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Three-Dimensional Computed Tomographic Volumetric Changes in Pancreas Before and After Living Donor Surgery for Pancreas Transplantation: Effect of Volume on Glucose Metabolism

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ABSTRACT

In the present study, we aimed to compare the pancreas volumetric changes before and after living donor surgery for pancreas transplantation, using three-dimensional (3D) computed tomography (CT) and glucose metabolism. Pancreatic volume (PV) measurement using 3D CT was performed in 13 consecutive donors who underwent distal pancreatectomy for simultaneous living donor pancreas and kidney transplantation. PV was measured using a workstation before and 3 months after living donor operation. As the parameters of glucose metabolism, hemoglobin A1c (HbA1c) level, fasting plasma glucose (FPG) level, body mass index (BMI), homeostasis model assessment of insulin resistance (HOMA-IR), and insulinogenic index (IGI) were examined simultaneously with the PV measurement. The preoperative and postoperative PVs of pancreas was 30 ± 5 mL and 42 ± 9 mL, respectively. The postoperative PV was significantly higher than the preoperative PV ($P < .01$) and increased by approximately 40% at 3 months after surgery. The postoperative FPG and HbA1c levels were significantly higher than the preoperative values ($P < .01$). BMI decreased significantly after surgery ($P < .01$). No differences in HOMA-IR and IGI were noted between before and after surgery. Diabetes mellitus was not observed any of the 13 living donors during this period. Distal pancreatectomy for living donors caused an increase in the PV and maintained insulin resistance, but it was not sufficient to maintain glucose metabolism at the preoperative state.

THE FIRST LIVING DONOR PANCREAS TRANSPLANTATION using a segmental pancreas (distal pancreas body and tail) was performed at the University of Minnesota on June 20, 1979 [1]. In 1994, the first simultaneous pancreas and kidney transplantation was also performed at the University of Minnesota [2]. Because of the severe shortage of deceased donors in Japan and the satisfactory outcomes of the living donor pancreas transplantations that have been performed at the University of Minnesota, living donor pancreas transplantation was introduced in Japan on January 7, 2004 [3]. A recently developed laparoscopic surgical procedure has been found to be minimally invasive and safe and has attracted more living donors, thus increasing the donor pool for pancreatic transplantation [4]. Although the satisfactory outcome of living donor operation has improved, the possible deterioration of glycemic controls in living donors, as a result of distal pancreatectomy, has been a long-standing concern.

Computed tomographic (CT) examination after pancreas transplantation has been shown to be a useful method for detecting postoperative complications of pancreas allograft transplantation [5]. Three-dimensional (3D) CT volumetry of the liver, kidney, and lung is considered to be a reliable and accurate method for volumetric assessment [6–8]. Pancreatic volumetry using 3D CT has also been shown to provide accurate measurements for pancreas transplantation [9]. In patients with neoplasms, pancreatic volumetric assessment is a useful predictor of new-onset diabetes mellitus following distal pancreatectomy [10].

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However, in the case of pancreas from living donors, no data are available preoperative and postoperative volumetric assessments.

This present study describes 3D CT volumetric changes in pancreas before and after living donor pancreas transplantation and the effect of the volume of the reserved pancreas on the glucose metabolism of living donors.

METHODS

Of the 13 donors examined, 3 were men and 10 were women. The median donor age at transplantation was 56 years (range, 28–66 years). All the donors were healthy and fulfilled the previously reported stringent criteria for living donors for pancreas transplantation [3]. Pancreatic volume (PV) measurement using 3D CT was performed in 13 consecutive living donors who underwent distal pancreatectomy for simultaneous transplantation of the pancreas and kidney between May 2007 and April 2011. CT examination was performed using a 4-channel CT scanner (Aquilion Super 4, Toshiba, Tokyo, Japan), with intravenous administration of iodine contrast media. Each CT scan was obtained using the following settings: tube voltage, 120 kV; tube current, 220 mA; section thickness, 1 mm; reconstruction interval, 0.5 mm; pitch factor, 5.5; field of view, 32 to 40 cm; and matrix, 512 × 512. To accurately estimate the volume of the pancreatic parenchyma, contrast enhancement with an intravenous contrast medium was applied during 3D CT. The pancreatic head volume was outlined by the left edge of a superior mesenteric vein, and PV was measured before and 3 months after the living donor operation (Fig 1), using the workstation Virtual Place Fujin (AZE Software Inc., Tokyo, Japan).

As parameters of glucose metabolism, hemoglobin A1c (HbA1c) level, fasting plasma glucose (FPG) level, and body mass index (BMI) were examined simultaneously during PV measurement. The insulin resistance of a pancreas was evaluated by the homeostasis model assessment of insulin resistance (HOMA-IR) [11], which was calculated as [FPG (mg/dL) × fasting insulin (μU/mL)/405], with lower values indicating a higher degree of insulin resistance. To evaluate the pancreatic β-cell function, we calculated the insulinogenic index (IGI) at 30 minutes during a 75-g oral glucose tolerance test (OGTT), as follows [12]:

$$\begin{aligned} \text{IGI} = {} & [\text{insulin at 30 minutes}(\mu\text{U/mL}) \\ & -\text{insulin at 0 minutes } (\mu\text{U/mL})]/ \\ & [\text{plasma glucose at 30 minutes } (\text{mg/dL}) \\ & -\text{plasma glucose at 0 minutes } (\text{mg/dL})]. \end{aligned}$$

This index can be used to evaluate the initial insulin secretion after glucose loading in healthy subjects and patients with impaired fasting glycemia/impaired glucose tolerance.

