

transplantation is categorized as tissue transplantation in Japan, which is operated with the use of special guidelines. Therefore, pancreata for islet transplantation have usually been obtained from donors after cardiac death (DCD).

DCD are a heterogeneous population, and the duration of cardiac death differs between subjects. A longer warm ischemia time (which may lead to organ damage) is a major concern with DCD. In Japan, most DCD suffer unexpected cardiac death. They are cannulated and perfused with cold preservation fluid within minutes after death to maintain organ viability, and are termed uncontrolled DCD. It has been reported that normally functioning pancreatic islets can be successfully isolated from pancreata from controlled DCD, and that they should be suitable for clinical isolation [1,2].

Previously, we reported that pancreatic islet transplantation from uncontrolled DCD ameliorated episodes of severe hypoglycemia, decreased levels of glycated hemoglobin (Hb_{A1c}), and sustained significant levels of C-peptide after a mean follow-up time of 41 months [3]. However, long-term outcomes and the utility of uncontrolled DCD in the clinical setting remain controversial.

Here, as a subsequent report from the Japan Islet Transplantation Registry, we summarize the outcomes from a mean follow-up of 76 months after pancreatic islet transplantations from uncontrolled DCD.

METHODS

Study Design

From September 2003 to March 2007, 64 isolations of pancreatic islets and 34 transplantations of pancreatic islets were performed in 18 T1DM patients (including 2 patients who had prior kidney transplantation). According to Maastricht donor categories, all DCD were considered to be uncontrolled and category V [4] at the time of harvesting. Six transplantation centers (Tohoku, Fukushima, Chiba, Kyoto, Kobe, and Fukuoka) were enrolled in this study for the isolation and transplantation of pancreatic islets. The Ethics Committee at each participating institution approved the study protocols. Each recipient was allowed up to 3 islet transplantations until achievement of insulin independence. Recipients were selected at each participating center based on regional priority, blood type, history of previous islet transplantation with a potential for insulin independence, and a long waiting period.

Isolation and Transplantation of Pancreatic Islets

Donors were cannulated and perfused with cold preservation fluid (in situ preservation) within minutes after death to prevent warm ischemia damage to the pancreas. Harvested pancreata were transported in chilled University of Wisconsin solution or in ET-Kyoto solution (Otsuka Pharmaceuticals, Tokyo, Japan). A 2-layer method with perfluorocarbon during transportation has been recommended [5]. Pancreatic islets were isolated locally at each facility, with each institution maintaining good practice guidelines. The method of isolation of pancreatic islets has been reported previously [6–8]. The pancreas specimen was digested with the use of Liberase HI (Roche Molecular Biochemicals, Indianapolis, Indiana). The release criteria were identical to those of the Edmonton protocol [6].

The fresh islet preparation without culture was infused into the portal vein. Two or 3 consecutive infusions of >5,000 islet equivalents (IEQ)/kg were planned for each recipient to achieve insulin independence.

The immunosuppression regimen comprised basiliximab induction and sirolimus/tacrolimus maintenance or the use of continuous immunosuppressive regimen in case of islet after kidney recipients, with basiliximab induction at the time of islet transplantation [3,6]. Sirolimus was replaced with mycophenolate mofetil in some cases.

Assessment of Islet Engraftment

Insulin independence was defined as freedom from the need to take exogenous insulin with adequate glycemic control. Partial graft function was defined as a C-peptide level ≥ 0.3 ng/mL and a requirement for insulin. Graft loss was defined as an initial increase in the C-peptide level but a decrease to < 0.3 ng/mL. Severe hypoglycemia unawareness was defined as an episode of neuroglycopenia with unawareness severe enough for the subject to require assistance [9].

Flow Panel Reactive Antibodies (PRAs)

Alloantibodies were detected by means of flow cytometric methods with the use of the fluorescent signal for each HLA-coated bead and normalized to the signal of negative control serum [10].

Statistical Analyses

Values are expressed as mean \pm standard error. Outcome measures for the overall data and strata-defined variables were estimated from Kaplan-Meier curves and compared with the use of logistic regression analyses. Statistical calculations were done with the use of Statistical Product and Services Solutions v15.0 (SPSS, Chicago, Illinois). A *P* value of $< .05$ was considered to be statistically significant.

RESULTS

Among 64 isolations of pancreatic islets, 34 isolations (53.1%) met the release criteria. Previously, we reported that the factors associated with islet isolation were analyzed by a logistic regression univariate analysis. We found that duration of hypotension before cardiac arrest, length of cold ischemia time, and use of ET-Kyoto solution for preservation were significant factors for islet release. According to multivariate analyses, use of ET-Kyoto solution was the only significant factor among these factors [3].

