomosis between the pancreatic duct and the mucosa of the urinary bladder to drain the pancreatic juice of the graft.

Induction of immunosuppression was achieved by quadruple therapy using tacrolimus, basiliximab, mycophenolate mofetil (MMF), and prednisone. Immunosuppression was maintained with triple therapy consisting of tacrolimus, MMF, and prednisone. Desensitization for the patients receiving transplants from ABO-incompatible donors was achieved according to a protocol for ABO-incompatible kidney transplantation, which included the administration of MMF for 4 weeks before transplantation; a splenectomy at −14 days; double-filtered plasmapheresis (DFPP) at −6, −4, and −2 days; and plasma exchange (PE) at −1 day.

Anticoagulation therapy was started at the time of the operation, using heparin (200 units/h), and 10,000–20,000 units was continuously given intravenously for 10 days after transplantation. Gabexate mesilate (600 mg) was continuously administrated for 7 days to inhibit graft pancreatitis and 100 units of octreotide was given every 12 h for 5 days to inhibit the secretion of pancreatic juice from the graft. In addition, we also administered antibacterial prophylaxis with piperacillin for a week, antifungal prophylaxis with fluconazole for a week, and anti-cytomegalovirus (CMV) prophylaxis with gancyclovir for 10 days. Insulin was continuously given intravenously to maintain plasma glucose levels of 100–150 mg/dl.

Oral intake was started at 7 days after transplantation. During the hospitalization, each recipient was monitored daily for pre- and postprandial serum glucose and amylase, blood cell count, electrolytes, creatinine, and urinary

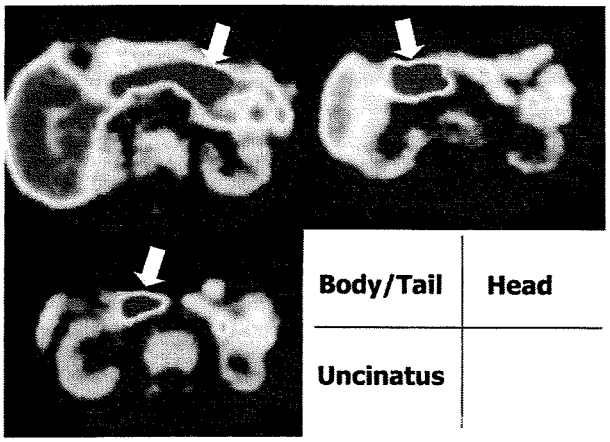

Fig. 2 Pancreatic function of donor evaluated by ^{11}C-methionine positron emission tomography (^{11}C-Met PET). The segmental pancreatic function was evaluated from the images (*arrows*) of the head and the body/tail

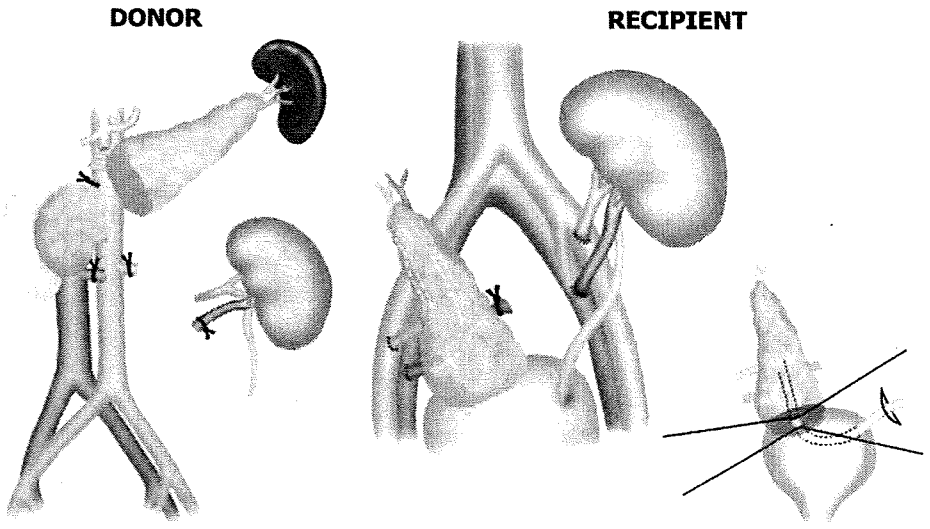

Fig. 3 Surgical method of simultaneous pancreas and kidney transplant from living donor (LDSPK). In the donor operation, left nephrectomy was performed, followed by distal pancreatectomy with splenectomy. The body/tail of the pancreas was excised at the left edge of the portal vein and procured as the pancreatic graft with the spleen. In the recipient operation, the kidney was transplanted into the left iliac fossa, followed by pancreas transplantation into the right iliac fossa, using a pancreaticocystostomy