The statistical significance of the differences was analyzed by a paired *t* test, and *P* values of <.01 were considered to be statistically significant.

RESULTS

The mean PV of the entire pancreas was 66 mL. The mean PV of the preserved pancreatic head and allograft pancreatic body and tail were 30 mL (46%) and 36 mL (54%), respectively (Fig 2). No differences in preoperative 3D CT volumetric measurements were noted between the pancreatic head and body and tail. Almost half of the pancreatic parenchyma was obtained by distal pancreatectomy during living donor operation.

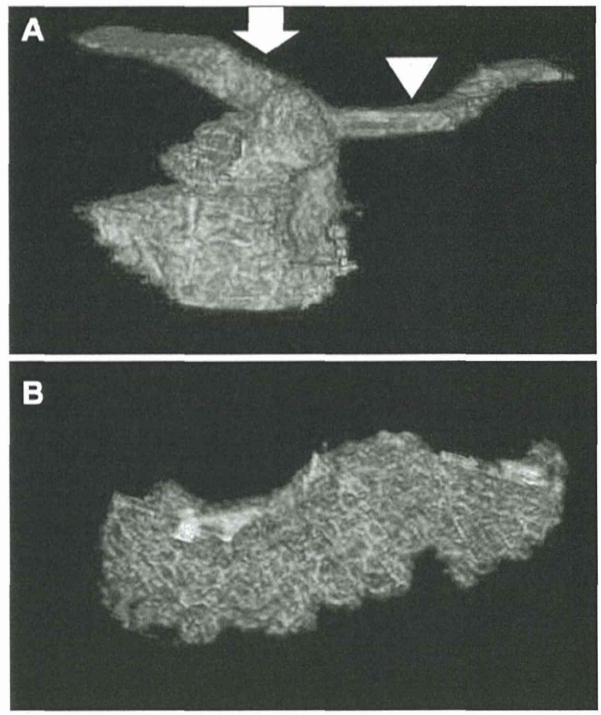

Fig 1. Preoperative images of three-dimensional computed tomography pancreatic volumetry. (**A**) The pancreatic head is outlined by the left edge of a superior mesenteric vein (arrow) conjoined with a splenic vein (arrowhead). (**B**) A pancreatic body–tail as an allograft.

FPG levels increased from 88 ± 1 before surgery to 104 ± 6 after surgery ($P < .01$). Likewise, the postoperative HbA1c level was significantly higher as the compared to the preoperative HbA1c level (6.1 ± 0.4 vs 5.6 ± 0.2,

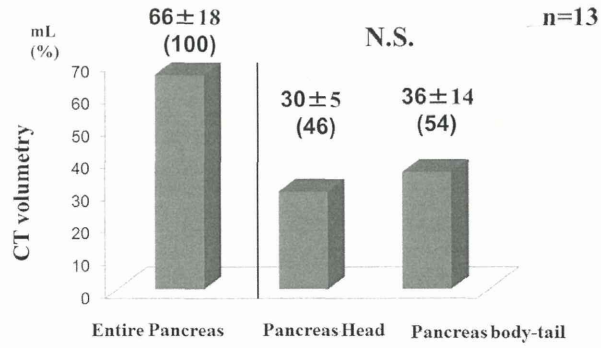

Fig 2. Preoperative three-dimensional (3D) computed tomography (CT) volumetry of an entire pancreas, pancreatic head, and body–tail from donors. No differences in preoperative 3D CT volumetric values were found between the pancreatic head and body–tail. N.S., not significant.

respectively; $P < .01$). No cases of diabetes mellitus was noted in among all the 13 living donors during this period. The BMI decreased from 23.0 ± 0.5 before surgery to 21.4 ± 2.2 after surgery ($P < .01$). No significant differences in HOMA-IR (1.3 ± 0.7 vs 1.0 ± 0.4, respectively) and IGI (1.1 ± 1.1 vs 0.6 ± 0.5, respectively) were noted between the values before and after surgery (Table 1).

The preoperative and postoperative PVs were 30 ± 5 mL and 42 ± 9 mL, respectively. The postoperative PV was significantly higher than the preoperative PV ($P < .01$) and increased by approximately 40% at 3 months after surgery (Fig 3).

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The preoperative PV on 3D CT was 42 mL (Fig 4A), and the postoperative PV was 52 mL (Fig 4B) at 3 months after surgery, thus indicating an obvious increase in the living donor PV after distal pancreatectomy.