Thirty-four transplantations of pancreatic islets were performed in 18 T1DM patients under the cover of immunosuppression with basiliximab, sirolimus, and tacrolimus. Of the 18 recipients, 8, 4, and 6 recipients received 1, 2, and 3 islet infusions, respectively. Among the 10 patients who received 2 or 3 transplantations, the intervals between transplantations ranged from 0 to 954 days. The follow-up time ranged from 58.7 months to 94.1 months, and the mean follow-up time was 76.4 ± 3.3 months. Overall graft survivals (defined as the C-peptide level) were 72.2%, 44.4%, and 22.2% at 1, 2, and 5 years, respectively (Fig 1A). When recipients were divided into 2 groups (one group who had 1 islet infusion, and the other group who had 2 or 3 islet infusions), we found that recipients receiving multiple islet infusions had significantly prolonged survival of islet grafts

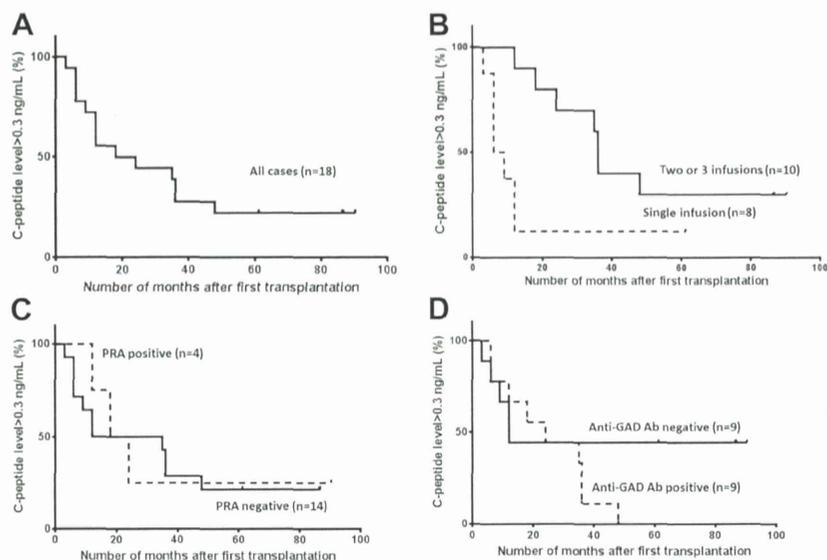


Fig 1. Islet graft survival according to Kaplan-Meier estimation. **(A)** Overall graft survival after islet transplantation from uncontrolled donors after cardiac death. Graft survivals (defined according to the C-peptide level) were 72.2%, 44.4%, and 22.2% at 1, 2, and 5 years, respectively. **(B)** Graft survival according to the number of islet infusions. Graft survivals of multiple infusions were 90.0%, 70.0%, and 30.0% at 1, 2, and 5 years, respectively, whereas the corresponding graft survival after a single infusion were 37.5%, 12.5%, and 12.5%, respectively. Multiple islet infusions significantly prolonged islet graft survival compared with a single infusion ($P = .017$). **(C)** Panel reactive antibody (PRA) positivity did not correlate with islet graft survival ($P = .85$). **(D)** Anti-glutamate decarboxylase (GAD) antibody positivity also did not correlate with islet graft survival ($P = .23$). The follow-up time ranged from 58.7 months to 94.1 months, and the mean follow-up time was 76.4 ± 3.3 months.

compared with those receiving a single infusion ($P = .017$). The graft survivals of multiple infusions were 90.0%, 70.0%, and 30.0% at 1, 2, and 5 years, respectively, whereas the corresponding graft survivals after a single infusion were 37.5%, 12.5%, and 12.5% (Fig 1B). Three of these recipients achieved insulin independence transiently after the 2nd transplantation for 215 days and after a 3rd transplantation for 14 days and 79 days.

Donor-specific alloantibodies were examined using flow PRA. Among these, 4 patients developed detectable levels of donor-specific alloantibodies. PRA positivity did not correlate with islet graft survival. Graft survivals for PRA-positive patients were 75.0%, 50.0%, and 25.0% at 1, 2, and 5 years, respectively, whereas the corresponding graft survivals for PRA-negative patients were 50.0%, 50.0%, and 21.4%, respectively (Fig 1C). Nine patients were positive for anti-glutamate decarboxylase (GAD) antibody. Being positive for anti-GAD antibodies also did not correlate with islet graft survival. The graft survivals of anti-GAD antibody-positive subjects were 66.7%, 44.4%, and 0% at 1, 2, and 5 years, respectively, whereas the corresponding graft survivals of anti-GAD antibody-negative subjects were 66.7%, 44.4%, and 44.4%, respectively (Fig 1D).

Hb_{A1c} levels and a requirement of exogenous insulin were improved before loss of graft function, but gradually worsened after the loss of graft function (Fig 2A). Serum creatinine levels were maintained even after the loss of graft function (Fig 2B).