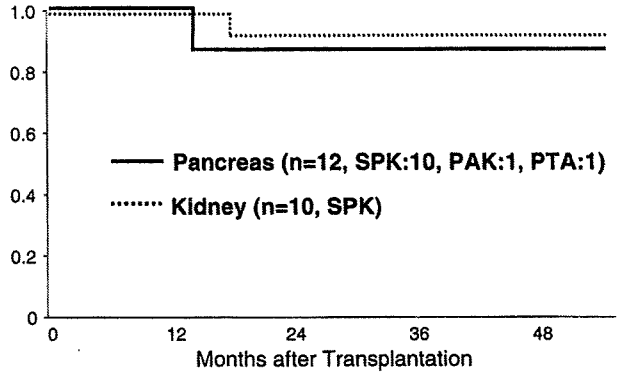

Fig. 4 Survival rates of pancreas and kidney grafts after living donor pancreas transplantation at Chiba-East National Hospital. The 1-year survivals of the kidney graft (LDSPK) and the pancreas graft were 100 and 100%. The 3-year survivals of the recipients, kidney grafts, and pancreas grafts were 91.7, 90, and 91.7%. *SPK* simultaneous pancreas and kidney transplantation, *PAK* pancreas after kidney transplantation, *PTA* pancreas transplant alone

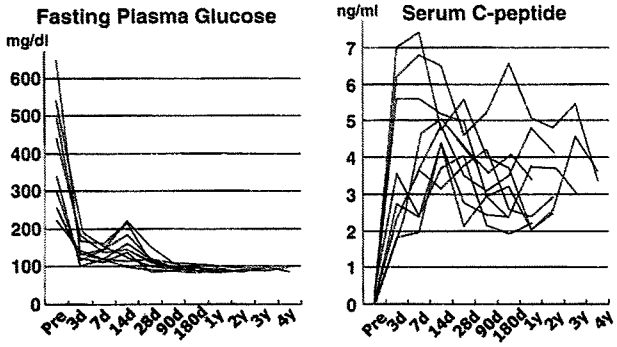

Fig. 5 Fasting plasma glucose levels and serum C-peptide levels in the patients who underwent living pancreas transplantation, excluding the patient with primary nonfunction of the graft. *Pre* before the operation, *d* day, *y* year

amylase excretion. All the above parameters were subsequently monitored continually at the outpatient clinic.

Results

Donor outcomes

No complications, including the formation of a pancreatic fistula or an intraabdominal abscess, were observed during hospitalization. The donors were discharged from the hospital at 23.3 ± 5.2 days after surgery and immediately returned to their normal life. Only one donor (donor 6) developed pancreatic pseudocysts, at 6 months after surgery with minor symptoms. The cyst was punctured from the stomach using gastro-fiberscopy and the cyst completely disappeared. The development of diabetes has not been observed in any donors during an observation period ranging from 6 months to 5 years.

Recipient outcomes

One patient, who underwent LDPAK, died of a cerebral hemorrhage at 13 months after transplantation with a functioning pancreas graft. The pancreas and kidney graft survivals of the recipients are shown in Fig. 4. The 1-year survivals of the patients, kidney grafts (LDSPK), and pancreas grafts were 100, 100, and 100%, respectively. The 3-year survivals were 91.7, 90, and 91.7%, respectively. Insulin independence was obtained in 11 patients immediately after transplantation. However, one patient, who underwent LDPTA, required a small amount of exogenous insulin injection from 3 months after transplantation even though his serum C-peptide was positive. Another patient, who underwent LDSPK, showed primary nonfunction of the pancreas graft. Her kidney graft functioned well and serum creatinine level had decreased to 0.8 mg/dl within 3 days after transplantation. Although neither arterial nor venous thromboses were observed, the serum C-peptide levels decreased to 0.05 ng/ml after transplantation. Except in the patient with primary nonfunction of the pancreas graft, the levels of HbA1C decreased to less than 6.0% within 3 months after transplantation. The fasting plasma glucose levels stabilized at under 100 mg/dl, and positive C-peptide levels ranging from 1.8 to 7.5 ng/ml were maintained (Fig. 5). The 75-g-OGTT performed at 6 months and at 1, 2, and 3 years after transplantation showed a normal pattern.