DISCUSSION

The effects of distal pancreatectomy on glucose metabolism and β-cell function of living donors have been studied [13–15]. Insulin secretion was found to be lower after distal pancreatectomy [13]. Our study showed that the IGI, calculated using the 75-g OGTT and used to assess β-cell function, did not decrease significantly and tended to decrease after donor surgery. Although FPG and HbA1c levels were reported to be significantly higher postoperatively than the values preoperatively, normal glucose and HbA1c levels were maintained [13–15]. In addition, our study demonstrated that plasma glucose and HbA1c levels increased significantly at 3 months after distal pancreatectomy and did not exceed the reference range. The effects of distal pancreatectomy on increased secretion levels have been limited to our donor operations.

Obesity is now a contraindication to living pancreas donation [15]. A living donor who is to undergo distal pancreatectomy should be strongly advised to avoid becoming obese. Our study showed the BMI of all the donors was maintained within the reference range, but decreased significantly after the operation. The HOMA-IR allows for a quantitative assessment of the contributions of fasting plasma insulin and glucose concentrations to insulin

Table 1. Glycemic Metabolism of Donors (n = 13) Before and After Surgery

	Before Surgery	After Surgery
Fasting plasma glucose (mg/dL)	88 ± 1	104 ± 6*
HbA1c (NGSP%)	5.6 ± 0.2	6.1 ± 0.4*
Body mass index (kg/m^2)	23.0 ± 0.5	21.4 ± 2.2*
HOMA-IR	1.3 ± 0.7	1.0 ± 0.4
Insulinogenic index	1.1 ± 1.1	0.6 ± 0.5

Abbreviations: NGSP, National Glycohemoglobin Standardization supported by the National Institutes of Diabetes and Digestive and Kidney Diseases; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance.
*Statistically significant ($P < .01$).

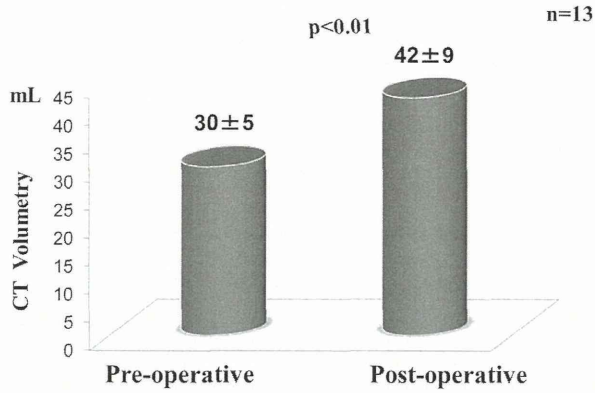

Fig 3. The postoperative computed tomography (CT) pancreatic volume (PV) was significantly higher than the preoperative PV and increased by approximately 40% at 3 months after surgery.

resistance. The HOMA-IR of our donors was maintained within normal levels. Thus the living donor operation did not diminish the ability of insulin resistance to maintain the postoperative body weight. These results on BMI and

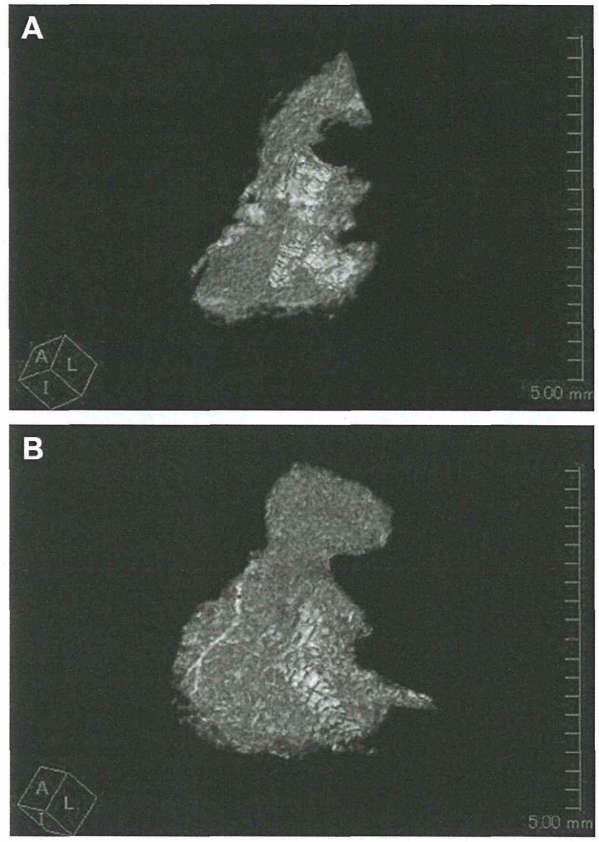

Fig 4. The three-dimensional computed tomography volumetric changes in a 42-year-old male donor before (**A**) and after distal pancreatectomy (**B**).

HOMA-IR may compensate for the decrease in insulin secretion after distal pancreatectomy.