All recipients became free of severe hypoglycemia unawareness, but at least 5 of 14 patients who had graft failure experienced recurrence of severe hypoglycemia after the loss of graft function.

DISCUSSION

Previously, we reported that pancreatic islet transplants from uncontrolled DCD sustained significant levels of C-peptide after a mean follow-up of 41 months [3]. The present report uses an extended follow-up from a multicenter study of outcomes after pancreatic islet transplantation from uncontrolled DCD.

Use of marginal-donor pancreata for islet isolation, such as DCD, is a way to alleviate donor shortages, particularly in countries such as Japan, where DBD are not readily available. According to the modified Maastricht classification [4], DCDs are classified into 5 categories; category I refers to subjects who are dead on arrival; category II is an unsuccessful resuscitation; category III (anticipated cardiac arrest) and category IV (cardiac arrest in a brainstem-dead donor) are described as controlled DCD; and category V (unexpected cardiac arrest in a patient in the intensive care unit) is described as uncontrolled DCD. Zhao et al reported that they isolated more viable islets from controlled DCD with short warm ischemia times than from pancreata from DBD, and that the islets from DCD were fully biofunctional [2]. Markmann et al reported that islets transplantation

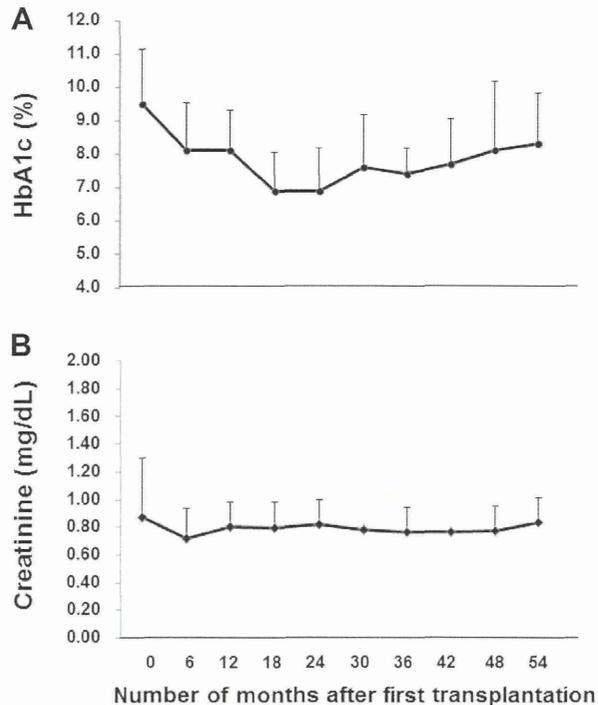


Fig 2. Changes in (A) Hb_{A1c} levels and (B) serum creatinine levels. Hb_{A1c} levels and the requirement of exogenous insulin were improved before loss of graft function, but gradually worsened after the loss of graft function. Serum creatinine levels were maintained even after the loss of graft function.

isolated from a single controlled DCD reversed diabetes of a T1DM recipient [1]. However, reports series of islet transplantations from DCD are limited. DCD are still not deemed to be suitable for donation.

In our series, all donors were considered to be uncontrolled DCD and category V of the modified Maastricht classification. Uncontrolled DCD have been used for kidney transplantation [11] and liver transplantation [12]. Islets are more likely to be damaged by warm ischemia in uncontrolled DCD. Damaged islets can be readily influenced by graft ischemia and/or instant blood-mediated inflammatory reactions [13]. Also, it has been suggested that DCD islets have lower contents of adenosine triphosphate and guanosine triphosphate, which could indicate energy loss [2]. The survival of transplanted islet grafts in our series reached only 22.2% at 5 years when >10,000 IEQ/kg were transplanted. However, in a publication from the Collaborative Islet Transplant Registry [14], the survival of transplanted islets from DBD after 5 years was 74%. Development of HLA antibodies against class I and/or II antigens can be associated with subsequent loss of islet grafts [15]. In our series, PRA-positive samples were detected less often, and a definitive association with graft survival could not be determined. Autoantibodies at the time of transplantation has been associated with reduced survival of islet grafts

[16,17]. The presence of autoantibodies did not significantly affect graft survival in our series. However, 5-year graft survival was not observed in the anti-GAD antibody-positive group (though this could have been due to the small study cohort in our series). Overall, the reason for lower graft survival at 5 years in our series is not known, but could reflect the adverse effect of long intervals between transplantations [3] or may be associated with energy depletion within grafts.

In conclusion, islet transplantation from uncontrolled DCD can relieve glucose instability and problems with hypoglycemia while the graft is functioning. However, islets from DCD may be associated with reduced long-term graft survival. Further improvements in outcome by modification of the protocols for the isolation and transplantation of islets are necessary to establish islet transplantation from DCD. Recently, the β -cell secretory reserve of engrafted islets was shown to be improved markedly with the use of a protocol involving induction of antithymocyte globulin (ATG) and inhibition of tumor necrosis factor (TNF) [18]. We have started a phase II clinical trial in T1DM patients for islet transplantation from DBD and DCD to evaluate a protocol involving induction of ATG and inhibition of TNF (UMIN-CTR: 000003977). This trial could play a critical part in establishing islet transplantation in Japan.