Although a biopsy-proven acute cellular rejection (ACR) was observed in two patients (16.7%), steroid pulse rescue therapy completely resolved the ACR in both patients. In addition, no antibody-mediated rejection (AMR) occurred in the three patients who had undergone LDSPKs from ABO-incompatible donors. The leakage of pancreatic juice was observed in three patients. One of them developed bleeding from the external iliac artery and required an additional operation to stop the bleeding. Cytomegalovirus antigenemia was detected in five patients (41.7%) from 30 to 56 days after transplantation and three patients required the intravenous administration of gancyclovir. The recipients were discharged from 37 to 148 days after transplantation and thereafter returned to their normal lives.

Discussion

In Japan, the number of diabetic patients has increased every year and has now reached more than eight million. Although type 1 diabetes is less frequent in this country

than in the United States and Europe, the quality of life in type 1 diabetic patients with ESRD is extremely low and the prognosis is very poor. Pancreas transplantation using brain-dead donors was begun again in 2000 for such patients. However, only 52 pancreas transplants have been performed over the past 8 years because of the severe shortage of deceased donors in this country. So far, 19 patients on the waiting list for pancreas transplantation have died due to diabetic complications such as hypoglycemic episodes and cardiovascular disease.

Living donor pancreas transplantation was introduced at the University of Minnesota in 1979 [8]. Initially, they performed living donor pancreas transplants only in recipients without uremia (LDPTA) or recipients who had received a kidney graft from the same donor (LDPAK) [15]. Subsequently, they performed the first successful LDSPK in March 1994 [9], and 20 LDSPKs had been done by March 1997 [10]. The 1-year survivals of the patients, kidney grafts, and pancreas grafts at that time were 100, 100, and 78%, respectively, which were higher than those of pancreas transplants from brain-dead donors at that time. An analysis in 2001 of 32 recipients of LDSPK showed that the 1-year survival of the pancreas graft had improved to 87% [15, 16]. Those results clearly demonstrated that the segmental pancreas was able to normalize the glucose metabolism in patients with severe diabetes.

Based on the shortage of deceased donors in Japan and the excellent outcome obtained at the University of Minnesota, the first LDSPK in this country was performed on 7 January, 2004, for a type 1 diabetic patient with ESRD for whom the donor was the father [11]. Donor safety has been the most important consideration in the conduct of LDSPK. The donor criteria for pancreas transplantation, as shown in Table 2, were determined by transplant surgeons, diabetologists, nephrologists, nurses, and transplant coordinators. The stringent Minnesota criteria were applied and were modified according to the lower ability among the Japanese to secrete insulin from the islets. As a tool for endocrinological evaluation, CS1, which is calculated by the sum of the C-peptide secretion rates from 0 to 5 min after glucose injection, is used in the IV-GTT. Tokuyama et al. [13] demonstrated that the sum of the C-peptide secretion rates was directly correlated with β-cell function and they showed that the CS1 expressed the first phase of insulin release.

The outcome of the 12 living pancreas transplants performed at this institution was excellent. The 1-year survivals of the patients, kidney grafts (LDSPKs), and pancreas grafts were 100, 100, and 100%, respectively, and the 3-year survivals were 91.7, 90, and 91.7%, respectively. The plasma glucose levels started to decrease at the time of the operation in almost all patients. Although exogenous insulin administration was required from 1 to 30 days after transplantation because of the administration of a high dose of steroid and hyperalimentation, all but one of the patients achieved insulin independence. One patient who underwent LDSPK showed primary nonfunction of the pancreas graft. Blood flow was recognized in both the pancreas and kidney grafts, using an ultrasonography power Doppler technique. Her kidney graft functioned immediately and the serum creatinine levels had decreased below 1.0 mg/dl at 3 days after transplantation. One-hour biopsy of the pancreas graft showed normal structure of both the exocrine tissue and islets. Although the mechanism of the development of primary nonfunction in this patient is unknown, an autoimmune response may be one of the possible explanations, because her anti-GAD antibody was extremely high, at 2,940 U/ml. The other patients who underwent LDSPK achieved both insulin independence and hemodialysis independence and showed a marked change in their outlook on life.