Through 3D CT volumetry, we were able to estimate the volume of each allograft, such as that of the liver, kidney, and lung, and obtain additional information on preoperative allograft anatomical architecture [6–8]. The information is useful to determine the living allograft to be resected and postoperatively evaluate transplants. This technique could be used more widely to assess the preserved organ of living donors. Previous studies reported that the pancreatic weight in rats increased significantly with the increase in the volume of the preserved pancreas by distal pancreatectomy [16,17]. Bombesin, a tetradecapeptide hormone analogue of a mammalian gastrin-releasing peptide, plays a role in pancreatic growth and regeneration. When no bombesin was administered, the pancreatic weights in rats increased twice as much as the preoperative values after 90% of the PV was resected by distal pancreatectomy [17].

In humans, distal pancreatectomy did not induce an increase in PV, as evidenced on 3D CT [18]. However, this report included cases of chronic pancreas, pancreatic carcinoma, and pancreatic metastasis, but did not include normal pancreas. Our study demonstrated that the normal pancreas that fulfilled the stringent donor criteria had apparently exhibited increased PV on 3D CT after distal pancreatectomy. PV assessment was used as a predictor of new-onset diabetes mellitus after distal pancreatectomy for pancreatic neoplasm [10]. This study conclude that preoperative HbA1clevels higher than 5.7% and a pancreatic resection rate higher than 44% were independent risk factors for new-onset diabetes mellitus after distal pancreatectomy. Our study showed that in the cases with preoperative HbA1c levels lower than 5.7% and mean pancreatic resection rates of almost 50%, no new-onset diabetes mellitus was observed. Distal pancreatectomy for living donors resulted in an increase in the volume of the reserved pancreas and maintenance of insulin resistance; however, these effects were not to sufficient to maintain the preoperative insulin secretion levels. Recently, local in vivo *GSK3β* knockdown was found to promote β-cell and acinar-cell regeneration in 90% pancreatectomized rats [19]. Intrapancreatic *GSK3β* knockdown leads to increased β-cell mass by promoting β-cell proliferation and differentiation. In the near future, this gene therapy may be helpful to promote human β-cell mass regeneration after donor distal pancreatectomy to maintain glucose metabolism.

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Association of DNA Amplification With Progress of BK Polyomavirus Infection and Nephropathy in Renal Transplant Recipients

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ABSTRACT

Purpose. BK polyomavirus-associated nephropathy (BKVAN) is an important cause of renal allograft loss. Immunosuppression therapy in renal transplant recipients can lead to the reactivation of latent BK polyomavirus (BKV) infection, leading to BK viruria and viremia. This single-center study aimed to clarify the association between quantitative measurement of BKV DNA and the progression of BKV infection, and secondly to identify the risk factors associated with the evolution of viruria to viremia.

Methods. We retrospectively analyzed 266 patients who underwent renal transplantation in our center from October 2006 to February 2013. We examined the viral loads of BKV in urine and plasma by quantitative real-time polymerase chain reaction assay after screening all of the recipients by urinary sediment examination. BKVAN was diagnosed by histological examination with immunohistochemistry of the large T antigen in biopsy specimens.

Results. Overall, 22 recipients showed BK viruria alone, whereas 22 progressed to BK viremia, of which 6 patients were diagnosed with BKVAN. Among BKVAN patients, 2 cases progressed to graft loss at 59 months and 31 months after diagnosis, respectively. In BKVAN group, the plasma viral loads were significantly higher than those in viremia without nephropathy ($P < .001$). Multivariate analysis revealed that the evolution of viruria to viremia was associated with recipient age over 55 years (odds ratio, 32.08; 95% confidence interval, 2.1–489.5) and tacrolimus exposure (odds ratio, 11.98; 95% confidence interval, 1.34–107.04).

Conclusions. The progression from viremia to BKVAN was strongly associated with increasing plasma viral loads for BKV DNA. The cutoff value of 1×10^4 copies/mL for plasma viral loads could differentiate between BKVAN and viremia alone. Further, recipient age over 55 years and tacrolimus exposure were independently associated with the evolution of viruria to viremia.

BK polyomavirus-associated nephropathy (BKVAN) is an important cause of renal allograft loss. Immunosuppression therapy can lead to the reactivation of latent BK polyomavirus (BKV) infection, leading to BK viruria and viremia in renal transplant recipients with stereotypical evolution [1]. The prevalence of BK viremia is in 10% to 30% [2] and BKVAN develops in 1% to 10% of renal transplant recipients [3,4]. Further, graft loss secondary to nephropathy has been demonstrated to occur at a rate of 46% [4].

Thus far, no effective agent is available for the treatment of BK infections; therefore, reduction in the immunosuppression is currently standard intervention. Early intervention provides the clearance of BK viremia in 70% to 90% of patients [3], and such clearance is associated with better graft survival at 5 years [2].

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The serial measurement of viral loads by quantitative polymerase chain reaction (PCR) is a useful tool in monitoring the course of BKV infection [5,6]. To start appropriate intervention after BK viral loads are observed, it is necessary to recognize the characteristics of BK infection as well as the risk factors. Despite many previous reports, the risk factors for BKVAN are not well defined due to discordant results in different transplant centers [3].

This single-center study aimed to demonstrate the association between quantitative measurement of BKV-DNA and the progression of BKV infection and to identify the risk factors associated with the evolution of viruria to viremia.