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A Novel Screening Test for Detecting Graft Thrombosis After Pancreatic Transplantation Using Contrast-enhanced Ultrasonography With Sonazoid

T. Ito^{a,*}, T. Kenmochi^a, T. Nishikawa^b, M. Maruyama^c, M. Kusaka^d, H. Sasaki^d, T. Asano^c, H. Matsubara^e, and K. Hoshinaga^d

^aDepartment of Organ Transplant Surgery, Fujita Health University, School of Medicine, Aichi, Japan; ^bDivision of Liver Biliary Tract and Pancreas Disease, Fujita Health University, School of Medicine, Aichi, Japan; ^cDepartment of Surgery, National Hospital Organization, Chiba East Hospital, Chiba, Japan; ^dDepartment of Urology, Fujita Health University, School of Medicine, Aichi, Japan; and ^eDepartment of Frontier Surgery, Chiba University, Graduate School of Medicine, Chiba, Japan

ABSTRACT

Pancreatic graft thrombosis is the primary cause of nonimmunologic graft loss, with an incidence ranging from 5% to 15%. Therefore, developing a screening test to detect graft thrombosis after pancreatic transplantation is important. We created a screening test to assess graft thrombosis after pancreatic transplantation using contrast-enhanced ultrasonography (CEUS) with Sonazoid in addition to Doppler ultrasonography. A total of seven patients were examined using CEUS after undergoing pancreatic transplantation. All patients were observed to have a clear blood flow from the horizontal region to the peripheral region of the splenic vein in the pancreatic graft, and only one of the seven patients exhibited a blood flow in the horizontal portion of the splenic vein on Doppler ultrasonography performed immediately after pancreatic transplantation. Results from CEUS with Sonazoid showed the blood flow in the splenic vein and parenchyma of the pancreatic graft in detail, despite the slow and lateral blood flow in the splenic vein of the pancreatic graft immediately after transplantation.

PANCREATIC graft thrombosis is the primary cause of nonimmunologic graft loss, with an incidence ranging from 5% to 15% [1–3]. Therefore, developing a screening test to detect graft thrombosis after pancreatic transplantation is important. However, it is difficult to apply enhanced computed tomography, which exhibits the highest sensitivity for thrombosis, as a screening test due to the use of nephrotoxic contrast agents, especially in simultaneous pancreas-kidney transplant recipients, who account for more than 80% of patients who undergo pancreatic transplantation. Although Doppler ultrasonography is a common modality used to evaluate the graft blood flow after transplantation, the presence of intestinal gas and a slow and lateral blood flow may disturb ultrasound images of the pancreatic graft.

Therefore, we developed a screening test to detect graft thrombosis after pancreatic transplantation using contrast-enhanced ultrasonography (CEUS) with Sonazoid (Daiichi Sankyo Pharmaceutical, Tokyo, Japan). Sonazoid is a second-

generation ultrasound contrast agent without nephrotoxicity that consists of stabilized gas microbubbles containing perfluorobutane surrounded by a phospholipid shell.

METHODS

The blood flow in the pancreatic graft was monitored using CEUS on days 1, 3, 5, 7, 14, 21, and 28 after transplantation. A total of 16 μ L of Sonazoid was dissolved in 2 mL of water, and an intravenous bolus injection of 0.5 mL of the solution was administered followed by a 10-mL normal saline flush. Doppler ultrasonography was performed simultaneously. The ultrasound equipment used in this examination was the GE Logiq E9 (General Electric Healthcare Medical Systems, Milwaukee, WI, United States) with a convex probe (3.75-MHz

*Address correspondence to Taihei Ito, MD, PhD, Department of Organ Transplant Surgery, Fujita Health University, 1-98 Dengakugakubo, Kutsukake, Toyoake, Aichi 470-1192, Japan. E-mail: i-taihei@fujita-hu.ac.jp

Table 1. Summary of the Seven Pancreatic Transplantation Patients Who Underwent CEUS*

Case	Age	Gender	Operation	Venous Flow	Venous Flow	Venous
				With Doppler US	With CEUS	Thrombus
1	39	Female	SPK	-	+	-
2	41	Female	SPK	-	+	-
3	45	Male	SPK	-	+	-
4	39	Female	PAK	-	+	-
5	37	Female	PAK	-	+	+
6	58	Female	SPK	+	+	-
7	44	Female	SPK	-	+	+

Abbreviations: US, ultrasound; CEUS, contrast-enhanced US; SPK, simultaneous pancreatic and kidney transplantation; PAK, pancreatic transplantation after kidney transplantation; +, the image obtained on day 1 after transplantation to evaluate the presence of venous thrombi and assess the venous blood flow was positive; -, the image obtained on day 1 after transplantation to evaluate the presence of venous thrombi and the venous blood flow was negative.