The leakage of pancreatic juice was the most frequent problem as a surgical complication after living pancreas transplant. Although a surgical procedure was required to treat the bleeding in one patient, three patients who developed leakage of the pancreatic juice maintained the function of the pancreatic graft. No other surgical complication was observed in the 12 patients, which demonstrated that the safety seemed to be almost the same as that of kidney transplantation. The frequency of acute rejection, including ACR and AMR, was also almost the same as that seen with kidney transplantation under standard immunosuppression.

In the series of living pancreas transplants conducted at, Chiba-East National Hospital, excellent outcomes were observed in both the recipients and the donors. Further consideration is needed in order to establish this procedure in this country as one of the therapies for patients with severe diabetes. The major issue must be the safety of the donor, especially of the donor for LDSPK. Hand-assisted laparoscopic surgery (HALS) was introduced for simultaneous nephrectomy and distal pancreatectomy in two recent donors for LDSPK. The operation was performed according to a previously reported technique [17]. The pancreas, however, was dissected directly from the open 7-cm wound using the Multiflap Gate (MD49611, Sumitomo Bakelite Co. Ltd., Tokyo). The two donors who underwent a HALS operation rapidly recovered after the operation and no analgesics were needed apart from the epidural administration of local anesthetics. The introduction of this procedure may therefore help to improve donor safety. In addition, long-term maintenance of the metabolism in the donor is still an important problem. In our present experience, the donors have not developed diabetes during an observation period of up to 5 years. Increased levels of HbA1C were, however, observed in two donors (6.0,

6.1%). Therefore, all donors are followed up by the diabetologist and a nephrologist, in addition to the transplant surgeons, at our hospital.

As previously reported, evaluation of the quality of life of LDSPK recipients, using a short-form 36 version 2 showed rapid increases in both the physical and mental summary scores in patients after LDSPK. In addition, the donors maintained their presurgical levels of both scores after the surgery [18].

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膵臓移植の最近の動向*

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* Current status of pancreas transplantation

キーワード：膵臓移植，生体膵臓移植，膵島移植，免疫抑制法

要旨：膵臓移植は1967年に米国で臨床例が開始され，現在では23,000例以上が施行されている．わが国では臓器移植法の施行後，40例の脳死・心停止膵臓移植，12例の生体膵臓移植が施行されている．膵臓移植の成績は，最近は他の臓器移植と同等に良好である．わが国では膵臓移植を移植施設＋National Teamで行い，40例に死亡例はなく良好な成績を得ている．脳死ドナー不足を背景に，当院では生体膵腎同時移植（SPK）を7例に施行した．ドナーは合併症もなく退院し，レシピエントは全例インスリン離脱が可能であった．膵島移植は成績が向上し，わが国でも臨床で開始された．全例で低血糖発作の消失・減少，血糖の安定化が得られ膵島移植の有効性が臨床的に示されたが，長期成績の改善が必須である．

はじめに

膵臓移植は1型糖尿病や高度慢性膵炎・膵全摘後などのインスリン依存型糖尿病に対する究極的治療法である．1967年，米国においてKellyら[1]により最初の臨床例が施行されたが，当時は拒絶反応に加えて移植手技に起因する合併症のため移植膵が廃絶する例が多く[1]，移植後血栓症予防，膵液ドレナージ法の実験的・臨床的研究が多数されている．臨床例が急増し，成績が飛躍的に向上したのは1980年代に入ってからであり，他の臓器移植と同様cyclosporine A（CsA）による免疫抑制法が登場したことによる．現在では膵臓移植は世界で23,000例以上が施行されており[2]，糖尿病根治療法として定着している．