METHODS

Study Population

We analyzed 266 patients who underwent renal transplantation in our center between October 2006 and February 2013, including 208 transplants from living donors, 36 from deceased donors, and 22 simultaneous pancreas–kidney transplants. Clinical data were obtained by reviewing the medical records.

Examinations for BKV Infection

All transplant recipients underwent a monthly screening urinary sediment examination by the Sternheimer staining method. If viral-infected cells were present, we began monitoring for viral loads in urine and blood samples. Quantitative real-time PCR assays were performed by SRL Inc. (Tokyo, Japan). The quantitative range for this assay is 1×10^2 to 5×10^7 copies/mL. Viruria and viremia was defined as 100 copies/mL or more on quantitative PCR in urine and plasma samples, respectively.

Diagnosis of BKVAN

Definitive BKVAN was diagnosed based on histological examination of biopsy specimens. Most transplant recipients with BK viremia and unexplained increase in serum creatinine levels underwent renal allograft biopsy. The diagnosis was confirmed using immunohistochemical examination with cross-reacting antibodies against the large T antigen of the related simian polyomavirus.

Statistical Analysis

Statistical analysis were performed using StatMateI V (ATMS Corp, Tokyo, Japan). We compared plasma BKV loads between patients with viremia without nephropathy and BKVAN patients using a Mann-Whitney *U* test. Logistic regression analysis was used to determine independent risk factors associated with viremia. Specific variables associated with $P < .05$ on univariate analysis were entered into multivariate analysis. Results were expressed as odds ratios with respective 95% confidence intervals. *P* values < .05 were considered statistically significant.

RESULTS

Between October 2006 and February 2013, 266 renal transplants were performed in our center. Of these, 1 case diagnosed as BKVAN deviated from the stereotypical evolution of BKV [1], showing polyomavirus-associated nephropathy diagnosed based on histological examination without the occurrence of viremia. There was a possibility of JC virus co-infection, which was atypical of BKVAN [7,8]. We therefore decided to exclude this case from analysis due to unconfirmed diagnosis.

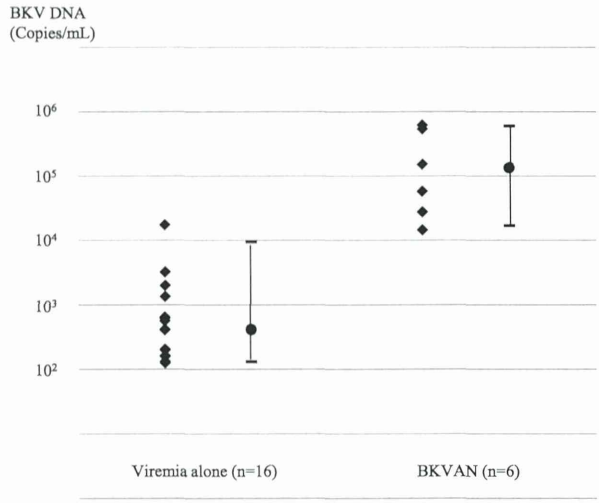

Fig 1. Viral loads in plasma of viremia without nephropathy and BK polyomavirus-associated nephropathy (BKVAN). Plasma viral loads between viremia alone (n = 16) and BKVAN (n = 6) were statistically analyzed using a Mann-Whitney *U* test. Plasma viral loads were significantly higher in the BKVAN group than that of viremia alone ($P < .001$). The interval between 5% and 95% of viral loads corresponded to the range of 2.30×10^4 to 7.75×10^5 copies/mL in BKVAN and 1.15×10^2 to 9.83×10^3 in viremia alone, respectively.

Thus, 265 recipients were included in this study. Of these, 22 (8.3%) cases showed viruria alone, 16 (6%) cases had viremia without nephropathy, and 6 (2.3%) cases were diagnosed as BKVAN based on histological examination of biopsy specimens after viremia. Of these 6 BKVAN patients, 2 (33.3%) patients progressed to graft loss at 59 months and 31 months after diagnosis, respectively.

We compared the plasma BKV loads between patients with viremia without nephropathy and BKVAN patients (Fig 1). Plasma viral loads were significantly higher in the BKVAN group than in the group with viremia alone ($P < .001$), indicating that the progression of viremia to BKVAN was associated with higher BKV DNA amplification in plasma. The interval between 5% and 95% of viral loads corresponded to a range of 2.30×10^4 to 7.75×10^5 copies/mL in BKVAN patients and 1.15×10^2 to 9.83×10^3 in patients with viremia alone. Thus, the cutoff value for differentiating between BKVAN and viremia alone was proposed to be 1×10^4 copies/mL in plasma, with a sensitivity of 100% and a specificity of 93.8% for BKVAN.

Of the 6 patients diagnosed with BKVAN, 3 (50%) patients showed a plasma viral load over 1×10^4 copies/mL at the first PCR examination; this included 2 patients who eventually suffered graft loss (plasma viral load: 3.8×10^4

and 1.8×10^4 copies/mL, respectively). In contrast, none of the patients with viremia alone showed a plasma viral load over 1×10^4 copies/mL at the first PCR examination. Moreover, 15 (68.2%) of the 22 patients with viruria in whom the viral load exceeded 5×10^7 copies/mL in urine even once progressed to viremia.