*The blood flow in the pancreatic graft was monitored using contrast-enhanced ultrasonography and Doppler sonography on days 1, 3, 5, 7, 14, 21, and 28 after transplantation.

frequency). The imaging mode was wideband harmonic imaging (pulse subtraction) with transmission/reception frequencies of 1.8 and 3.5 MHz, respectively. The mechanical index of the acoustic output was set to 0.2, and the dynamic range was set to 50 to 65 dB.

RESULTS

A total of seven patients were examined with CEUS after undergoing pancreatic transplantation. All patients were observed to have a clear blood flow from the horizontal region to the peripheral region of the splenic vein in the pancreatic graft 1 day after transplantation, and only one of seven patients exhibited a blood flow in the horizontal portion of the splenic vein on Doppler ultrasonography (Table 1).

Two of seven recipients were found to have graft thrombosis. The patient in case 5 had thrombi in both the venous and arterial systems 1 day after pancreatic transplantation (Fig 1). We conservatively followed the thrombi because the pancreatic body and tail were receiving an adequate blood flow through the superior mesenteric artery and exhibited

good drainage. Fifty days after transplantation, the venous thrombus dissolved, whereas the arterial thrombus in the SPA remained (Fig 2).

The patient in case 7 had melena on days 7 and 11 after transplantation. The hemostatic agents affected the patient's hemostatic status, thus resulting in graft thrombosis 12 days after transplantation. Unfortunately, the patient required graftectomy.

DISCUSSION

Recent reports have documented the use of CEUS after pancreatic transplantation [4-6], all of which used SonoVue (Bracco, Milan, Italy) as a contrast-enhanced agent. This is the first report of the application of CEUS after pancreatic transplantation using Sonazoid, a second-generation ultrasound contrast agent that consists of stabilized gas microbubbles containing perfluorobutane surrounded by a phospholipid shell. This agent has the longest activity for ultrasound contrast enhancement among contrast-enhanced agents and can be used to evaluate both the blood flow in the splenic vein and the degree of parenchymal perfusion in the pancreatic graft.

Evaluating parenchymal perfusion provides information regarding the need for additional treatments, such as thrombolytic therapy, to treat pancreatic graft thrombosis. We generally try to manage such cases without administering additional treatment for graft thrombosis, with the exception of the routine administration of heparin to prevent other surgical complications, such as hemorrhage, when the blood flow maintains proper pancreatic parenchymal perfusion.

Usually, physicians encounter opportunities to detect graft thrombosis in the pancreas 1 or 2 days after transplantation; however, in this study, the patient in case 7 exhibited graft thrombosis at least 10 days after transplantation because we screened out the possibility of graft thrombosis on day 9 using CEUS. Additionally, no serum blood glucose elevation was observed in that case when the graft thrombosis was detected. During graftectomy, it was confirmed that the anastomosis did not show stenosis.

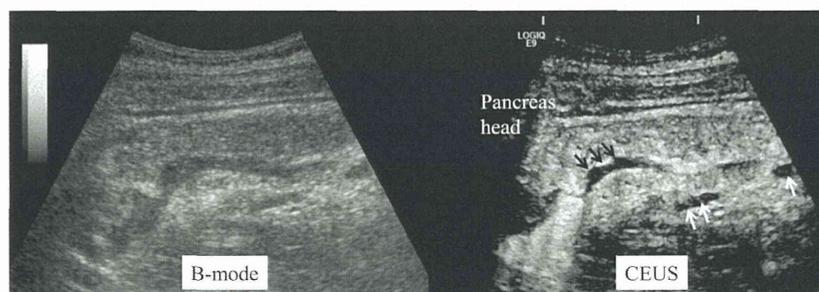


Fig 1. CEUS performed on day 1 after pancreatic transplantation in case 5. CEUS provided clear images of the blood flow in the pancreatic graft, showing thrombi in the splenic vein (black arrows) and splenic artery (white arrows) as defects of enhancement. The remaining venous flow was detected on the side of thrombus.



Fig 2. CEUS performed on day 50 after pancreatic transplantation in case 5. CEUS showed clear images of the venous flow without thrombi (*black arrows*). The arterial thrombus in the splenic artery remained (*white arrows*), although the parenchymal perfusion was sufficient.

Therefore, we concluded that the hemorrhage observed on day 7 originated from the anastomosis between the graft duodenum and jejunum, after which the discontinuation of heparin and the administration of hemostatic agents induced hypercoagulation, resulting in graft thrombosis.