わが国では1984年に筑波大学で脳死ドナーからの膵腎同時移植（simultaneous pancreas-kidney transplantation：SPK）が行われたが[3]，その後は心停止ドナーからのSPKが主流となり，1993年までに東京女子医科大学を中心に14例が行われた[4]．以後，法整備のため一時中断したが，2000年4月に大阪大学において臓器移植法施行後初めての脳死・膵腎同時移植が行われた[5]．以後，現在までに40例の脳死・心停止膵臓移植が行われている．また，12例の生体膵臓移植も施行されている．

本稿では膵臓移植の方法，世界およびわが国の現況と成績に加え，当院での生体膵臓移植の成績，さらには膵臓移植のオプションである膵島移植について最近の動向を中心に述べる．

膵臓移植の方法

膵臓移植の手技は長く実験的・臨床的に研究されてきた．全膵を用いるか部分膵（膵体尾部）を用いるかの検討のほか，膵液ドレナージ法として腸管ドレナージ，膀胱ドレナージがあり，さらに

表1　生体膵臓移植の免疫抑制法（国立病院機構千葉東病院外科）

ABO 血液型一致または適合
1．移植前（5 日間）：tacrolimus 0.15 mg/kg p. o.　または cyclosporine A 8 mg/kg p. o.
2．移植手術中：methylprednisolone 250 mg i. v.（血流再開時）
3．移植後
①steroid　prednisolone　50 mg/day i. v.（1～7 日）
40 mg/day p. o.（8～13 日）
30 mg/day p. o.（14～20 日）
20 mg/day p. o.（21～27 日）
10 mg/day（28 day～）
②calcineurin inhibitor　tacrolimus　0.05 mg/kg i. v.（0～6 日）
0.15 mg/kg p. o.（7 日～）
cyclosporine A　2.5 mg/kg/day i. v.（0～6 日）
6～10 mg/kg/day p. o.（7 日～）
血中濃度により投与量を調節する．
③MMF　1.5 g p. o.（1 日～）
④basiliximab　20 mg i. v.（0，4 日）
ABO 血液型不適合（既存抗体 DSA 陽性も準ずる）
1．移植前：MMF　1.0 g p. o.（28 日間）
tacrolimus　0.15 mg/kg p. o.（10 日間）
prednisolone　10 mg p. o.（10 日間）
抗体除去処置：脾臓摘出術（14 日前）
2 重濾過プラスマフェレーシス（DFPP）（−6，−4，−2 日）
血漿交換（-1 日）
2．移植手術中：methylprednisolone　250 mg i. v.（血流再開時）
3．移植後：ABO 血液型一致または適合と同じ

以上のプロトコールは副作用などにより変更し得る．

膵管内にシリコンなどを充塡して外分泌機能を廃絶させる方法もある．現在でも種々の方法が選択されるが，脳死・心停止膵臓移植の場合には全膵・十二指腸を移植し，腸管にドレナージする手技が一般的である．また，生体膵臓移植の場合には部分膵のみを用い，膀胱または腸管にドレナージする．

膵臓移植は糖尿病腎不全の患者に腎臓と同時に行われることが多く，腎臓移植との関係で SPK，腎移植後膵臓移植（pancreas after kidney transplantation：PAK），膵臓単独移植（pancreas transplant alone：PTA）の 3 つのカテゴリーに分類される．世界の例では全症例の 78%は SPK である．また，PAK は 16%を占める．すなわち膵臓移植は腎臓と同時性または異時性に行われることがほとんどといえる（94%）．わが国でも 40 例の脳死・心停止膵臓移植のうち 32 例（80%）が SPK である．

膵臓移植後の免疫抑制法としては，現在は腎臓・肝臓のプロトコールと原則的に同じと考えてよい．膵臓移植のレシピエントは自己免疫疾患である 1 型糖尿病がほとんどであり，いわゆる拒絶反応ではなく自己免疫機序により移植された膵臓が障害されることが知られており[6]，ALG や ATG などの抗体製剤が移植後早期に必要であるとされる．現在は抗 CD25 抗体製剤である basiliximab を投与することにより，他の臓器移植と同等の生着率を示している．また，当院における 3 例の ABO 血液型不適合生体 SPK の経験より，腎移植と同様に ABO 血液型不適合間の膵臓移植は十分可能であることが実証された．

表 1 に当院での生体膵臓移植の免疫抑制法を示す．当院で施行している腎臓移植とほぼ同様のプロトコールであり，カルシニューリンインヒビターとして tacrolimus または cyclosporine A，代謝拮抗剤として mycophenolate mofetil（MMF），ステロイド剤として prednisolone を使用し，移植当日と