After the reduction of immunosuppression with monitoring for plasma viral loads, 13 of 16 (81.3%) recipients with viremia alone showed BK virus clearance in plasma. In 1 patient among the remaining 3 patients, the plasma viral load was 1.2×10^2 copies/mL, which was close to the lowest detectable limit. Further, 1 of the 16 (6.3%) recipients with viremia alone suffered chronic active antibody-mediated rejection, which was probably associated with the former reduction in immunosuppression.

We statistically analyzed the factors associated with the evolution of viruria to viremia, as shown in Table 1. In univariate analysis, recipient age over 55 years, tacrolimus exposure, and viruria over 5×10^7 copies/mL were associated with BK viremia. In multivariate analysis, recipient age over 55 years and tacrolimus exposure remained independently associated with BK viremia.

DISCUSSION

In the present study, we found that 8.3% of kidney transplant recipients in our center had BK viruria alone, 6% had BK viremia alone, and 2.3% were diagnosed with BKVAN; this incidence was not as high as that demonstrated by previous reports [2,3,9]. Overall, 2 (33.3%) of the 6 patients diagnosed with BKVAN progressed to graft loss. When these 2 cases were diagnosed with BKVAN, we lacked the clinical information to recognize BKV infection and therefore could not initiate intervention early enough.

We demonstrated that the progression of viremia to BKVAN was strongly associated with BKV DNA amplification in plasma, similar to previous reports [5]. Interestingly, we observed a possible association between viruria over 5×10^7 copies/mL and progression to viremia; viremia developed in 68.2% of patients with viral loads over 5×10^7 copies/mL in urine. This finding suggested that viral loads over 5×10^7 copies/mL in urine might be a suitable index for initiating intervention at viruria, rather than waiting until viremia.

We proposed a cutoff value of 1×10^4 copies/mL for plasma viral loads for differentiation between BKVAN and viremia alone, which was in agreement with Kidney Disease: Improving Global Outcomes clinical practice guideline [6]. Hirsch et al. found BKVAN to be associated with viral loads of over 7.7×10^3 copies/mL in plasma [9], whereas Randhawa et al. determined the cutoff between viremia and BKVAN to be 5.0×10^3 copies/mL in plasma, with a sensitivity of 100% but a false-positive rate of 15.2% [5]. Regarding the predictive value for BKVAN in our center, the cutoff value proposed here showed a sensitivity of 100% and a specificity of 93.8%. Interestingly, we found that the 2 patients who experienced graft loss secondary to BKVAN had viral loads over 1×10^4 copies/mL in plasma at the first PCR examination. Based on our experience, we consider that recipients with viral loads over 1×10^4 copies/mL in plasma would possibly progress to BKVAN if appropriate and timely intervention was not provided. Thus, a cutoff value of 1×10^4 copies/mL in plasma may be considered acceptable for predicting the occurrence of BKVAN.

Previous studies have proposed that a reduction in immunosuppression should be initiated when the viral load is persistently over 1×10^4 copies/mL in plasma [6,10]. However, early intervention has been shown to lead to

Table 1. Univariate and Multivariate Analysis of Risk Factors Associated With BK Viremia

	Univariate analysis			Multivariate analysis		
Factors	Odds ratio	95% Confidence interval	*P*-value	Odds ratio	95% Confidence interval	*P*-value
Recipient age > 55 y	14.538	1.646–128.449	0.016	32.084	2.103–489.503	0.013
Sex	1.200	0.367–3.922	0.763			
BMI	0.929	0.798–1.082	0.346			
CNI tacrolimus	5.278	1.203–23.158	0.027	11.975	1.340–107.042	0.026
ABO incompatible*	3.750	0.952–14.764	0.059			
Desensitization	2.667	0.759–9.368	0.126			
Duration of HD	1.002	0.995–1.010	0.508			
History of blood transfusion	1.071	0.299–3.838	0.916			
Viruria > 5×10^7	4.592	1.291–16.331	0.019			
Donor age > 55 y	0.825	0.245–2.783	0.757			
Graft weight	0.996	0.984–1.009	0.587			
Complication†	0.833	0.255–2.724	0.763			
Operation time	0.998	0.989–1.006	0.573			
Bleeding	1.001	0.998–1.003	0.642			
TIT	0.999	0.996–1.002	0.411			

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor; TIT, total ischemic time.

*All cases underwent desensitization with rituximab and mycophenolate mofetil (MMF) along with double filtration plasmapheresis (DFPP) and/or plasma exchange (PE).

†Requiring surgical, endoscopic, or radiological intervention during postoperative hospitalization.

clearance of BK viremia in 70% to 90% patients [3]; therefore, in our center, we began to reduce the immunosuppression dose when the plasma viral load was found to be less than 1×10^4 copies/mL in plasma. It was essential to periodically monitor plasma viral loads to avoid unnecessary reduction and subsequent acute rejection [1]. In our center, 81.3% of the patients with viremia alone showed clearance of the BK viremia, and only 1 (6.3%) of the 16 patients with viremia alone suffered chronic active antibody-mediated rejection associated with a reduction in immunosuppression. This indicated that our intervention strategy was thought to bring a good outcome with no inferiority compared to those reported by other studies [1,3].