One of the most important keys for successful pancreatic transplantation is to manage graft thrombosis, including monitoring the patient. For this purpose, we also plan to create additional images from CEUC using ultrasonic angiography and/or three-dimensional angiography. CEUS with Sonazoid can be used to create clear ultrasonic dynamic images of the blood flow in the pancreatic graft. Another factor for successful pancreatic transplantation is to manage allograft rejection. It is well known that performing pancreatic graft biopsies is more difficult than performing other types of organ transplantation. Kersting et al reported that the time intensity curve in rejected pancreatic grafts is lower than that observed in pre-rejected grafts, whereas the time intensity curve in treated grafts recovers. We recorded all the recipients' ultrasonic dynamic image data obtained using CEUS to plot time intensity curves for rejection; however, fortunately, no recipients have suffered from rejection thus far.

CEUS performed using Sonazoid provides important information for achieving successful pancreatic transplantation.

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Single-Institution Outcomes in the First Year of Pancreas Transplantation From Brain-Dead Donors

T. Ito, T. Kenmochi, A. Suzuki, M. Maruyama, M. Kusaka, H. Sasaki, T. Asano, H. Matsubara, and K. Hoshinaga

ABSTRACT

Background. Under a revision to the law in 2010, the number of pancreas transplantations from brain-dead donors has been increasing in Japan. We started a new Pancreatic Transplant Program at Fujita Health University Hospital in September 2012.

Methods. A total of 11 cases of pancreas transplantation from brain-dead donors performed at Fujita Health University Hospital were analyzed in terms of the background characteristics of the donors and recipients and the outcomes.

Results. The mean age of the recipients was 45.2 years, and all recipients had a long-term history of diabetes (mean: 32.5 years). In the simultaneous pancreas and kidney transplantation (SPK) cases, the patients also had a long history of hemodialysis (mean: 8.0 years). Although the average donor age was 42.5 years, 90% of the donors were marginal donors, defined according to the following factors: (1) >45 years old, (2) death from cardiovascular disease, (3) episodes of cardiac arrest, (4) use of high doses of catecholamines. The pancreatic graft survival rate was 100%, although 1 patient required a small amount of insulin to maintain euglycemia. In addition, the kidney graft survival rate was also 100% in the SPK cases.

Conclusions. The new Pancreatic Transplant Program at Fujita Health University has provided excellent outcomes for type 1 diabetic patients.

IN JAPAN, ONLY 64 CASES of pancreas transplantation from brain-dead donors were performed over the 11-year period prior to 2009 [1]. Following a revision to the law in 2010, 81 cases of pancreas transplantation from brain-dead donors were performed within 2.5 years [2].

We previously performed 30 pancreas transplantations, including 18 cases involving living donors, at the National Chiba-East Hospital since January 2004 [3,4], achieving successful results with a pancreatic graft survival rate of 94% and a kidney graft survival rate of 100%. Based on these results, we started a new Pancreatic Transplant Program at Fujita Health University Hospital in 2012, and 11 pancreas transplantations were performed in the first year. In this report, we describe the outcomes of pancreas transplantation at Fujita Health University in the first year.

METHODS

A total of 11 pancreas transplantations (8 simultaneous pancreas and kidney transplantations [SPK], 2 pancreas after kidney transplantations [PAK], 2 pancreas transplantation alone [PTA]) from

brain-dead donors were performed at Fujita Health University Hospital between August 2012 and July 2013. The data were analyzed in terms of the background characteristics of the donors (age, body mass index [BMI], hemoglobin A1c [HbA1C], serum creatinine [s-Cre], cause of death, episodes of cardiopulmonary arrest [CPA] and dose of catecholamines), the total ischemic time (TIT) of the pancreatic graft, the background characteristics of the

From the Department of Organ Transplant Surgery (T.I., T.K.), Fujita Health University, School of Medicine, Aichi, Japan; Division of Endocrinology and Metabolism (A.S.), Fujita Health University, School of Medicine, Aichi, Japan; Department of Surgery (M.M., T.A.), National Hospital Organization, Chiba East Hospital, Chiba, Japan; Department of Urology (M.K., H.S., K.H.), Fujita Health University, School of Medicine, Aichi, Japan; and Department of Frontier Surgery (H.M.), Chiba University, Graduate School of Medicine, Chiba, Japan.

Address reprint requests to Taihei Ito, MD, PhD, Department of Organ Transplant Surgery, Fujita Health University, 1-98 Dengakugakubo, Kutsukake, Toyoake, Aichi 470-1192, Japan. E-mail: i-taihei@fujita-hu.ac.jp

0041-1345/14/\$—see front matter
<http://dx.doi.org/10.1016/j.transproceed.2013.11.062>

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360 Park Avenue South, New York, NY 10010-1710

recipients (age, duration of diabetes mellitus, preoperative HbA1C and duration of hemodialysis), and outcomes (pancreatic graft survival, serum C-peptide > 0.3 ng/mL), insulin-free status, hemodialysis-free status, basal serum C-peptide level at 1 month after transplantation, glucagon-stimulated serum C-peptide level and the time course of the HbA1C and s-Cre levels.