4日後に抗CD25抗体製剤のbasiliximabを投与する．ABO血液型不適合の場合には腎移植のプロトコールに準じ，移植2週間前に腹腔鏡下脾臓摘出術，3回の2重濾過プラスマフェレーシス(DFPP)，移植前日に血漿交換（PE）を行っている．

膵臓移植の現況

膵臓移植は世界で23,000例以上が施行されており，糖尿病の治療法として確立している．1987年10月～2004年6月までに米国で行われた15,333例の膵臓移植例の解析では，カテゴリー別症例数はSPKが11,898例（78%）と大半を占め，PAKが2,427例（16%），PTAが1,008例（7%）であった[2]．最近の動向としてPAKの比率が増加していることが挙げられる．それぞれのカテゴリー別の成績（1年膵生着率）はSPK 85%，PAK 78%，PTA 76%であり，膵臓移植全体の成績は近年は腎臓・肝臓と同等の成績といえる．カテゴリー別ではSPKの成績が最もよいが，PAK，PTAの成績は年々向上しておりSPKに近づいている．これは近年の免疫抑制法の進歩によるところが大きい．膵液のドレナージ法は膵臓移植が開始された当時は膀胱ドレナージが主流であり，1987～1996年に米国で施行された膵臓移植の90%以上が膀胱ドレナージであったが，最近では腸管ドレナージが主流であり，2002～2003年の症例ではSPKの82%，PAKの72%，PTAの57%が腸管ドレナージであった[2]．

わが国の脳死膵臓移植が本格的に開始されたのは1997年10月に臓器移植法が実施されてからである．膵臓移植特別委員会（現膵臓移植中央調整委員会）が主導で膵臓移植の施設認定（現在14施設：**表2**），地域適応検討委員会の整備，日本臓器移植ネットワークへのレシピエント登録体制整備が行われ，2000年4月に大阪大学で臓器移植法施行後初めての脳死膵腎同時移植が行われた[5]．2007年8月31日までに脳死膵臓移植が38例（SPK 32例，PAK 6例），心停止膵臓移植が2例（SPK 2例）行われている．わが国の膵臓移植ドナーの特徴は，死因として動脈硬化性疾患の頻度が高い，高齢者が多いなど条件の悪いドナー，いわゆるmarginal donorが多いことである．このようなドナーを有効に活用し，少ないドナーより効率的に膵臓移植を行っていく必要がある．

表2　脳死下膵臓移植実施認定施設（2007年8月現在）

1. 北海道大学病院
2. 東北大学病院
3. 福島県立医科大学附属病院
4. 国立病院機構千葉東病院
5. 東京女子医科大学病院
6. 東京医科大学八王子医療センター
7. 新潟大学医歯学総合病院
8. 名古屋第2赤十字病院
9. 京都府立医科大学附属病院
10. 奈良県立医科大学附属病院
11. 大阪大学医学部附属病院
12. 神戸大学病院
13. 広島大学病院
14. 九州大学病院

わが国では膵臓移植を移植施設＋National Team（膵臓移植実務者委員会）で行っており，成績の向上をめざすとともに他施設の症例についても十分検討できるチャンスがシステムとして構築されている．移植成績をみると40例の膵臓移植後に死亡例はなく，移植後急性期に静脈血栓症などで3例が移植膵摘出術を余儀なくされた．うち1例は2年後に再度膵臓移植（PAK）を受けた．また，1例が移植後2年目でイレウスに伴って移植片十二指腸穿孔，汎発性腹膜炎を併発し，移植膵摘出術を施行した．他の例はいずれもインスリンを離脱して良好に経過している．移植腎は1例が抗体関連性拒絶反応により透析再導入となったが，ほかは全例生着している．治療成績を論じるにはさらなる症例の積み重ねと長期の経過をみる必要があるが，marginal donorが多いわが国の背景を考慮すると欧米の膵臓移植の成績を凌駕する良好な結果といえる．

当院の生体膵臓移植の成績

わが国では2007年7月31日現在，154名の膵臓移植希望患者が日本臓器移植ネットワークに登録されている（SPK 128名，PAK 19名，PTA 7名）．