In our study, recipient age over 55 years and tacrolimus exposure were the independent risk factors associated with the evolution of viremia after the onset of viruria. Hirsch et al. [11] showed that cyclosporine A is associated with a significantly lower risk than tacrolimus regarding BK viremia at 6 and 12 months posttransplantation, whereas older age contributes as an independent risk factor for BK viremia later in the first year posttransplantation.

Egli et al. [12] analyzed the effects of calcineurin inhibitors on BKV-specific T-cell responses. Both of tacrolimus and cyclosporine A inhibited BKV-specific T-cell responses at the concentrations equivalent to clinical target trough levels. The inhibition of tacrolimus appeared to be slightly stronger than that of cyclosporine A. Therefore, we suggest that conversion of tacrolimus to cyclosporine A without a reduction in the dose should be considered for a specified group of viruria patients over age 55 years with viral loads over 5×10^7 copies/mL in urine. In summary, early intervention at onset of viremia and a specified viruria may prevent the progression of BK infection.

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ELSEVIER

Utility of Glucagon Stimulation Test in Type 1 Diabetes After Pancreas Transplantation

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ABSTRACT

Background. Despite recent progress of immunosuppressive therapy with newly developed agents, long-term pancreatic graft survival after pancreas transplantation still remains low. Therefore, precise assessment of β-cell function after pancreas transplantation is necessary.

Methods. Pancreatic β-cell secretory activity was measured by means of the peripheral plasma fasting serum C-peptide (CPR) response to 1 mg of glucagon intravenously in 23 patients after pancreas transplantation. The utility of ΔCPR after injection was compared with other indices that reflect insulin secretion.

Results. When we performed the test, 6 patients still needed insulin injection after the transplantation. Mean CPR before and after glucagon intravenously were 1.9 ± 0.98 ng/mL and 4.6 ± 2.29 ng/mL, respectively. Fasting serum CPR, secretory unit of islet in transplantation (SUIT) index, and ΔCPR after glucagon injection were significantly different between insulin users and nonusers. During follow-up (501 ± 228 days), 3 patients could stop using insulin, and their increase of CPR (1.8 ± 0.5 ng/mL) was significantly higher than that in continuous insulin users (0.3 ± 0.3 ng/mL).

Conclusion. Fasting CPR, SUIT index, and ΔCPR after glucagon injection could reflect β-cell function for post–pancreas transplant patients, and glucagon stimulation test could give us additional information to predict insulin-free treatment.

SIMULTANEOUS PANCREAS AND KIDNEY TRANSPLANTATION is now considered as beneficial treatment for patients with type 1 diabetes (T1DM) and end-stage renal diseases [1]. Despite recent progress of immunosuppressive therapy with newly developed agents, long-term pancreatic graft survival still remains low. Therefore, precise assessment of β-cell function after pancreas transplantation is necessary. Fasting serum C-peptide (CPR) could reflects β-cell function in part, but CPR level is known to be affected by renal function [2]. Oral and intravenous glucose tolerance tests are used to estimate both glucose intolerance and insulin secretion, and the insulin response after exogenous glucagon are used for estimating the insulin secretary capacity in patients with diabetes [3]. Nauck et al reported that acute response to glucagon injection was associated with oral glucose tolerance also in pancreas-kidney transplant recipients [4]. However, a comparative evaluation of measures of β-cell function in the recipients of pancreas transplant is still an important issue to predict the graft function and graft survival. In the present study, we aim to explore the utility of several indices including fasting CPR and glucagon stimulation test for the assessment of β-cell function of post–pancreas transplantation patients.

METHODS

T1DM patients (n = 23, 6 males, age 44.0 ± 7.4 years) after pancreas transplantation from March 2009 to June 2013 at Fujita Health University Hospital were recruited for this study (Table 1).

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Table 1. Difference Between Insulin-Free Patients and Insulin Users After Pancreas Transplantation

	Insulin-Free (n = 17) Median [25th–75th]	Insulin User (n = 6) Median [25th–75th]	P Value
FPG (mg/dL)	94 [85–100]	92 [88–97]	.944
IRI (mU/mL)	7.6 [5.9–11.2]	18 [7.5–23.1]	.074
CPR (ng/mL)	2.0 [1.6–2.6]	1.0 [0.5–1.7]	.033*
HOMA-R	1.8 [1.4–2.5]	4.0 [1.6–5.0]	.086
HOMA-β	107 [63–144]	224 [108–618]	.151
SUIT index	129 [78–146]	68 [30–88]	.030*
ΔCPR (6 min after 1 mg glucagon injection)	3.1 [2.3–4.5]	0.95 [0.3–2.0]	.004*
Creatinine (mg/dL)	1.01 [0.77–1.3]	1.23 [0.77–1.78]	.344
Dose of insulin (U/d)	0	13 [6–31]	<.001*

Abbreviations: FPG, fasting plasma glucose; IRI, immunoreactive insulin; CPR, C-peptide; HOMA, homeostasis model assessment; SUIT, secretory unit of islet in transplantation; ΔCPR, difference between 6- and 0-minute CPR measurement after 1 mg glucagon injection.
*P < .05, Mann–Whitney U test.