Glucagon stimulation tests were performed using intravenous loading of 1 mg of glucagon at almost 1 month after transplantation. The serum samples were obtained at 0 and 6 minutes after loading, and the ΔC-pep was calculated based on the difference between these values.

RESULTS

The mean age of the donors was 38.8 years (17–66), including 4 patients (36.4%) over 45 years of age who were considered to be marginal donors (Table 1). The mean BMI of the donors was 22.8 (18.7–29.4) and the mean HbA1C level was 5.23% (4.9–5.7). The s-Cre level in 4 donors exceeded 2.0 mg/dL right before procurement; however, all minimum s-Cre levels were under 1.0 mg/dL during the patients’ stay in the intensive care unit. The cause of death was cardiovascular disease in 6 cases, and 6 donors had a history of episodes of CPA; both of these factors are considered to be criteria for marginal donors. The mean TIT of the pancreatic grafts was 853.9 minutes (697–964).

The mean age of the recipients was 45.8 years (37–58), and all recipients had a long-term history of diabetes (mean: 31.1 years, 19–43; Table 2). In the SPK cases, the patients also had a long-term history of hemodialysis (mean: 8.6 years, 2–12), except for the patient in case 2 who underwent SPK as a second kidney transplantation procedure and did not receive hemodialysis after the first transplantation. The mean pre-operative HbA1C level in the recipients was 6.65% (5.0–8.2).

Table 1. Summary of Brain-Dead Donors for Pancreas Transplantation and the Total Ischemic Time of the Pancreatic Grafts

Donor Case	Age (y)	Gender	Cause of Death	Episode of CPA	BMI	HbA1C (%)	s-Cre (mg/dL)	TIT (min)
1	62	Female	CVA	No	20.3	5.1	0.7	815
2	21	Male	Hypoxia	Yes	29.4	5.2	2.2	911
3	30	Male	Hypoxia	Yes	18.7	4.9	1.1	931
4	66	Female	CVA	No	25.3	5.7	4.5	844
5	35	Male	CVA	No	22.2	5.7	6.81	697
6	55	Female	CVA	Yes	18.7	5.5	0.79	843
7	25	Male	Hypoxia	Yes	21.4	5.3	0.82	859
8	43	Female	Hypoxia	Yes	28.1	5	0.57	813
9	17	Male	CVA	Yes	23.1	5.1	4	743
10	24	Male	Trauma	No	20.7	5	0.7	877
11	49	Female	CVA	No	23	5	0.5	964

Four (36.4%) donors were over 45 years of age, which is considered to be a marginal donor. The cause of death was CVA in 6 cases, and 6 donors had a history of episodes of CPA; both of these factors are considered to be criteria for marginal donors. No patient received high doses of catecholamines to maintain blood pressure. Ten of 11 donors had factors considered to be marginal, half of whom had multiple factors. The data for the s-Cre levels obtained right before procurement were used.

Abbreviations: CVA, cardiovascular disease; CPA, cardiopulmonary arrest; BMI, body mass index; HbA1C, hemoglobin A1c; s-Cre, serum creatinine; TIT, total ischemic time.

Table 2. Summary of Recipients of Pancreas Transplantation

Case	Age (y)	Gender	Period of DM (y)	HbA1C (%)	Period of HD (y)
1	58	Female	36	7.3	11
2	49	Female	43	8.2	0
3	44	Female	25	5.5	7
4	53	Male	38	5	12
5	41	Male	19	6.2	N/A
6	39	Female	28	7.3	6
7	41	Female	36	6.5	10
8	45	Male	22	6.5	2
9	39	Female	29	8	N/A
10	37	Female	26	7.3	N/A
11	58	Female	40	5.3	12

All recipients had a long-term history of diabetes, and a long-term history of hemodialysis was observed in the SPK cases, except in case 2 in which the patient underwent SPK as a second kidney transplantation procedure and did not receive hemodialysis after the first transplantation. The data for the HbA1C levels obtained before transplantation were used.

Abbreviations: DM, diabetes mellitus; HbA1C, hemoglobin A1c; HD, hemodialysis; N/A, not available.

All recipients were positive for serum C-peptide after undergoing pancreas transplantation, and the glucagon stimulation test performed at 1 month after transplantation showed a high level of insulin secretion in the pancreatic graft (Table 3). The average HbA1C level at 1 month after transplantation was 5.3% and was maintained below 6.0% (Fig 1A). Among the SPK cases, all recipients also achieved a hemodialysis-free status after transplantation and have maintained an s-Cre level below 2.0 mg/dL (Fig 1B).

DISCUSSION

Under a revision to the law made in 2010, the number of annual donors in Japan has increased more than 5 times, and the rate of pancreas transplantation from brain-dead donors has also increased [1,2]. However, the severe shortage of donors continues. Therefore, approximately 80% of donors for pancreas transplantation in Japan are

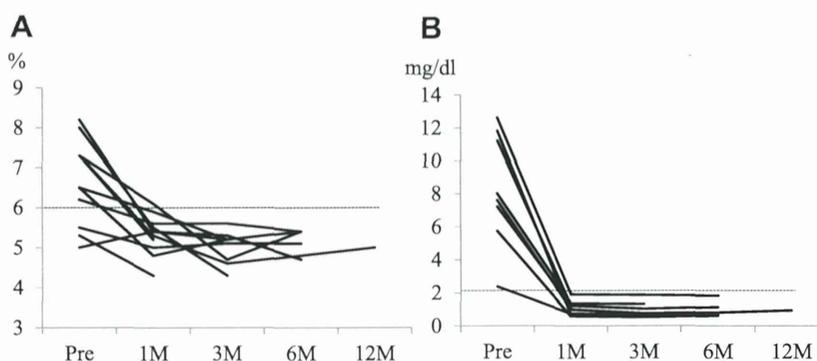
Table 3. Summary of the Results of Transplantation

Case	Operation	HD-Free	Insulin-Free	C-pep (ng/mL)	ΔC-pep (ng/mL)	HbA1C (%)
1	SPK	Yes	Yes	1.3	0.9	5.3
2	SPK	Yes	Yes	1.9	4.7	5.6
3	SPK	Yes	Yes	4.3	1.4	5
4	SPK	Yes	No	1	0.6	5.2
5	PTA	N/A	Yes	0.9	0.9	5.6
6	SPK	Yes	Yes	2	2.5	6.2
7	SPK	Yes	Yes	1.6	3.6	4.8
8	SPK	Yes	Yes	2	3.4	5.9
9	PAK	N/A	Yes	2.2	2.1	5.5
10	PAK	N/A	Yes	2.9	3.5	5.2
11	SPK	Yes	Yes	3	3.1	4.3

All data were obtained at 1 month after transplantation. All recipients exhibited positive levels of serum C-peptide after pancreas transplantation, and the insulin secretion in the pancreatic graft was evaluated using a glucagon stimulation test.

Abbreviations: SPK, simultaneous pancreas and kidney transplantation; PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; HD, hemodialysis; C-pep, C-peptide; N/A, not available; HbA1C, hemoglobin A1c.

Fig 1. (A) Time course of the hemoglobin A1c (HbA1C) levels after pancreas transplantation ($n = 11$). The HbA1C levels of all recipients decreased to below 6.0% and were maintained within the normal range after pancreas transplantation. (B) Time course of the serum creatinine (s-Cre) levels after pancreas transplantation in the simultaneous pancreas and kidney transplantation (SPK) cases ($n = 8$). All SPK recipients achieved a hemodialysis-free status after transplantation and maintained an s-Cre level below 2.0 mg/dL.



marginal donors. At our institution, 10 of 11 donors had marginal factors, half of whom had multiple factors.

The severe shortage of donors results in a long waiting period for pancreas transplantation [1]. Therefore, SPK recipients usually have a long history of diabetes mellitus and hemodialysis. The patient survival rate is 95.5% at 5 years after transplantation, and the pancreatic graft survival rate is 85.7%, 79.4%, and 72.1% at 1, 3, and 5 years after transplantation, respectively, in Japan. At our institution, all pancreatic grafts have maintained a good function after pancreas transplantation, resulting in an insulin-free status, except in case 4. The patient in case 4 required a small amount of insulin injections to maintain euglycemia, although the serum C-peptide level was positive. The partial function of the pancreatic graft observed in case 4 resulted in the stability of the serum glucose level, and a kidney graft-induced hemodialysis-free status promises to improve the poor prognosis of type 1 diabetic patients with end-stage renal disease [5–7].

The glucagon stimulation test was performed in all recipients at almost 1 month after pancreas transplantation. The \otimes C-pep level derived using this test is considered to be one of the most reliable parameters for evaluating glucagon stimulation after pancreas transplantation in our institution. The \otimes C-pep levels in both cases 1 and 4, in which the donor age was over 60 years, were under 1.0. To avoid pancreas transplantation using older donors, a solution to the severe shortage of donors is awaited in Japan.

In conclusion, Fujita Health University is a high-volume center for pancreas transplantation in Japan. In this study,

only 1 patient with SPK required a small amount of insulin after transplantation, and pancreatic graft survival was achieved in 100% of cases, although 10 of 11 donors were considered to be marginal and the recipients had a long history of both diabetes and dialysis. Our new Pancreatic Transplant Program has thus provided excellent outcomes for patients with type 1 diabetes.

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