Exclusion criteria were inability of agreement or unwillingness to participate in the study. There was only one patient who underwent the repeated pancreas transplantation. Mean age of onset of T1DM was 13.0 ± 5.5 years old. Sixteen of 23 patients were on hemodialysis at the time of transplantation. Simultaneous pancreas and kidney transplantation was done in 20 cases, and solitary pancreas transplantation in the other 3 cases. The study was performed at discharge after the transplantation or at regularly scheduled visit of outpatient clinic. Median duration after transplantation was 36 days (interquartile range: 25–98 days). The study was approved by the Review Board for Epidemiology and Clinical Studies of Fujita Health University (Aichi, Japan). It was therefore undertaken in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from each subject.

Fasting plasma glucose (FPG), serum immunoreactive insulin (IRI), and CPR levels were measured at fasting state. Glucagon stimulation test was performed by intravenous loading of 1 mg glucagon. The acute response to glucagon was measured by the elevation of CPR levels from 0 to 6 minutes after glucagon challenge (Δ-CPR). Indices for insulin secretion and resistance were calculated from the following formulae [5,6]:

$$\text{HOMA-R (homeostasis model assessment of insulin resistance)} = [\text{Fasting IRI}(\mu\text{U/mL}) \times \text{FPG}(\text{mg/dL})]/405$$

$$\text{HOMA-}\beta = [\text{Fasting IRI}(\mu\text{U/mL}) \times 360]/[\text{FPG}(\text{mg/dL}) - 63]$$

$$\text{SUIT (secretory unit of islet in transplantation)} = [1485 \times \text{fasting CPR}(\text{ng/mL})]/[\text{FPG}(\text{mg/dL}) - 61.8]$$

Statistical Analyses

All data analyses were undertaken using SPSS, ver11.0 (SPSS, Chicago, Ill, United States). Continuous data are mean ± standard deviation, and skewed variables are medians and interquartile ranges. Continuous variables were analyzed using the unpaired Student t test. As for the difference of fasting CPR and CPR at 6 minutes after glucagon stimulation, the data were analyzed by paired t test. If data were not distributed normally, the Mann-Whitney U test was used. $P < .05$ was considered significant.

RESULTS

Pancreas recipients were divided into 2 groups: 17 patients without insulin treatment at the study (insulin-free) and 6 patients with regularly scheduled insulin treatment (insulin user). Median dose of insulin in insulin user was 13 U (interquartile range 6–31). Fasting serum CPR and SUIT index in insulin-free group were higher than in insulin users, and FPG, fasting IRI, HOMA-R, and HOMA-β were similar between the 2 groups (Table 1). Figure 1 shows the results of glucagon stimulation test in all cases. Overall, CPR at 6 minutes after glucagon injection was significantly higher than CPR before the stimulation (Fig 1). In addition, ΔCPR after glucagon stimulation in the insulin-free group was also significantly higher than that in insulin users (Table 1). Among 6 insulin users, 3 patients could stop using insulin, and the others had to continue to use insulin during the follow-up period (501 ± 228 days). SUIT index and ΔCPR after glucagon injection in insulin-discontinuation group (group D) were higher than those in continuous insulin users (group C; Table 2).

DISCUSSION

We compared the performance of several indices including HOMA-β, fasting CPR, SUIT, and ΔCPR shortly after glucagon injection in post–pancreas transplant patients with T1DM. Our current data showed that HOMA-R and HOMA-β were not significantly different between insulin users and insulin-free subjects after pancreas transplantation.

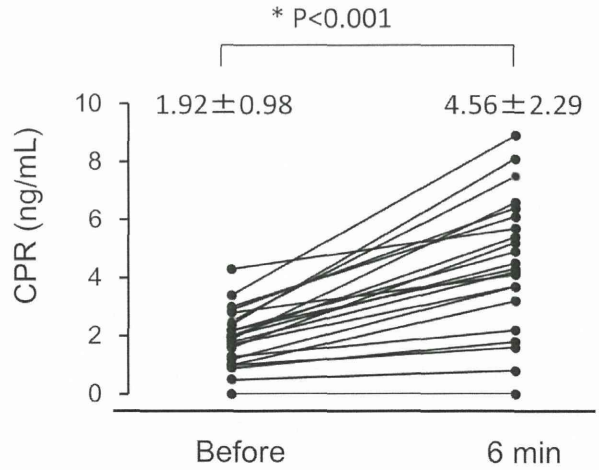

Fig 1. Glucagon stimulation test in patients with type 1 diabetes after pancreas transplantation. The β-cell function was evaluated in the outpatient clinic after an overnight fast by measuring serum C-peptide (CPR) concentrations before and 6 minutes after intravenous injections of 1 mg glucagon. The data were analyzed by using paired t test.